06-108741

Industria y Comercio

SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

06-108741

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO DERIVADOS DE FENOL Y TIOFENOL 3-O 4-MONOSUSTITUIDOS UTILES COMO LIGANDOS DE H3

SOLICITANTE WARNER LAMBERT COMPANY LLC

DIRECCIÓN 201 Tabor Road, Morris Plains, New Jersey 07950, E U A

55

APODERADO CARLOS R OLARTE

BOGOTÁ 25 de Octubre de 2006

P2005/000217

OLARTERAISPECK 06|217 1

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-108741- -00000-0000
Fec: 2006-10-26 17:22:36 Dep: 2020 NUEVAS CREACIONES
Tra: 11 PATENTES II
Cla: 379 FASE NACIONAL II

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL 07-Dic-06

SOLICITUD DE:

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

[ ] Capítulo I. [X] Capítulo II.

(2) **SOLICITANTE (71)**	**Nombre:** WARNER LAMBERT COMPANY LLC **Dirección:** 201 Tabor Road, Morris Plains, New Jersey 07950, E.U.A. **Nacionalidad o Domicilio:** ESTADOUNIDENSE **Lugar de Constitución:** Estados Unidos de América. **Teléfono:** _____ **Fax:** _____ **E-mail:** _____	**IDENTIFICACIÓN** C.C. [ ] NIT [ ] C.E. [ ] Otro [ ] Cual _____ Número _____
REPRESENTANTE O APODERADO	**Nombre:** CARLOS R. OLARTE **Dirección:** World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10 **Teléfono:** 601-7700 **Fax:** 601-7799 **E-mail:** office@olarteraisbeck.com	**IDENTIFICACIÓN** C.C. [X] NIT [ ] C.E. [ ] Otro [ ] Cual _____ Número 79782747Bta TP 74.295
INVENTOR (ES) (72)	**Nombre:** VER PAGINA ADJUNTA **Dirección:** VER PAGINA ADJUNTA **Nacionalidad o Domicilio:** VER PAGINA ADJUNTA	

(5) **PCT (86)**

Solicitud Internacional No. PCT/IB2005/001114 Fecha Abril 19, 2005

Publicación Internacional No. WO 2005/108384 A1 Fecha Noviembre 17, 2005

(6) **Título (54)** **DERIVADOS DE FENOL Y TIOFENOL 3- O 4-MONOSUSTITUIDOS UTILES COMO LIGANDOS DE H3.**

Clasificación Internacional (51) **C07D 309/06, 405/12, 309/08, 295/12, 405/06, 405/14, 295/14, 417/04, 417/06, A61K 31/55, A61P 25/06, C07D 405/14, 405/06, 405/12, 405/04.**

Prioridad SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
EP	Mayo 7, 2004	04291187.5
GB	Marzo 4, 2005	0504564.6

(9) **Comprobante de pago No.** 06-81.843 **Fecha** Octubre 24, 2006

(10) **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Ver expediente No. 05-124.741. Adjunto copia simple
- [ ] 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.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

( ) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

LISTA DE INVENTORES PCT/IB2005/001114

Patrick BERNARDELLI
Ramsgate Road, Sandwich,
Kent CTI3 9NJ,
Reino Unido
Nacionalidad: Francesa

ANDREW MICHAEL CRONIN
Ramsgate Road, Sandwich,
Kent CTI3 9NJ,
Reino Unido
Nacionalidad: Británica

ALEXIS DENIS
Ramsgate Road, Sandwich,
Kent CTI3 9NJ,
Reino Unido
Nacionalidad: Francesa

STEPHEN MARTIN DENTON
Ramsgate Road, Sandwich,
Kent CTI3 9NJ,
Reino Unido
Nacionalidad: Británica

HENRY JACOBELLI
Ramsgate Road, Sandwich,
Kent CTI3 9NJ,
Reino Unido
Nacionalidad: Francesa

MARK IAN KEMP
Ramsgate Road, Sandwich,
Kent CTI3 9NJ,
Reino Unido
Nacionalidad: Británica

EDWIGE LORTHIOIS
Ramsgate Road, Sandwich,
Kent CTI3 9NJ,
Reino Unido
Nacionalidad: Francesa

FIONA ROUSSEAU
Ramsgate Road, Sandwich,
Kent CTI3 9NJ,
Reino Unido
Nacionalidad: Británica

DELPHINE SERRADEIL-CIVIT
Ramsgate Road, Sandwich,
Kent CTI3 9NJ,
Reino Unido
Nacionalidad: Francesa

FABRICE VERGNE,
Ramsgate Road, Sandwich,
Kent CTI3 9NJ,
Reino Unido
Nacionalidad: Francesa

4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-108741--00000-0000
Fec: 2006-10-25 17:22:36 Dep: 2000 NUECREACIONES
Tra: 11 PATENTEYII
Eve: 379 FASENACIONALII

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 81,843
FECHA : OCTUBRE 24 DE 2006

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEGR	CONSIGNACION	BANCO POPULAR	050-00110-6	52335570	23/10/2006	2,778,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	463,000.00
		TOTAL : $	463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

WARNER- LAMBERT COMPANY LLC.

Bilingüe inglés- español otorgado en Nueva York, Estados Unidos el 14 de julio de 2003 y firmado por J. Trevor Lumb, Vicepresidente de Pfizer Products Inc.

Sello: recibido el 21 julio de 2003 Departamento de Patentes NYD- Pfizer Inc.

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 14 de julio de 2003 el suscrito notario Kenneth Greenwood certifica que J. Trevor Lumb, domiciliado en Nueva York ejercia funciones de Secretario Asistente de Warner-Lambert Company LLC, con sede en Morris Plains, Nueva Jersey, Estados Unidos.

Firma del notario: Kenneth Greenwood

Sello notarial: certificado, verificado y autenticado en la Localidad de Egham en Surrey, 14 julio, 2003 por el Notario Kenneth Greenwood-Horne Engall & Freeman

Sello Notario Público en alto relieve rojo.

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)
REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País :Reino Unido de Gran Bretaña e Irlanda del Norte
   Este documento Público 2.ha sido firmado por K. Greenwood
3. ejerce funciones de Notario Público
4. Lleva el sello de dicho Notario Público

CERTIFICADO 5. En Londres 6. El 17 de julio de 2003

7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad.
8. No. G210433
9. Sello del Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
10. Firma de R. Bawden - Por Secretario de Estado

Si el documento se usa en un país que no es parte de la convención de la Haya del 5 de octubre 1961, debe presentarse en sección consular de la misión que representa el país.
Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 25 de julio-2003. Marlen Neira C

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 OCT 1993

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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

www.olarteraisbeck.com

RECEIVED
JUL 21 2003
PFIZER INC.
PATENT DEPT. NYO

Power of Attorney

The undersigned,

domiciled in

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

Poder

El suscrito,

Warner-Lambert Company LLC

domiciliado en

201 Tabor Road, Morris Plains, New Jersey 07950 USA

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

Signature/Firma: _____

Date/Fecha: July 14, 2003

City,Country/Ciudad,País: New York, USA

1937

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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

www.olarteraisbeck.com

Notarial Certification

On this date,
July 14, 2003
The undersigned Notary Public certifies:

1. That J. Trevor Lumb
of legal age and domiciled in New York, USA
signed the foregoing document.

2. That the grantor has executed the foregoing document as Assistant Secretary of Warner-Lambert Company LLC

3. That Warner-Lambert Company LLC, having its principal place of business located in Morris Plains, New Jersey, U.S.A. is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

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

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):

NOTARY PUBLIC (Signature):

EXECUTION
Certified Verified and Authenticated
In The Town Of Egham In Surrey
This 14th Day Of July 2003

KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGALL AND FREEMAN

Certificación Notarial

En esta fecha,
el Notario Público suscrito certifica:

1. Que
J. Trevor Lumb
mayor de edad y domiciliado
New York
suscribió el documento que antecede.

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

4. Que
con sede principal ubicada en

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

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

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

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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

   This public document / Le présent acte public

2. Has been signed by — K Greenwood
   a été signé par

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

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

   Certified/Attesté

5. at London/à Londres — 6. the/le 17 July 2003

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

8. *Number/sous No* **G210433**

9. Stamp:
   timbre:

10. Signature: R. Bawden

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

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

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 November 2005 (17.11.2005)

PCT

(10) International Publication Number
WO 2005/108384 A1

(51) International Patent Classification[7]: C07D 309/06, 405/12, 309/08, 295/12, 405/06, 405/14, 295/14, 417/04, 417/06, A61K 31/55, A61P 25/06, C07D 405/14, 405/06, 405/12, 405/04

(21) International Application Number: PCT/IB2005/001114

(22) International Filing Date: 19 April 2005 (19.04.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
04291187.5 7 May 2004 (07.05.2004) EP
0504564.6 4 March 2005 (04.03.2005) GB

(71) Applicant (*for all designated States except US*): WARNER-LAMBERT COMPANY LLC [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): BERNARDELLI, Patrick [FR/FR]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). CRONIN, Andrew, Michael [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). DENIS, Alexis [FR/FR]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). DENTON, Stephen, Martin [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). JACOBELLI, Henry [FR/FR]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). KEMP, Mark, Ian [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). LORTHIOIS, Edwige [FR/FR]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). ROUSSEAU, Fiona [GB/GB]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). SERRADELL-CIVIT, Delphine [FR/FR]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB). VERGNE, Fabrice [FR/FR]; Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ (GB).

(74) Agents: FULLER, Grover, F., Jr. et al.; C/o WOOD, David, J., Pfizer Research and Development, Ramsgate Road, Kent, Sandwich CT13 9NJ (GB).

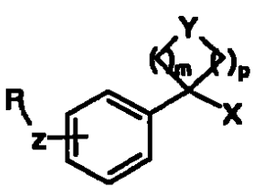
(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK,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

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

Published:
— *with international search report*

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

(54) Title: 3- OR 4-MONOSUBSTITUTED PHENOL AND THIOPHENOL DERIVATIVES USEFUL AS H3 LIGANDS



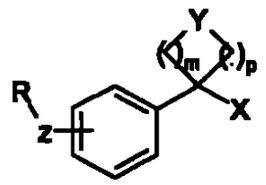
(1)

(57) Abstract: The invention relates to 3- or 4-monosubstituted phenol and thiophenol derivatives of formula (1) and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives. Said 3- or 4-monosubstituted phenol and thiophenol derivatives are H_3 ligands and are useful in numerous diseases, disorders and conditions, in particular inflammatory, allergic and respiratory diseases, disorders and conditions.

WO 2005/108384 A1

3- OR 4-MONOSUBSTITUTED PHENOL AND THIOPHENOL DERIVATIVES USEFUL AS H3 LIGANDS

The present invention relates to 3- or 4-monosubstituted phenol and thiophenol derivatives of general formula :



(1)

in which R, X, Y, Z, m and p have the meanings indicated below,
and to processes for the preparation of, intermediates used in the preparation of, compositions containing and the uses of, such derivatives.

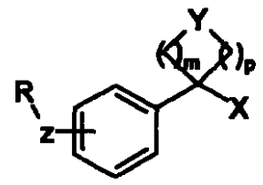
Histamine H_3 receptors are found inter alia on presynaptic terminals of peripheral nerves, where they modulate autonomic neurotransmission and modulate a variety of end organ responses under control of the autonomic nervous system. They are also heteroreceptors, modulating the release of numerous other neurotransmitters such as dopamine, glutamate, noradrenaline, serotonin, GABA, acetylcholine, some peptides and co-transmitters.

Recently numerous histamine H_3 receptor ligands have been developed. An overview of the current advance in H_3 ligand research and patenting is given in *Expert Opin. Ther. Patents* (2003) 13(6). Examples of Histamine H_3 receptor ligands can be found in WO02/76925, WO00/06254, WO02/12190, WO02/12214 and WO02/06223.

H_3 receptor ligands are believed to be suitable for the treatment of various diseases including both disorders of the central nervous system and inflammatory disorders. Examples of diseases where treatment with H_3 ligands is believed to be useful are inflammatory bowel disease, Crohn's disease, colitis ulcerosa, sleep disorders, migraine, dyskinesia, stress-induced anxiety, psychotic disorders, epilepsy, Cognition deficiency diseases such as Alzheimer's disease or mild cognitive impairment, depression, mood disorders, schizophrenia, anxiety disorders, attention-deficit hyperactivity disorder (ADHD), psychotic disorders, obesity, dizziness, epilepsy, motion sickness, vertigo, respiratory diseases such as adult respiratory distress syndrome, acute respiratory distress syndrome, bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis, chronic sinusitis, allergy, allergy-induced airway responses, allergic rhinitis, viral rhinitis, non-allergic rhinitis, perennial and seasonal rhinitis, nasal congestion and allergic congestion.

Although H_3 ligands are known there is still a need to provide new H_3 ligands that are good drug candidates. In particular, preferred compounds should bind potently to the histamine H_3 receptor whilst showing little affinity for other receptors. They should be well absorbed from the gastrointestinal tract, be metabolically stable and possess favourable pharmacokinetic properties. They should be non-toxic and demonstrate few side-effects.

In this context, the present invention concerns new substituted phenol and thiophenol derivatives of general formula (1) :



(1)

or a pharmaceutically acceptable salt and/or thereof wherein :

the substituent of formula –Z-R is in the meta or para position of the phenyl group;

X is selected from -CN, $-CH_2OH$, $-CH_2-O-(C_1-C_4)$alkyl, -C(O)OH, $-C(O)O(C_1-C_4)$alkyl, $-CH_2-NR^1R^2$, -C( )NR^3R^4, $-CH_2-O-het^2$, $-CH_2-het^1$ and het^1, the group het^1 in both $-CH_2-het^1$ and het^1 being optionally substituted by one or two substituents independently selected from halo, cyano, (C_1-C_4)alkyl, $-S-(C_1-C_4)$alkyl and (C_1-C_4)alkoxy;

R^1 is hydrogen or (C_1-C_4)alkyl optionally substituted by (C_3-C_8)cycloalkyl;

R^2 is selected from the group consisting of :

hydrogen,

(C_1-C_8)alkyl optionally substituted by one or two substituents independently selected from (C_3-C_8)cycloalkyl, hydroxy, $-S-(C_1-C_4)$alkyl, $-O-(C_1-C_4)$alkyl, $-SO_2-(C_1-C_4)$alkyl, $-SO-(C_1-C_4)$alkyl, halo, het^1, amino, (C_1-C_4)alkylamino [(C_1-C_4)alkyl]$_2$amino and phenyl, said phenyl being optionally substituted by one or two substituents independently selected from halo, hydroxy, cyano, (C_1-C_4)alkyl and (C_1-C_4)alkoxy,

(C_3-C_8)cycloalkyl,

het^2, optionally substituted by one or two substituents independently selected from halo, cyano, (C_1-C_4)alkyl, NH_2 and (C_1-C_4)alkoxy,

$-SO_2-R^5$ wherein R^5 is selected from the group consisting of (C_1-C_4)alkyl, amino, (C_1-C_4)alkylamino, [(C_1-C_4)alkyl]$_2$amino, phenyl and $-(C_1-C_4)$alkyl-phenyl, said phenyl being optionally substituted by one or two substituents independently selected from halo, cyano, (C_1-C_4)alkyl and (C_1-C_4)alkoxy, and

$-C(O)-R^6$ wherein R^6 is selected from the group consisting of (C_1-C_4)alkyl, amino, (C_1-C_4)alkylamino, [(C_1-C_4)alkyl]$_2$amino, phenyl and $-(C_1-C_4)$alkyl-phenyl, said phenyl being optionaly substituted by one or two substituents independently selected from halo, cyano, (C_1-C_4)alkyl and (C_1-C_4)alkoxy;

or R^1 and R^2 form together with the N atom to which they are attached a 3-, 4-, 5-, 6- or 7-membered saturated heterocycle wherein one C atom may be replaced by N, O, S, SO or SO_2 and wherein said

saturated heterocycle is optionally substituted by one or two groups independently selected from hydroxy, halo, =O, (C_1-C_4)alkyl, -(C_1-C_4)alkyl(C_3-C_8)cycloalkyl, (C_1-C_4)alkoxy, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, -$SO_2(C_1-C_4)$alkyl, -C(O)(C_1-C_4)alkyl, [(C_1-C_4)alkyl]$_2$amino, amino, (C_1-C_4)alkylamino, -C(O)NH_2, C(O)O(C_1-C_4)alkyl and pyrrolidinone;

R^3 and R^4 are each independently selected from hydrogen, (C_3-C_8)cycloalkyl, and (C_1-C_4)alkyl, said (C_3-C_8)cycloalkyl and (C_1-C_4)alkyl being optionally substituted by amino, (C_1-C_4)alkylamino, [(C_1-C_4)alkyl]$_2$amino or (C_3-C_8)cycloalkyl, or R^3 and R^4 form together with the N atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocycle wherein one C atom may be replaced by N or O and wherein said saturated heterocycle is optionally substituted by (C_1-C_4)alkyl, [(C_1-C_4)alkyl]$_2$amino, amino, (C_1-C_4)alkylamino, or –C(O)(C_1-C_4)alkyl, said –C(O)(C_1-C_4)alkyl being optionally substituted by methoxy or ethoxy,

Y is selected from CH_2, CH(OH), O, C=O and N, said N being substituted by H, (C_1-C_4)alkyl, C(O)(C_1-C_4)alkyl or (C_1-C_4)alkoxy(C_1-C_4)alkyl;

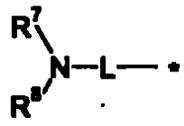
Z is selected from O, S, SO and SO_2;

m and p are both integers which are independently 1, 2 or 3, with the condition that m+p is equal to or less than 4 so that the ring formed by :

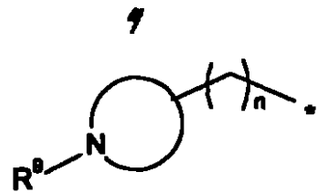


is a 4-, 5- or 6-membered ring;

and R is either a group of formula :



wherein * represents the attachment point to Z, L is a straight chain or branched (C_2-C_8)alkylene and R^7 and R^8 are each independently selected from hydrogen, (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, hydroxy(C_1-C_8)alkyl or R^7 and R^8 form together with the N atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocycle wherein one C atom is optionally replaced by N, O, S, SO or SO_2 and wherein said saturated heterocycle is optionally substituted by one or two groups independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkoxy(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, hydroxy, C(O)O(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl-NH_2, -C(O)NH_2, halo, amino, (C_1-C_4)alkylamino and [(C_1-C_4)alkyl]$_2$amino,
or R is a group of formula:



wherein * represents the attachment point to Z, the N-containing ring is a 4- to 7-membered saturated heterocycle, n is an integer equal to 0, 1 or 2, and R^9 represents a substituent selected from hydrogen, (C_1-C_4)alkyl, hydroxy$(C_1-C_4$ alkyl) and (C_3-C_6)cycloalkyl;

het[1] is selected from monocyclic or bicyclic heteroaromatic groups having 5 to 10 ring members, which contain 1, 2, 3 or 4 heteroatom(s) selected from nitrogen, oxygen and sulphur and het[2] is selected from monocyclic or bicyclic heteroaromatic groups having 5 to 10 ring members, which contain 1, 2, 3 or 4 heteroatom(s) selected from nitrogen, oxygen and sulphur.

It has been found that these compounds are H3 ligands and are thus particularly useful for the treatment of H3-related diseases such as neurologic disorders, or inflammatory, respiratory and allergic diseases, disorders and conditions.

In the present description the following definitions are used, unless otherwise specified.

"halo" denotes a halogen atom selected from the group consisting of fluoro, chloro, bromo and iodo.

"(C_1-C_x)alkyl" denotes a saturated, straight-chain or branched hydrocarbon group having from 1 to x carbon atoms and includes for example (when x= 4) methyl, ethyl, propyl, l-propyl, n-butyl, l-butyl, sec-butyl and t-butyl and further (when x=6) pentyl, l-pentyl, n-pentyl and hexyl. This also applies if the alkyl group carries substituents or is a substituent for another group, e.g. in $-S-(C_1-C_4)$alkyl, $-O-(C_1-C_4)$alkyl, $-SO_2-(C_1-C_4)$alkyl, $-SO-(C_1-C_4)$alkyl, $-CH_2-O-(C_1-C_4)$alkyl, $-C(O)O(C_1-C_4)$alkyl, (C_1-C_4)alkylamino, $[(C_1-C_4)alkyl]_2$amino, $-(C_1-C_4)$alkyl-phenyl, $-(C_1-C_4)$alkyl(C_3-C_6)cycloalkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, $-C(O)(C_1-C_4)$alkyl.

"(C_1-C_4)alkoxy" denotes straight-chain and branched alkoxy groups and includes for example methoxy, ethoxy, n-propoxy, l-propoxy, n-butoxy, l-butoxy, sec-butoxy and t-butoxy.

"(C_2-C_6)alkylene" denotes a divalent radical derived from straight-chain or branched alkane containing from 2 to 6 carbon atoms. Examples of (C_2-C_6)alkylene radicals are methylene, ethylene (1,2-ethylene or 1,1-ethylene), trimethylene (1,3-propylene), tetramethylene (1,4-butylene), pentamethylene and hexamethylene.

"hydroxy(C_1-C_4)alkyl" radicals are alkyl radicals substituted by hydroxy. They can contain 1 or several hydroxy substituents, if not stated otherwise. Examples of suitable hydroxy(C_1-C_4)alkyl radicals are hydroxymethyl, 1-hydroxyethyl or 2-hydroxyethyl.

"(C_3-C_6)cycloalkyl" denotes a saturated monocyclic carbocyclic group having 3 to 6 carbon atoms and includes for example cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In the case where the (C_1-C_x)alkyl radicals are substituted by halo, such radical can contain 1 or several halogen atoms, if not stated otherwise. Said halo is preferably a fluoro, a chloro, a bromo or a iodo, in particular fluoro or chloro. For example in a fluoro-substituted alkyl radical, a methyl group can be present as a difluoromethyl or a trifluoromethyl group.

"saturated heterocycle" denotes a saturated monocyclic group having 4 to 7 ring members, which contains 1 nitrogen atom and optionally a further heteroatom selected from nitrogen, oxygen and sulphur. Examples of saturated heterocycles are azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazepanyl and azepanyl.

het^1 and het^2 are monocyclic or bicyclic heteroaromatic groups having 5 to 10 ring members, which contain 1, 2, 3 or 4 heteroatom(s) selected from nitrogen, oxygen and sulphur. In particular the heteroaromatic group contains either (a) 1 to 4 nitrogen atoms, (b) one oxygen atom or one sulfur atom or (c) 1 oxygen atom or 1 sulfur atom and 1 or 2 nitrogen atoms. het^2 is preferably C-linked, which means that the group is linked to the adjacent atom by a ring carbon atom. het^1 can be C-linked or N-linked. The heteroaryl group can be unsubstituted, monosubstituted or disubstituted, as indicated in the definition of X and R^2 hereabove for general formula (1) according to the present invention. Examples of heteroaryl groups include, but are not limited to thiophenyl, furanyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyranyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thiadiazinyl, isobenzofuranyl, benzofuranyl, chromenyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolinyl, isoquinolyl, cinnolinyl, phthalazinyl, naphthyridinyl, quinazolinyl, quinoxalinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, pyrrolopyrazinyl, pyrrolopyridinyl, and imidazopyridinyl. Preferred definitions for het^1 and het^2 will follow hereafter.

In the general formula (1) according to the present invention, when a radical is mono- or poly-substituted, said substituent(s) can be located at any desired position(s), unless otherwise stated. Also, when a radical is polysubstituted, said substituents can be identical or different, unless otherwise stated.

According to a preferred aspect of the invention, X is selected from -CN, $-CH_2OH$, -C(O)OH, $-CH_2-NR^1R^2$, $-C(O)NR^3R^4$, $-CH_2$-het^1 and het^1, het^1 in both $-CH_2$-het^1 and het^1 being optionally substituted once or twice by (C_1-C_4)alkyl, more preferably X is selected from $-CH_2-NR^1R^2$, $-CONR^3R^4$, $-CH_2$-het^1 and het^1, het^1 in both $-CH_2$-het^1 and het^1 being optionally substituted once or twice by (C_1-C_4)alkyl, wherein R^1, R^2, R^3, R^4 and het^1 are as previously defined.

het^1 is preferably selected from a 5 or 6 membered monocyclic heteroaromatic group, or a 9 membered bicyclic heteroaromatic group, each heteroaromatic group containing 1 to 3 nitrogen atoms, or 1 to 2 nitrogen atoms and 1 oxygen atom, or 1 nitrogen atom and 1 sulphur atom, and each heteroaromatic group being optionally substituted once or twice by (C_1-C_4)alkyl, and preferably, optionally substituted once or twice by (C_1-C_3)alkyl.

More preferably, X is thiazolyl, benzimidazolylmethyl-, pyridinyl, oxazolyl, imidazopyridinylmethyl-, pyrimidinyl, imidazolyl, imidazolylmethyl- or triazolylmethyl-, said thiazolyl, benzimidazolylmethyl-, pyridinyl, oxazolyl, imidazopyridinylmethyl-, pyrimidinyl, imidazolyl, imidazolylmethyl- and triazolylmethyl- each being optionally substituted with one methyl group.

R^1 is preferably hydrogen, methyl or ethyl.

R^2 is preferably selected from the group consisting of .

hydrogen,

(C_1-C_6)alkyl optionally substituted by one or two substituents independently selected from -S-(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -SO_2-(C_1-C_4)alkyl, and phenyl, said phenyl being optionally substituted by one or two substituents independently selected from halo, hydroxy, cyano, (C_1-C_4)alkyl and (C_1-C_4)alkoxy,

(C_3-C_8)cycloalkyl,

het^2 optionally substituted by one or two substituents independently selected from halo, cyano, (C_1-C_4)alkyl and (C_1-C_4)alkoxy, wherein het^2 is defined as above,

-SO_2-R^5 wherein R^5 is selected from the group consisting of (C_1-C_4)alkyl, $[(C_1-C_4)alkyl]_2$amino, phenyl, and -(C_1-C_4)alkyl-phenyl, wherein said phenyl is optionally substituted by 1 substituent independently selected from halo and cyano and

-C(O)-R^5 wherein R^5 is selected from the group consisting of (C_1-C_4)alkyl, $((C_1-C_4)alkyl]_2$amino, amino, and -(C_1-C_4)alkyl-phenyl, said phenyl being optionally substituted by one or two substituents independently selected from halo, cyano, (C_1-C_4)alkyl and (C_1-C_4)alkoxy.

More preferably R^2 is selected from the group consisting of

(C_1-C_3)alkyl optionally substituted by –O-(C_1-C_3)alkyl, preferably methoxy,

(C_3-C_6)cycloalkyl,

het^2, wherein het^2 is preferably selected from the group consisting of 5 or 6 membered monocyclic heteroaromatic ring systems containing 1 to 2 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom or 1 nitrogen atom and 1 sulphur atom, said het^2 being optionally substituted by one or two substituents independently selected from halo, cyano, (C_1-C_4)alkyl and (C_1-C_4)alkoxy, preferably (C_1-C_4)alkyl,

SO_2-R^5 wherein R^5 is selected from the group consisting of (C_1-C_4)alkyl, $[(C_1-C_4)alkyl]_2$amino, phenyl, and -(C_1-C_4)alkyl-phenyl, wherein said phenyl is optionally substituted by 1 substituent independently selected from halo and cyano and wherein R^5 is preferably (C_1-C_4)alkyl,

C(O)-R^5 wherein R^5 is selected from the group consisting of (C_1-C_4)alkyl, $((C_1-C_4)alkyl]_2$amino, amino, and -(C_1-C_4)alkyl-phenyl, said phenyl being optionally substituted by one or two substituents independently selected from halo, cyano, (C_1-C_4)alkyl and (C_1-C_4)alkoxy, and wherein R5 is preferably (C_1-C_4)alkyl.

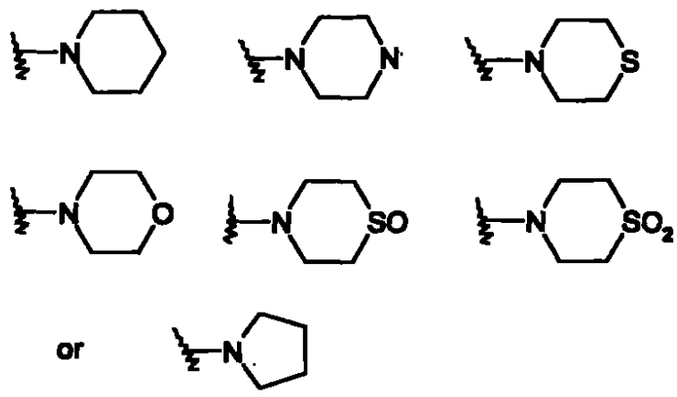
In another aspect of the invention, R^2 is preferably (C_1-C_3)alkyl optionally substituted by methoxy.

het^2 is preferably selected from the group consisting of 5 or 6 membered monocyclic heteroaromatic ring systems containing 1 or 2 nitrogen atoms.

In another aspect of the invention, R^2 is preferably a pyridazinyl group.

According to a further preferred aspect of the invention R^1 and R^2 form together with the N atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocycle wherein one C atom may be replaced by N, O, S, SO or SO_2 and wherein said saturated heterocycle is optionally substituted by one or two groups independently selected from hydroxy, halo, =O, (C_1-C_4)alkyl, -(C_1-C_4)alkyl(C_3-C_8)cycloalkyl, $(C_1-$

C_4)alkoxy, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, -SO_2(C_1-C_4)alkyl, -C(O)(C_1-C_4)alkyl, [(C_1-C_4)alkyl]$_2$amino, -C(O)NH_2, C(O)O(C_1-C_4)alkyl and pyrrolidinone, more preferably R^1 and R^2 form together with the N atom to which they are attached a 5- or 6-membered saturated heterocycle selected from



optionally substituted by one or two groups independently selected from hydroxy, fluoro, hydroxymethyl, methoxymethyl, SO_2(C_1-C_4)alkyl, -C(O)(C_1-C_4)alkyl, -$CONH_2$, and pyrrolidinone.

Even more preferably, R^1 and R^2 form together with the N atom to which they are attached a morpholinyl group.

Preferably R^3 and R^4 are each independently selected from hydrogen and (C_1-C_4)alkyl or R^3 and R^4 form together with the N atom to which they are attached a 4, 5 or 6 membered saturated heterocycle wherein one C atom may be replaced by N or O and wherein said saturated heterocycle is optionally substituted by (C_1-C_4)alkyl.

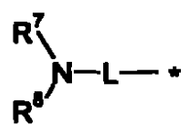
More preferably, R^3 and R^4 are selected independently from hydrogen, methyl and ethyl, or R^3 and R^4 form together with the N atom to which they are attached a pyrrolidinyl, piperidinyl, piperazinyl or azetidinyl ring, (each pyrrolidinyl, piperidinyl, piperazinyl and azetidinyl ring being optionally methyl substituted).

Preferably, Y is selected from CH_2, CH(OH), O and C=O, more preferably Y is O.

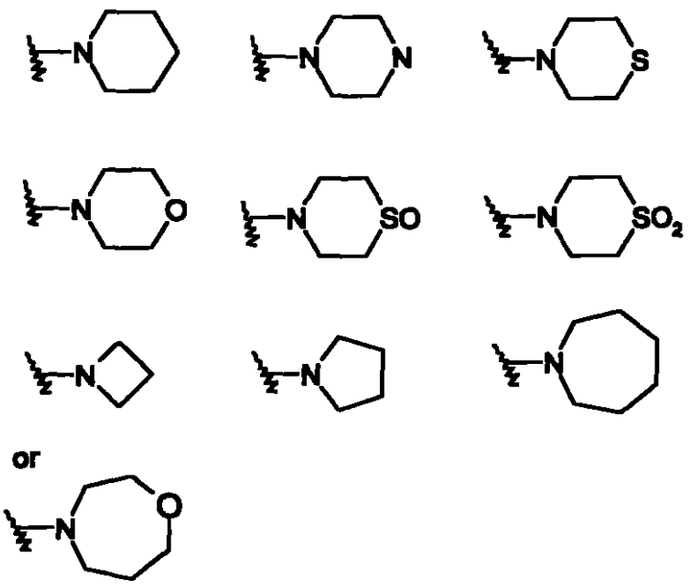
Preferably, Z is O

Preferably m is equal to 1 or 2 and p is equal to 2, more preferably m and p are both 2.

In one preferred aspect of the invention R is a group of formula :



wherein * represents the attachment point to Z, L is a (C_2-C_5)alkylene and R^7 and R^8 are each independently selected from hydrogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl or R^7 and R^8 form together with the N atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocycle wherein one C atom is optionally replaced by N, O, S, SO or SO_2 and wherein said saturated heterocycle is optionally substituted by one or two groups independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkoxy(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, hydroxy, C(O)O(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl-NH_2, -C(O)NH_2 and halo. Examples of the 4-, 5-, 6- or 7-membered saturated heterocycle are :

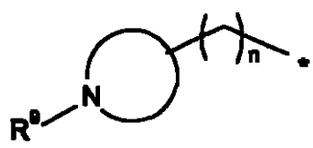


Even more preferably, R^7 and R^8 form together with the N atom to which they are attached a morpholinyl or oxazepanyl group.

In another preferred aspect, R^7 and R^8 form together with the N atom to which they are attached a 4-, 5- or 6-membered saturated heterocycle, optionally substituted by one or two (C_1-C_4)alkyl, preferably methyl. In another more preferred aspect, the saturated heterocycle is a pyrrolidinyl group, optionally substituted by one or two methyl groups.

Preferably, L is propylene.

According to another preferred aspect of the invention R is a group of formula:



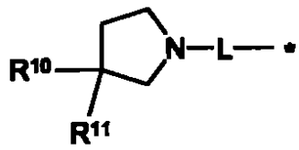
wherein * represents the attachment point to Z, the N-containing ring is a 4- or 6-membered saturated heterocycle, n is an integer equal to 0 or 1, and R^9 represents a substituent selected from hydrogen, (C_1-C_4)alkyl and (C_3-C_6)cycloalkyl.

Preferably, R^9 is isopropyl or cyclobutyl.

When one of the groups in the compound of formula (1) is substituted by halo, generally fluoro or chloro, in particular fluoro is preferred.

Particularly preferred compounds of the invention include those in which each variable in formula (1) is selected from the suitable and/or preferred groups for each variable. Even more preferable compounds of the invention include those where each variable in formula (1) is selected from the more preferred or most preferred groups for each variable.

According to a particular aspect of the invention the following compounds are excluded from the invention: compounds of formula (1), wherein Y is O, Z is O, R is a group of formula :



wherein R^{10} is hydrogen or (C_1-C_4)alkyl, R^{11} is (C_1-C_4)alkoxy, hydroxy or N((C_1-C_4)alkyl)$_2$ and X is -CN, -CH_2OH, -CH_2-O-(C_1-C_4)alkyl, -C(O)OH, -C(O)O(C_1-C_4)alkyl, -$CONR^3R^4$ or $CH_2NR^1R^2$ wherein R^1 is hydrogen or a (C_1-C_4)alkyl group and R^2 is either hydrogen, (C_1-C_4)alkyl (optionally substituted by phenyl) or -C(O)(C_1-C_4)alkyl.

In another embodiment of the present invention, there is provided a compound of formula (1) selected from:

3-(4-{4-[(dimethylamino)methyl]tetrahydro-2H-pyran-4-yl}phenoxy)-N,N-dimethylpropan-1-amine

1-isopropyl-4-[4-[4-(4-methyl-1,3-thiazol-2-yl)tetrahydro-2H-pyran-4-yl]phenoxy}piperidine

4-methyl-2-{4-[4-(4-pyrrolidin-1-ylbutoxy)phenyl]tetrahydro-2H-pyran-4-yl}-1,3-thiazole

2-{4-[4-(4-pyrrolidin-1-ylbutoxy)phenyl]tetrahydro-2H-pyran-4-yl}-1,3-thiazole

4-(4-{3-[ethyl(methyl)amino]propoxy}phenyl)tetrahydro-2H-pyran-4-carbonitrile

4-[4-(4-pyrrolidin-1-ylbutoxy)phenyl]tetrahydro-2H-pyran-4-carboxamide

1-({4-[4-(4-pyrrolidin-1-ylbutoxy)phenyl]tetrahydro-2H-pyran-4-yl}carbonyl)pyrrolidine

N-ethyl-N',N'-dimethyl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)ethane-1,2-diamine

1-(4-{4-[4-(azetidin-1-ylcarbonyl)tetrahydro-2H-pyran-4-yl]phenoxy}butyl)pyrrolidine

N,N-dimethyl-4-[4-(4-pyrrolidin-1-ylbutoxy)phenyl]tetrahydro-2H-pyran-4-carboxamide

N-methyl-1-pyridin-2-yl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)methanamine

1-cyclohexyl-N-methyl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)methanamine
N,N-dimethyl-1-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}carbonyl)azetidin-3-amine
N,N,N'-trimethyl-N'-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)ethane-1,2-diamine
N,N-dimethyl-1-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)azetidin-3-amine
N-(3-{4-[4-(aminomethyl)tetrahydro-2H-pyran-4-yl]phenoxy}propyl)cyclobutanamine
3-{4-[4-(aminomethyl)tetrahydro-2H-pyran-4-yl]phenoxy}-N-ethyl-N-methylpropan-1-amine
N-cyclobutyl-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxamide
N-cyclopentyl-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxamide
N-(cyclopropylmethyl)-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxamide
N-cyclohexyl-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxamide
1-(4-{4-[(2-pyrrolidin-1-ylethyl)thio]phenyl}tetrahydro-2H-pyran-4-yl)methanamine
N,N-dimethyl-1-(4-{4-[(2-pyrrolidin-1-ylethyl)thio]phenyl}tetrahydro-2H-pyran-4-yl)methanamine
1-[3-(4-{4-[(dimethylamino)methyl]tetrahydro-2H-pyran-4-yl}phenoxy)propyl]pyrrolidin-3-ol
1-[4-(4-{3-[(2R,6S)-2,6-dimethylmorpholin-4-yl]propoxy}phenyl)tetrahydro-2H-pyran-4-yl]-N,N-dimethylmethanamine
1-[(4-{4-[(3-pyrrolidin-1-ylpropyl)thio]phenyl}tetrahydro-2H-pyran-4-yl)carbonyl]piperidine
1-[3-({4-[4-(pyrrolidin-1-ylcarbonyl)tetrahydro-2H-pyran-4-yl]phenyl}thio)propyl]pyrrolidine
(4-{4-[(3-pyrrolidin-1-ylpropyl)thio]phenyl}tetrahydro-2H-pyran-4-yl)methanol
N-ethyl-N-({4-[4-(3-thiomorpholin-4-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)acetamide
N,N-dimethyl-1-[4-(4-{3-[(3R)-3-methylmorpholin-4-yl]propoxy}phenyl)tetrahydro-2H-pyran-4-yl]methanamine
N-[(4-{4-[(3-pyrrolidin-1-ylpropyl)thio]phenyl}tetrahydro-2H-pyran-4-yl)methyl]acetamide
N-[(4-{4-[(3-pyrrolidin-1-ylpropyl)thio]phenyl}tetrahydro-2H-pyran-4-yl)methyl]ethanamine
N-methyl-N-[(4-{4-[(3-pyrrolidin-1-ylpropyl)thio]phenyl}tetrahydro-2H-pyran-4-yl)methyl]ethanamine
N-ethyl-N-[(4-{4-[(3-pyrrolidin-1-ylpropyl)thio]phenyl}tetrahydro-2H-pyran-4-yl)methyl]acetamide
N-methyl-N-({4-[4-(3-thiomorpholin-4-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)ethanamine
N-ethyl-N-({4-[4-(3-thiomorpholin-4-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)ethanamine
4-(3-{4-[4-(pyrrolidin-1-ylcarbonyl)tetrahydro-2H-pyran-4-yl]phenoxy}propyl)thiomorpholine
N-ethyl-N-[(4-{4-[(3-pyrrolidin-1-ylpropyl)thio]phenyl}tetrahydro-2H-pyran-4-yl)methyl]ethanamine
N-({4-[4-(3-thiomorpholin-4-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)pyridin-2-amine
4-[(4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2H-pyran-4-yl)methoxy]pyridine
4-[3-(4-{1-[(4-methylpiperazin-1-yl)carbonyl]cyclohexyl}phenoxy)propyl]morpholine
4-(3-{4-[1-(piperazin-1-ylcarbonyl)cyclohexyl]phenoxy}propyl)morpholine
(4-{4-[(1-isopropylazetidin-3-yl)methoxy]phenyl}tetrahydro-2H-pyran-4-yl)methanol
4-[3-(4-{4-[(4-methylpiperazin-1-yl)carbonyl]tetrahydro-2H-pyran-4-yl}phenoxy)propyl]morpholine
4-(3-{4-[4-(piperazin-1-ylcarbonyl)tetrahydro-2H-pyran-4-yl]phenoxy}propyl)morpholine
4-[(4-{4-[(1-isopropylazetidin-3-yl)methoxy]phenyl}tetrahydro-2H-pyran-4-yl)methoxy]pyridine
4-[(4-{4-[(1-isopropylazetidin-3-yl)methoxy]phenyl}tetrahydro-2H-pyran-4-yl)carbonyl]morpholine
4-{4-[4-(1H-imidazol-1-ylmethyl)tetrahydro-2H-pyran-4-yl]phenoxy}-1-isopropylpiperidine
4-[4-(1-methyl-3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carbonitrile

4-(4-{3-[(3R)-3-hydroxypyrrolidin-1-yl]propoxy}phenyl)tetrahydro-2H-pyran-4-carbonitrile
4-[4-[(1-ethylpiperidin-4-yl)oxy]phenyl]tetrahydro-2H-pyran-4-carbonitrile
4-[4-[(1-propylpiperidin-4-yl)oxy]phenyl]tetrahydro-2H-pyran-4-carbonitrile
(3R)-N,N-dimethyl-1-[3-(4-[4-[(methylamino)methyl]tetrahydro-2H-pyran-4-yl}phenoxy)propyl]pyrrolidin-3-amine
N-[[4-(4-{3-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]propoxy}phenyl)tetrahydro-2H-pyran-4-yl]methyl]-N-methylmethanesulfonamide
(3R)-1-{3-[4-(4-[[(2-methoxyethyl)(methyl)amino]methyl}tetrahydro-2H-pyran-4-yl)phenoxy]propyl}-N,N-dimethylpyrrolidin-3-amine
N-[[4-(4-{3-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]propoxy}phenyl)tetrahydro-2H-pyran-4-yl]methyl]-N,N',N'-trimethylurea
(3R)-N,N-dimethyl-1-(3-{4-[4-(1,3-thiazol-2-yl)tetrahydro-2H-pyran-4-yl]phenoxy}propyl)pyrrolidin-3-amine
(3R)-N,N-dimethyl-1-(3-{4-[4-(morpholin-4-ylcarbonyl)tetrahydro-2H-pyran-4-yl]phenoxy}propyl)pyrrolidin-3-amine
N-[[4-(4-{3-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]propoxy}phenyl)tetrahydro-2H-pyran-4-yl]methyl]-N-methylpyrimidin-2-amine
(3R)-N,N-dimethyl-1-(3-{4-[4-(morpholin-4-ylmethyl)tetrahydro-2H-pyran-4-yl]phenoxy}propyl)pyrrolidin-3-amine
1-Isopropyl-4-{4-[4-(piperidin-1-ylcarbonyl)tetrahydro-2H-pyran-4-yl]phenoxy}piperidine
4-[(4-{4-[(1-Isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2H-pyran-4-yl)carbonyl]morpholine
N-Isopropyl-4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}-N-methyltetrahydro-2H-pyran-4-carboxamide
N*4*-[4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-pyridine-3,4-diamine
N*2*-[4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-pyridine-2,3-diamine

Particularly preferred compounds of formula (1) are as described in the Examples section hereafter. Where the salt form is obtained in the Examples, a compound of the present invention includes the free base thereof, for example:

{4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine,
{4-[4-(3-Piperidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine, and
Dimethyl-{4-[4-(3-piperidin-1-ylpropoxy)phenyl]tetrahydro-pyran-4-ylmethyl}amine.

In another embodiment of the invention, particularly preferred examples are:
{4-[4-(1-Isopropylpiperidin-4-yloxy)phenyl]tetrahydropyran-4-ylmethyl}dimethyl-amine
Dimethyl-[4-[4-(4-pyrrolidin-1-ylbutoxy)phenyl]tetrahydro-pyran-4-ylmethyl]amine
{4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine
Dimethyl-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]-tetrahydropyran-4-ylmethyl]amine
{4-[4-(3-Piperidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine
Dimethyl-[4-[4-(3-piperidin-1-ylpropoxy)phenyl]tetra-hydropyran-4-ylmethyl]amine
1-Methyl-4-{4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl}-piperazine
(R)-2-Methoxymethyl-1-{4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl}-pyrrolidine
(S)-2-Methoxymethyl-1-{4-[4-(3-pyrrolidin-1-ylpropoxy)-phenyl]tetrahydropyran-4-ylmethyl}pyrrolidine

1-{4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl}piperidine

methyl-{4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]-tetrahydropyran-4-ylmethyl}amine

isopropyl-methyl-{4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]-tetrahydropyran-4-ylmethyl}amine

1-{4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl}pyrrolidine

4-{4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl}-morpholine

(2-methoxyethyl)-methyl-{4-[4-(3-pyrrolidin-1-ylpropoxy)-phenyl]tetrahydropyran-4-ylmethyl}amine

4-[4-(1-Isopropylpiperidin-4-yloxy)phenyl]tetrahydropyran-4-carbonitrile

4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxylic acid amide

N-methyl-1-{1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]-cyclohexyl}methanamine

N-ethyl-*N*-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}methyl)ethanamine

N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}methyl)ethanamine

N-methyl-*N*-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]-tetrahydro-2*H*-pyran-4-yl}methyl)ethanamine

4-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}tetrahydro-2*H*-pyran-4-carbonitrile

4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-carboxamide

4-[4-[(1-Isopropylpiperidin-4-yl)oxy]phenyl]-*N*,*N*-dimethyltetrahydro-2*H*-pyran-4-carboxamide

4-[4-[(1-Isopropylpiperidin-4-yl)oxy]phenyl]-*N*,*N*-diethyltetra-hydro-2*H*-pyran-4-carboxamide

4-{4-[(1-Isopropylpiperidin-4-yl)oxy]phenyl)tetrahydro-2*H*-pyran-4-yl]carbonyl}pyrrolidine

4-methyl-2-[4-(4-(3-pyrrolidin-1-ylpropoxy)phenyl)tetrahydro-2*H*-pyran-4-yl]-1,3-thiazole

2-[4-(4-(3-pyrrolidin-1-ylpropoxy)phenyl)tetrahydro-2*H*-pyran-4-yl]-1,3-thiazole

N-[(4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-yl)methyl]-*N*-methylamine

N-[(4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-yl)methyl]-*N*-ethylamine

N-[[4-(4-[(1-isopropylpiperidin-4-yl)oxy]phenyl)tetrahydro-2*H*-pyran-4-yl]methyl}pyrimidin-2-amine and

N-[[4-(4-(3-Pyrrolidin-1-ylpropoxy)phenyl)tetrahydro-2*H*-pyran-4-yl]methyl]pyrimidin-2-amine.

1-(4-[4-[(1-cyclopentylazetidin-3-yl)methoxy]phenyl]tetrahydro-2H-pyran-4-yl)-N,N-dimethylmethanamine

3-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)-3H-imidazo[4,5-b]pyridine

2-[[methyl({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)amino]methyl]phenol

N-methyl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)cyclopentanamine

2-[methyl({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)amino]ethanol

N-methyl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)cyclopropanamine

1-(3-[4-[4-(aziridin-1-ylmethyl)tetrahydro-2H-pyran-4-yl]phenoxy}propyl)pyrrolidine

N-({4-[4-(3-thiomorpholin-4-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)ethanamine

1-(4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-yl)-N,N-dimethylmethanamine

N,N-dimethyl-1-(4-[4-[(3-pyrrolidin-1-ylpropyl)thio]phenyl]tetrahydro-2H-pyran-4-yl)methanamine

N-methyl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)cyclohexanamine

1-[3-({4-[4-(pyrrolidin-1-ylmethyl)tetrahydro-2H-pyran-4-yl]phenyl}thio)propyl]pyrrolidine

1-({1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl}methyl)piperidin-4-ol

1-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)-1H-benzimidazole

4-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}tetrahydro-2H-pyran-4-carboxamide

N-methyl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)hexan-1-amine

1-cyclopropyl-N-(cyclopropylmethyl)-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)methanamine

N-[2-(dimethylamino)ethyl]-N-ethyl-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxamide
N-methyl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)butan-1-amine
4-{4-[4-(4,5-dimethyl-1H-imidazol-2-yl)tetrahydro-2H-pyran-4-yl]phenoxy}-1-isopropylpiperidine
3-[[methyl({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)amino]methyl}phenol
4-[(4-{4-[(1-cyclopentylazetidin-3-yl)methoxy]phenyl}tetrahydro-2H-pyran-4-yl)methyl]morpholine
N-methyl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)pentan-1-amine
4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}-N,N-dimethyltetrahydro-2H-pyran-4-carboxamide
N,N-dimethyl-1-(4-{4-[3-(1,4-oxazepan-4-yl)propoxy]phenyl}tetrahydro-2H-pyran-4-yl)methanamine
N,3,3-trimethyl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)butan-1-amine
4-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}-N-isopropyltetrahydro-2H-pyran-4-carboxamide
1-methyl-4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)-1,4-diazepane
1-cyclobutyl-4-{4-[4-(1,3-thiazol-2-yl)tetrahydro-2H-pyran-4-yl]phenoxy}piperidine
N-[(4-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}tetrahydro-2H-pyran-4-yl)methyl]pyridin-2-amine
N-methyl-1-{4-[4-(3-morpholin-4-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methanamine
1-[(4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2H-pyran-4-yl)carbonyl]-4-methylpiperazine
1-cyclopentyl-N-methyl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)methanamine
4-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}-N-ethyltetrahydro-2H-pyran-4-carboxamide
N-[(4-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}tetrahydro-2H-pyran-4-yl)methyl]pyrimidin-2-amine
N,N-diethyl-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxamide
4-[(4-{4-[(1-cyclobutylazetidin-3-yl)methoxy]phenyl}tetrahydro-2H-pyran-4-yl)methyl]morpholine
4-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}-N-methyltetrahydro-2H-pyran-4-carboxamide
1-cyclobutyl-4-{4-[4-(4-methyl-1,3-thiazol-2-yl)tetrahydro-2H-pyran-4-yl]phenoxy}piperidine
4-[(4-{4-[(1-isopropylazetidin-3-yl)methoxy]phenyl}tetrahydro-2H-pyran-4-yl)methyl]morpholine
1-isopropyl-4-{4-[4-(1,3-thiazol-2-yl)tetrahydro-2H-pyran-4-yl]phenoxy}piperidine
1-(4-{4-[(1-cyclobutylazetidin-3-yl)methoxy]phenyl}tetrahydro-2H-pyran-4-yl)methanamine
1-ethyl-4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}carbonyl)piperazine
N-ethyl-N-methyl-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxamide
1-(4-{4-[(1-isopropylazetidin-3-yl)methoxy]phenyl}tetrahydro-2H-pyran-4-yl)methanamine
1-[(4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2H-pyran-4-yl)methyl]-4-methylpiperazine
1-(cyclopropylmethyl)-4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)piperazine
N,N-dimethyl-1-[4-[4-(3-morpholin-4-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl]methanamine
N-[2-(dimethylamino)ethyl]-N-methyl-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxamide
1-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}carbonyl)piperazine
1-ethyl-4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)piperazine
4-[(4-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}tetrahydro-2H-pyran-4-yl)carbonyl]morpholine
N-[(4-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}tetrahydro-2H-pyran-4-yl)methyl]pyridin-3-amine
1-methyl-4-({1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl}carbonyl)piperazine
1-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)-1H-imidazole
N-[(4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2H-pyran-4-yl)methyl]pyridin-2-amine

1-isopropyl-4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)piperazine
1-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)-1H-imidazo[4,5-c]pyridine
N-({4-[4-(3-piperidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)pyridin-2-amine
1-propyl-4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}carbonyl)piperazine
N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)pyridazin-4-amine
N-ethyl-4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl]-N-methyltetrahydro-2H-pyran-4-carboxamide
1-methyl-4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}carbonyl)piperazine
1-propyl-4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)piperazine
N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)pyridin-2-amine
4-{4-[4-(azetidin-1-ylcarbonyl)tetrahydro-2H-pyran-4-yl]phenoxy}-1-isopropylpiperidine
1-(2-methoxyethyl)-4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)piperazine
2-{4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}pyridine
N-[(4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2H-pyran-4-yl)methyl]pyridazin-4-amine
N-[(4-[4-[(1-isopropylazetidin-3-yl)methoxy]phenyl}tetrahydro-2H-pyran-4-yl)methyl]pyridin-2-amine
4-[(4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2H-pyran-4-yl)methyl]morpholine
1-methyl-4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}carbonyl)-1,4-diazepane
4-(3-[4-[4-(morpholin-4-ylmethyl)tetrahydro-2H-pyran-4-yl]phenoxy}propyl)-1,4-oxazepane
1-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}carbonyl)piperidine
1-methyl-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]piperidine-4-carbonitrile
1-(3-[4-[4-(pyrrolidin-1-ylcarbonyl)tetrahydro-2H-pyran-4-yl]phenoxy}propyl)pyrrolidine
2-(methylthio)-1-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)-1H-imidazole
4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]piperidine-4-carbonitrile
N-[(4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2H-pyran-4-yl)methyl]pyridin-3-amine
6-methyl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)pyridin-3-amine
N-[(4-[4-[(1-ethylpiperidin-4-yl)oxy]phenyl}tetrahydro-2H-pyran-4-yl)methyl]pyridin-2-amine
N,N-dimethyl-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxamide
4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)-4H-1,2,4-triazole
1-({1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl}methyl)piperazine
1-isopropyl-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]piperidine-4-carbonitrile
5-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl]-1,3-oxazole
1-acetyl-4-({1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl}methyl)piperazine
4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methoxy)pyridine
1-acetyl-4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)piperazine
N-({4-[4-(4-pyrrolidin-1-ylbutoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)pyridin-2-amine
1-[3-(4-[4-[(dimethylamino)methyl]tetrahydro-2H-pyran-4-yl}phenoxy)propyl]-N,N-dimethylazetidin-3-amine
1-(3-[4-[4-(azetidin-1-ylcarbonyl)tetrahydro-2H-pyran-4-yl]phenoxy}propyl)pyrrolidine
N-[(4-[4-[(1-cyclobutylazetidin-3-yl)methoxy]phenyl}tetrahydro-2H-pyran-4-yl)methyl]pyridin-2-amine
N-[[4-(4-[3-[cyclobutyl(methyl)amino]propoxy}phenyl)tetrahydro-2H-pyran-4-yl]methyl]pyridin-2-amine
N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)pyridin-3-amine
4-(3-[4-[4-(morpholin-4-ylmethyl)tetrahydro-2H-pyran-4-yl]phenoxy}propyl)morpholine
N,N-dimethyl-1-(4-[4-[3-(4-methyl-1,4-diazepan-1-yl)propoxy]phenyl}tetrahydro-2H-pyran-4-yl)methanamine

1-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)-1H-imidazo[4,5-b]pyridine

4-({4-[4-(3-azetidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)morpholine

2-{4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}-1H-imidazole

4-(3-{4-[4-(piperazin-1-ylcarbonyl)tetrahydro-2H-pyran-4-yl]phenoxy}propyl)-1,4-oxazepane

4-[3-(4-{4-[(4-methylpiperazin-1-yl)carbonyl]tetrahydro-2H-pyran-4-yl}phenoxy)propyl]-1,4-oxazepane

4-{4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}pyrimidine

4-methyl-1-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)-1H-imidazole

4-{4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}-1H-imidazole

4-[4-(4-{3-[*ethyl*(*methyl*)amino]propoxy}phenyl)tetrahydro-2H-pyran-4-ylmethyl]-morpholine

Another embodiment of the invention is an intermediate as described herein.

Pharmaceutically acceptable salts of the compounds of formula (1) include the acid addition and base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the *acetate*, *aspartate*, *benzoate*, *besylate*, *bicarbonate/carbonate*, *bisulphate/sulphate*, *borate*, *camsylate*, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, *arginine*, *benzathine*, *calcium*, *choline*, *diethylamine*, diolamine, *glycine*, *lysine*, *magnesium*, *meglumine*, olamine, potassium, sodium, tromethamine and zinc salts.

Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Pharmaceutically acceptable salts of compounds of formula (1) may be prepared by one or more of three methods:

(i) by reacting the compound of formula (1) with the desired acid or base;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula (1) or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or

(iii) by converting one salt of the compound of formula (1) to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionised, partially ionised, or non-ionised. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblian (August 1975).

Hereinafter all references to compounds of formula (1) include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

The compounds of the invention include compounds of formula (1) as hereinbefore defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of formula (1).

As indicated, so-called 'pro-drugs' of the compounds of formula (1) are also within the scope of the invention. Thus certain derivatives of compounds of formula (1) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (1) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in 'Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and 'Bioreversible Carriers in Drug Design', Pergamon Press, 1987 (ed. E. B Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula (1) with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in "Design of Prodrugs" by H. Bundgaard (Elsevier, 1985).

Some examples of prodrugs in accordance with the invention include:

(i) where the compound of formula (1) contains a carboxylic acid functionality (-C(O)OH), an ester thereof, for example, a compound wherein the hydrogen of the carboxylic acid functionality of the compound of formula (1) is replaced by (C_1-C_8)alkyl;

(ii) where the compound of formula (1) contains an alcohol functionality (-OH), an ether thereof, for example, a compound wherein the hydrogen of the alcohol functionality of the compound of formula (1) is replaced by (C_1-C_6)alkanoyloxymethyl; and

(iii) where the compound of formula (1) contains a primary or secondary amino functionality (-NH_2 or -NHR where R ≠ H), an amide thereof, for example, a compound wherein, as the case may be, one or both hydrogens of the amino functionality of the compound of formula (1) is/are replaced by (C_1-C_{10})alkanoyl.

Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references.

Moreover, certain compounds of formula (1) may themselves act as prodrugs of other compounds of formula (1).

Also included within the scope of the invention are metabolites of compounds of formula (1), that is, compounds formed *in vivo* upon administration of the drug. Some examples of metabolites in accordance with the invention include :

(i) where the compound of formula (1) contains a methyl group, an hydroxymethyl derivative thereof (-CH_3 → -CH_2OH):

(ii) where the compound of formula (1) contains an alkoxy group, an hydroxy derivative thereof (-OR → -OH);

(iii) where the compound of formula (1) contains a tertiary amino group, a secondary amino derivative thereof (-NR^aR^b → -NHR^a or –NHR^b);

(iv) where the compound of formula (1) contains a secondary amino group, a primary derivative thereof (-NHR^a → -NH_2);

(v) where the compound of formula (1) contains a phenyl moiety, a phenol derivative thereof (-Ph → -PhOH); and

(vi) where the compound of formula (1) contains an amide group, a carboxylic acid derivative thereof (-$CONR^cR^d$ → COOH).

Compounds of formula (1) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where structural isomers are interconvertible *via* a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in compounds of formula (1) containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of formula (1), including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the

counterion is optically active, for example, *d*-lactate or *l*-lysine, or racemic, for example, *dl*-tartrate or *dl*-arginine.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (1) contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art - see, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel (Wiley, New York, 1994).

The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of formula (1) wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

Certain isotopically-labelled compounds of formula (1), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

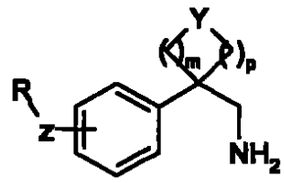
Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of formula (1) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying *Examples and Preparations* using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

The phenol and thiophenol derivatives of formula (1) can be prepared using conventional procedures such as by the following illustrative methods in which R, X, Y, Z, m, p, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are as previously defined unless otherwise stated.

The compounds of formula (1), wherein X is $-CH_2NR^1R^2$, may be prepared from compounds of formula (2) :



(2)

using standard techniques for functional group interconversion known to those skilled in the art, for example as described in *Comprehensive Organic Transformations*, R.C. Larock, 1st Edition, 1989 VCH *Publishers Inc.*

These techniques include:

1) Reductive alkylation with aldehydes or ketones with a reducing agent (e.g. formic acid or $NaHB(OAc)_3$) in a suitable solvent (e.g. dichloromethane, tetrahydrofuran), optionally with the addition of acetic acid, at between room temperature (about 20°C) and reflux;
2) Alkylations with alkyl halides and a base (e.g. potassium carbonate, potassium *tert*-butoxide) in a suitable solvent (e.g. acetonitrile, tetrahydrofuran) at between room temperature (about 20°C) and reflux;
3) Sulphonylation with a sulphonyl chloride and a base (e.g. triethylamine, N-ethyldiisopropylamine) in a suitable solvent (e.g. dichloromethane) at between room temperature and reflux;
4) Heteroarylation with a haloheteroaromatic or heteroaromatic sulphonic acid compound and a base (e.g. potassium carbonate) in a suitable solvent (e.g. acetonitrile) at between room temperature (about 20°C) and reflux. Alternatively this reaction may be performed under microwave radiation, alternatively using *N*-ethyldiisopropylamine as base, optionally in a suitable solvent (e.g.N-methyl pyrrolidinone, acetonitrile).

5) Urea formation with a dialkylcarbamoyl chloride or a cyanate salt, optionally in the presence of a base (e.g. triethylamine) or an acid (e.g. acetic acid) in a suitable solvent (e.g. dichloromethane or water) at between room temperature and reflux;

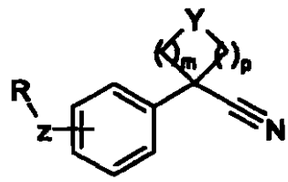
6) Sulphonyl urea formation with a dialkylsulphamoyl chloride and a base (e.g. triethylamine) in a suitable solvent (e.g. dichloromethane) at between room temperature and reflux;

7) Acylation with an activated acid (e.g. an acyl chloride or anhydride) and a base (e.g. triethylamine) in a suitable solvent (e.g. dichloromethane) at between room temperature and reflux.

8) By palladium catalysed cross-coupling with a haloheteroaromatic compound, using a suitable palladium source (e.g. tris(dibenzylideneacetone)palladium (0)), optionally in the presence of a chelating ligand (e.g. BINAP) and in the presence of a suitable base (e.g. sodium *tert*-butoxide) in a solvent (e.g. toluene), at between room temperature and reflux.

These transformations can be performed sequentially to prepare compounds in which R^1 and R^2 are as here above defined.

The compounds of formula (2) may be prepared by reduction of the corresponding cyano derivatives of formula (3) :

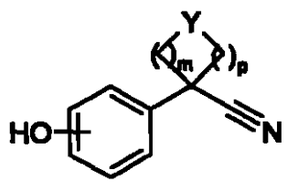


(3)

with a suitable reducing agent (e.g. $LiAlH_4$ or hydrogen gas in the presence of a catalyst such as PtO_2) in a suitable solvent (e.g. Et_2O/dichloromethane, tetrahydrofuran or isopropanol) at between room temperature and reflux.

The compounds of formula (3) above correspond actually to the compounds of formula (1) wherein X is a CN group.

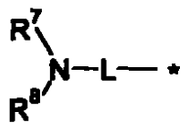
The compounds of formula (3) wherein Z is O may be prepared by alkylation of the corresponding hydroxy derivatives of formula (4) :



(4)

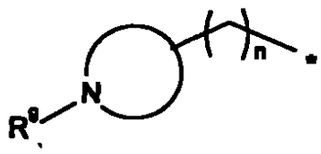
with a derivative of formula $R\text{-}R^{LG}$ wherein R^{LG} is a leaving group such as halo, mesylate or tosylate, in the presence of a base (e.g. potassium carbonate) and optionally in the presence of an additive (e.g. potassium iodide) in a suitable solvent (e.g. dimethylformamide) at between room temperature and reflux.

When R is a group of formula:



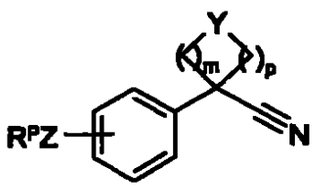
as previously defined, then the derivative of formula $R\text{-}R^{LG}$ may be prepared by alkylation of the corresponding amino derivative of formula NHR^7R^8 with a derivative of formula $R^{LG}\text{-}L\text{-}R^{LG}$ and a base (e.g. NaOH, Na_2CO_3, K_2CO_3, Cs_2CO_3), optionally in the presence of an additive (e.g. potassium iodide) in a suitable solvent (e.g. N,N-dimethylformamide, acetonitrile, acetone/H_2O) at between room temperature and reflux. The amino derivative of formula NHR^7R^8 is either commercial or made using procedures known to the skilled person.

When R is a group of formula :



as previously defined, then the derivative of formula $R\text{-}R^{LG}$ is either commercial or may be prepared using literature procedures well-known to the skilled person.

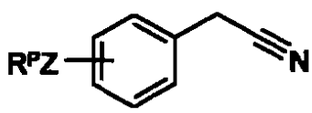
The compounds of formula (4) may be prepared by deprotection of the corresponding derivatives of formula (5) wherein Z is O:



(5)

wherein R^P is a protecting group (e.g. methyl, deprotected with BBr_3 in dichloromethane at between 0°C and room temperature).

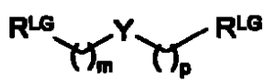
The compounds of formula (5) are either commercial or may be prepared by double alkylation of the compounds of formula (6) :



(6)

wherein R^P is as previously defined,

with the compounds of formula (7) :



(7)

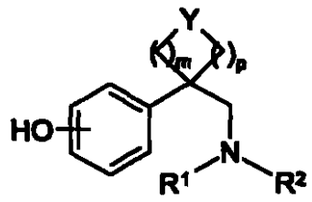
wherein R^{LG} is as previously defined, and a base (e.g. NaH), optionally in the presence of an additive (e.g. potassium iodide) in a suitable solvent (e.g. N,N-dimethylformamide, N-methyl pyrrolidinone) at between room temperature and reflux.

The compounds of formula (6) and (7) are each either commercially available or made using literature procedures well-known to the skilled person.

Compounds of formula (3), wherein Z represents S may be prepared from compounds of formula (5) wherein Z represents S and R^P is Me by a Pummerer rearrangement, followed by alkylation of the resulting intermediate with a derivative of formula $R\text{-}R^{LG}$. The reaction is achieved by treatment of the compound of formula (5) with a suitable oxidant (e.g.m-CPBA) in a suitable solvent (e.g. dichloromethane) at 0°C to provide the corresponding sulphide. Treatment of this intermediate with trifluoroacetic anhydride in the presence of a suitable base (e.g. 2,6-lutidine) in a suitable solvent (e.g. acetonitrile) at about -15°C, followed by reaction with $R\text{-}R^{LG}$, in the presence of a base (e.g. triethylamine, potassium carbonate) in a suitable solvent (e.g. N,N-dimethylformamide) at between 0°C and room temperature provides the compound of formula (3).

Alternatively, the compounds of formula (3) wherein Z is O may be prepared by alkylation of the compounds of formula (4) with the alcohol derivative of formula ROH, which is either commercial or made using literature procedures well-known to the skilled person, using Mitsunobu reagents such as PPh_3 and DIAD in a suitable solvent (e.g. THF) at between 0°C and reflux.

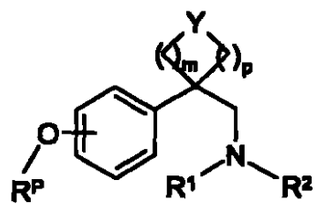
Persons skilled in the art will appreciate that, in order to obtain compounds of formula (1) in an alternative or more convenient manner, the individual process steps mentioned in this section may be performed in a different order. For example compounds of formula (1) wherein Z is O and X is $-CH_2NR^1R^2$, may be prepared by alkylation of the compounds of formula (8) :



(8)

with a derivative of formula $R\text{-}R^{LG}$ or ROH as previously defined, using conditions analogous to those decribed for the preparation of compounds of formula (3).

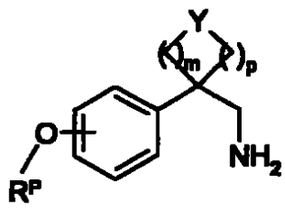
The compounds of formula (8) may be prepared by deprotection of the compounds of formula (9) :



(9)

wherein R^P is as previously defined,
using conditions appropriate for the protecting group and the nature of R^1 and R^2 (e.g. using NaSMe in dimethylformamide at 130°C wherein R^P is methyl and R^1 and R^2 are (C_1-C_4)alkyl) .

The compounds of formula (9) may be prepared from the corresponding amino derivatives of formula (10) :

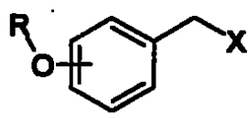


(10)

using analogous conditions to those described for the preparation of compounds of formula (1) from compounds of formula (2).

The compounds of formula (10) may be prepared from compounds of formula (5) wherein Z is O using analogous reduction conditions to those described for the preparation of compounds of formula (2) from compounds of formula (3).

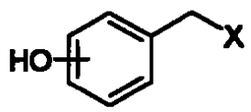
A further example of performing the individual process steps described in this section in a different order to obtain compounds of formula (1) in an alternative or more convenient manner, is the preparation of compounds of formula (1) wherein Z is O by double alkylation of the compounds of formula (11) :



(11)

with the compounds of formula (7) as previously defined, using analogous conditions described for the preparation of compounds of formula (5) from compounds of formula (6).

The compounds of formula (11) may be prepared from the corresponding hydroxy derivatives of formula (12) :

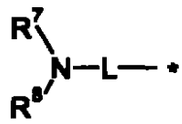


(12)

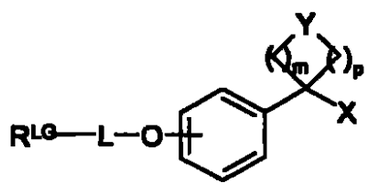
using analogous conditions described for the preparation of compounds of formula (3) from compounds of formula (4).

The compounds of formula (12) are either commercial or made using literature procedures well-known to the skilled person.

An example of performing the individual process steps described in this section in a different order to obtain compounds of formula (1) wherein Z is O and R is a group of formula :



is the preparation of these compounds by reaction of the compounds of formula (13) :

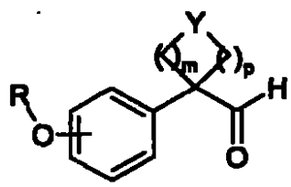


(13)

wherein R^{LG} is as previously defined, with the amino derivatives of formula NHR^7R^8 using analogous conditions to those previously described for the preparation of $R\text{-}R^{LG}$.

Alternatively, the same transformation can be achieved by heating the compounds of formula (13) with the amino derivatives of formula NHR^7R^8 and a base (e.g. diisopropylethylamine) in a suitable solvent (e.g. N-methylpyrrolidinone) at 150-200°C for 5-10 min using a microwave oven.

Alternatively, the compounds of formula (1) wherein Z is O, X is $-CH_2NR^1R^2$ and R^1 and R^2 are hydrogen or an optionally substituted (C_1-C_4)alkyl or together with the N atom to which they are attached form an optionally substituted 4-, 5- or 6-membered saturated heterocycle wherein a C atom may be replaced by N, O, S, SO or SO_2, may be prepared by reductive amination of the compounds compounds of formula (14) :



(14)

with the amino derivative of formula HNR^1R^2 and a reducing agent (e.g. $NaHB(OAc)_3$), optionally in the presence of a Lewis acid (e.g. $Ti(O^iPr)_4$) in a suitable solvent (e.g. EtOH) at between 0°C and reflux.

The compounds of formula (14) may be prepared by reduction of the compounds of formula (3) wherein Z is O with a reducing agent (e.g. diisobutylaluminium hydride) in a suitable solvent (e.g. toluene) at between –78°C and room temperature (about 20°C).

Alternatively, the compounds of formula (14) may be prepared by oxidation of the compounds of formula (1) wherein Z is O and X is $-CH_2OH$, using an oxidant (e.g. pyridinium chlorochromate) in a suitable solvent (e.g. dichloromethane) at between 0°C and reflux.

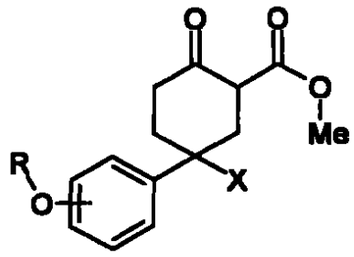
The compounds of formula (1) wherein X is $-CH_2OH$, may be prepared by reduction of the compounds of formula (1) wherein X is $-C(O)O(C_1-C_4)$alkyl, with a reducing agent (e.g. $LiAlH_4$) in a suitable solvent (e.g. tetrahydrofuran) at between –78°C and reflux.

The compounds of formula (1) wherein X is $-C(O)O(C_1-C_4)$alkyl, may be prepared by esterification of the compounds of formula (1) wherein X is COOH, using the standard procedures well-known to the skilled person. For example, the esterification can be achieved by using a reagent capable of activating a carboxylic acid (e.g. thionyl chloride) and $HO(C_1-C_4)$alkyl, optionally in the presence of an additional solvent (e.g. dichloromethane) at between 0°C and reflux.

The compounds of formula (1) wherein X is C(O)OH, may be prepared by hydrolysis of the compounds of formula (3) as previously defined with a mineral acid (e.g. concentrated aqueous HCl), optionally in the presence of a suitable co-solvent (e.g. dioxane), at between 0°C and reflux.

The compounds of formula (1) wherein m and p are both equal to 2, Z is O and Y is CH(OH), may be prepared by reduction of the compounds of formula (1) wherein m and p are both equal to 2 and Y is C=O, with a reducing agent (e.g. $LiAlH_4$) in a suitable solvent (e.g. Et_2O) at between 0°C and reflux.

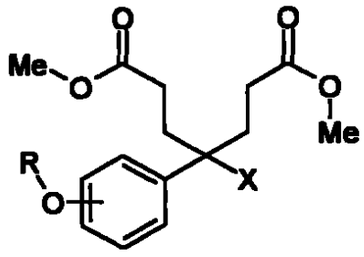
The compounds of formula (1) wherein m and p are both equal to 2, Z is O and Y is C=O, may be prepared by treatment of the compounds of formula (15) :



(15)

with sodium chloride in a suitable solvent (e.g. dimethylsulphoxide/water) at between 100°C and reflux.

The compounds of formula (15) may be prepared by treatment of the compounds of formula (16) :



(16)

with a base (e.g. NaH) in a suitable solvent (e.g. 1,2-dimethoxyethane) at between room temperature and reflux.

The compounds of formula (16) may be prepared by alkylation of the compounds of formula (11) as previously defined with methyl acrylate and a base (e.g. benzyltrimethylammonium hydroxide) in a suitable solvent (e.g. methanol/acetonitrile) at between room temperature and reflux.

The compounds of formula (1) wherein X is $-CONH_2$, may be prepared by treatment of the compounds of formula (3) as previously defined with polyphosphoric acid or boron trifluoride-acetic acid complex at between room temperature and 100°C.

The compounds of formula (1) wherein X is $-CONR^3R^4$, may be prepared by reaction of the compounds of formula (1) wherein X is COOH, sequentially with a reagent capable of activating a carboxylic acid (e.g. thionyl chloride,) and then with the amino derivative of formula HNR^3R^4, in a suitable solvent (e.g. dichloromethane) at between 0°C and reflux. Alternatively the acid may be treated with the amine of formula HNR^3R^4, in the presence of a coupling agent (e.g. TBTU, O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride), optionally in the presence of a suitable additive (e.g. 1-hydroxybenzotriazole) and base (e.g. triethylamine) in a suitable solvent (e.g. dichloromethane, N,N-dimethylformamide) at room temperature.

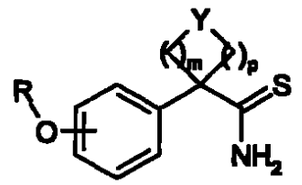
Compounds of formula (1) wherein X is $CH_2NR^1R^2$ may be prepared by reduction of compounds of formula (1) wherein X is $-CONR^3R^4$ and NR^1R^2 equals NR^3R^4, with a reducing agent (e.g. lithium aluminium hydride) in a suitable solvent (e.g. tetrahydrofuran, ether) at between room temperature and 50°C.

The compounds of formula (1) wherein X is $-CH_2-O-(C_1-C_4)$alkyl may be prepared by alkylation of the compounds of formula (1) wherein X is $-CH_2-OH$, with a derivative of formula $R^{LG}(C_1-C_4)$alkyl, wherein R^{LG} is as previously defined, and a base (e.g. NaH) in a suitable solvent (e.g. dimethylformamide) at between room temperature and reflux.

The compounds of formula (1) wherein X is $-CH_2-O-het^2$ may be prepared by alkylation of the compounds of formula (1) wherein X is $-CH_2-OH$, with a derivative of formula $R^{LG}Het^2$, by palladium catalysed cross-coupling with a haloheteroaromatic compound, using a suitable palladium source (e.g. tris(dibenzylideneacetone)palladium (0)), optionally in the presence of a chelating ligand (e.g. BINAP) and in the presence of a suitable base (e.g. sodium *tert*-butoxide) in a solvent (e.g. toluene), at between room temperature and reflux.

Compounds of formula (1) wherein X is het^1, may be prepared from compounds of formula (1) wherein X is COOH, or alternatively from compounds of formula (3) or (14) using methods known to those skilled in the art, such as those described in general heterocyclic texts such as *Heterocyclic Chemistry*, J.A. Joule and K. Mills, 4th Edition, Blackwell publishing, 2000 or Comprehensive Heterocyclic chemistry I and II, Pergamon Press.

For example, compounds of formula (1) where X is optionally substituted 2-thiazolyl and Z is O may be prepared by treating compounds of formula (17) :



(17)

with a suitable reagent (e.g. bromoacetaldehyde dimethyl acetal, chloroacetone) and HCl in a suitable solvent (e.g. EtOH) at reflux.

Compounds of formula (17) may be prepared by reacting compounds of formula (3) wherein Z is O with diethyldithiophosphate and water at 60°C.

Compounds of formula (1) wherein X is $-CH_2$-het^1, and where said het^1 is N-linked, may be prepared from compounds of formula (1) wherein X is $-CH_2-NH_2$ using methods known to those skilled in the art, such as those described in general heterocyclic texts such as *Heterocyclic Chemistry*, J.A. Joule and K. Mills, 4th Edition, Blackwell publishing, 2000 or Comprehensive Heterocyclic chemistry I and II, Pergamon Press.

Compounds of formula (1) wherein X is $-CH_2$-het^1, and where said het^1 is C-linked, may be prepared from compounds of formula (1) wherein X is -COOH by a two step process of CH_2 homologation using the Arndt-Eistert synthesis (*Advanced Organic Chemistry*, J. March, 4th edition, Wiley-Interscience publication, 1992) followed by standard techniques for heterocycle construction from a carboxylic acid known to those skilled in the art.

The compounds of formula (1) and their precursors which contain a sulphide group can be oxidised to the corresponding sulphoxides or sulphones using standard techniques well-known to those skilled in the art, for example as described in *Comprehensive Organic Transformations*, R.C. Larock, 1st Edition, 1989 VCH Publishers Inc.

It will be appreciated by those skilled in the art that, certain compounds of formula (1) may be converted to alternative compounds of formula (1) using standard chemical transformations. Examples of these include, acylation and sulphonation of amine functions (e.g see examples 166, 229, 230), reductive amination reactions (e.g. see examples 167, 168), alkylation (e.g. see example 228) or hydrogenation of halo atoms (e.g. see examples 202, 203).

It will be appreciated by those skilled in the art that, in the course of carrying out the processes described above, the functional groups of intermediate compounds may need to be protected by protecting groups.

These functional groups include hydroxyl, amino and carboxylic acid. Suitable protecting groups for hydroxyl include trialkylsilyl and diarylalkylsilyl (e.g. *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl), alkyl (e.g. methyl or methoxyethyl) and tetrahydropyranyl. Suitable protecting groups for amino include *tert*-butyloxycarbonyl, 9-fluorenylmethoxycarbonyl or benzyloxycarbonyl. Suitable [protecting groups for carboxylic acid include (C_1-C_4)alkyl or benzyl esters.

The protection and deprotection of functional groups may take place before or after any of the reaction steps described hereinbefore.

The introduction and removal of protecting groups is fully described in *Protective Groups in Organic Chemistry*, edited by J.W.F. McOmie, Plenum Press (1973), *Protective Groups in Organic Synthesis*, 2nd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience Publication, 1991) and *Protecting Groups*, P.J. Kocienski, Thieme, 1994.

Also, the compounds of formula (1) as well as intermediates for the preparation thereof, can be purified according to various well-known methods such as recrystallisation and chromatography.

The compounds of formula (1), their pharmaceutically acceptable salts and/or derived forms, are valuable pharmaceutically active compounds, which are suitable for the therapy and prophylaxis of numerous disorders in which the histamine H_3 receptor is involved or in which agonism or antagonism of this receptor may induce benefit.

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

They may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term 'excipient' is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

According to another aspect of the invention, there is provided a pharmaceutical composition including a compound of the formula (1) or a pharmaceutically acceptable salt and/or solvate thereof, as defined in any one of the preceding claims, together with a pharmaceutically acceptable excipient.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in Remington's Pharmaceutical Sciences, 19th Edition (Mack Publishing Company, 1995).

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films, ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986, by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 weight % to 80 weight % of the dosage form, more typically from 5 weight % to 60 weight % of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 weight % to 25 weight %, preferably from 5 weight % to 20 weight % of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 weight % to 5 weight % of the tablet, and glidants may comprise from 0.2 weight % to 1 weight % of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 weight % to 10 weight %, preferably from 0.5 weight % to 3 weight % of the tablet.

Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 weight % to about 90 weight % binder, from about 0 weight % to about 85 weight % diluent, from about 2 weight % to about 10 weight % disintegrant, and from about 0.25 weight % to about 10 weight % lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

The formulation of tablets is discussed in Pharmaceutical Dosage Forms: Tablets, Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

Consumable oral films for human or veterinary use are typically pliable water-soluble or water-swellable thin film dosage forms which may be rapidly dissolving or mucoadhesive and typically comprise a compound of formula (1), a film-forming polymer, a binder, a solvent, a humectant, a plasticiser, a stabiliser or emulsifier, a viscosity-modifying agent and a solvent. Some components of the formulation may perform more than one function.

The compound of formula (1) may be water-soluble or insoluble. A water-soluble compound typically comprises from 1 weight % to 80 weight %, more typically from 20 weight % to 60 weight %, of the solutes. Less soluble compounds may comprise a greater proportion of the composition, typically up to 88 weight % of the solutes. Alternatively, the compound of formula (1) may be in the form of multiparticulate beads.

The film-forming polymer may be selected from natural polysaccharides, proteins, or synthetic hydrocolloids and is typically present in the range 0.01 to 99 weight %, more typically in the range 30 to 80 weight %.

Other possible ingredients include anti-oxidants, colorants, flavourings and flavour enhancers, preservatives, salivary stimulating agents, cooling agents, co-solvents (including oils), emollients, bulking agents, anti-foaming agents, surfactants and taste-masking agents.

Films in accordance with the invention are typically prepared by evaporative drying of thin aqueous films coated onto a peelable backing support or paper. This may be done in a drying oven or tunnel, typically a combined coater dryer, or by freeze-drying or vacuuming.

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Pharmaceutical Technology On-line, 25(2), 1-14, by Verma *et al* (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of formula (1) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and poly(*dl*-lactic-coglycolic)acid (PGLA) microspheres.

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958, by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (*e.g.* Powderject™, Bioject™, *etc.*) injection.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1µg to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1µl to 100µl. A typical formulation may comprise a compound of formula (1), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, PGLA. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 1 µg to 4000 µg of the compound of formula (1). The overall daily dose will typically be in the range 1 µg to 20 mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (*e.g.* absorbable gel sponges, collagen) and non-biodegradable (*e.g.* silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

Inasmuch as it may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two

or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (1) in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

For administration to human patients, the total daily dose of the compounds of the invention is typically in the 0.001 mg to 2000 mg depending, of course, on the mode of administration. For example, oral administration may require a total daily dose of from 1 mg to 2000 mg, while an intravenous dose may only require from 0.01 mg to 100 mg. The total daily dose may be administered in single or divided doses and may, at the physician's discretion, fall outside of the typical range given herein.

These dosages are based on an average human subject having a weight of about 60kg to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

For the avoidance of doubt, references herein to "treatment" include references to curative, palliative and prophylactic treatment.

According to another embodiment of the present invention, the compounds of the formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, can also be used as a combination with one or more additional therapeutic agents to be co-administered to a patient to obtain some particularly desired therapeutic end result. The second and more additional therapeutic agents may also be a compound of the formula (1), or a pharmaceutically acceptable salt, derived forms or compositions thereof, or one or more histamine H_3 receptor ligands known in the art. More typically, the second and more therapeutic agents will be selected from a different class of therapeutic agents.

As used herein, the terms "co-administration", "co-administered" and "in combination with", referring to the compounds of formula (1) and one or more other therapeutic agents, is intended to mean, and does refer to and include the following:

- simultaneous administration of such combination of compound(s) of formula (1) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated together into a single dosage form which releases said components at substantially the same time to said patient,

- substantially simultaneous administration of such combination of compound(s) of formula (1) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at substantially the same time by said patient, whereupon said components are released at substantially the same time to said patient,
- sequential administration of such combination compound(s) of formula (1) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated apart from each other into separate dosage forms which are taken at consecutive times by said patient with a significant time interval between each administration, whereupon said components are released at substantially different times to said patient; and
- sequential administration of such combination of compound(s) of formula (1) and therapeutic agent(s) to a patient in need of treatment, when such components are formulated together into a single dosage form which releases said components in a controlled manner whereupon they are concurrently, consecutively, and/or overlapingly administered at the same and/or different times by said patient,

where each part may be administered by either the same or different route.

Suitable examples of other therapeutic agents which may be used in combination with the compound(s) of formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, include, but are by no means limited to :

- Histamine H_1 receptor antagonists, for instance loratidine, desloratidine, fexofenadine and cetirizine
- Histamine H_4 receptor antagonists
- Histamine H_2 receptor antagonists
- Leukotriene antagonists, including antagonists of LTB_4, LTC_4, LTD_4, and LTE_4, in particular Montelukast
- Phosphodiesterase inhibitors such as PDE4 inhibitors or PDE5 inhibitors,
- neurotransmitter re-uptake inhibitors, for instance fluoxetine, sertraline, paroxetine, ziprasidone
- 5-Lipoxygenase (5-LO) inhibitors or 5-lipoxygenase activating protein (FLAP) antagonists,
- α_1- and α_2-adrenoceptor agonist vasoconstrictor sympathomimetic agents for decongestant use,
- Muscarinic M3 receptor antagonists or anticholinergic agents,
- β_2-adrenoceptor agonists,
- Theophylline,
- Sodium cromoglycate,
- COX-1 inhibitors (NSAIDs) and COX-2 selective inhibitors,
- Oral or inhaled Glucocorticosteroids,
- Monoclonal antibodies active against endogenous inflammatory entities,
- Anti-tumor necrosis factor (anti-TNF-α) agents,
- Adhesion molecule inhibitors including VLA-4 antagonists,
- Kinin-B_1- and B_2-receptor antagonists,
- Immunosuppressive agents,
- Inhibitors of matrix metalloproteases (MMPs),
- Tachykinin NK_1, NK_2 and NK_3 receptor antagonists,

- Elastase inhibitors,
- Adenosine A2a receptor agonists,
- Inhibitors of urokinase,
- Compounds that act on dopamine receptors, e.g. D2 agonists,
- Modulators of the NFκβ pathway, e.g. IKK inhibitors,
- Agents that can be classed as mucolytics or anti-tussive,
- antibiotics,
- modulators of cytokine signalling pathways such as p38 MAP kinase, syk kinase or JAK kinase inhibitors,
- HDAC (histone deacetylase) inhibitors and
- PI3 kinase inhibitors

According to the present invention, combination of the compounds of formula (1) with :

- Histamine H_1 receptor antagonists, for instance loratidine, desloratidine, fexofenadine and cetirizine
- Histamine H_4 receptor antagonists
- Histamine H_2 receptor antagonists
- Leukotriene antagonists, including antagonists of LTB_4, LTC_4, LTD_4, and LTE_4, in particular Montelukast
- Phosphodiesterase PDE4 inhibitors
- neurotransmitter re-uptake inhibitors, for instance fluoxetine, sertraline, paroxetine, ziprasidone

are preferred.

The compounds of formula (1) have the ability to interact with the H_3 receptor and thereby have a wide range of therapeutic applications, as described further below, because of the essential role which the H_3 receptor plays in the physiology of all mammals. According to this invention H_3 ligands are meant to include H_3 receptor antagonists, agonists and inverse agonists. For the preferred indications to be treated according to the invention, H_3 antagonists are believed to be most suitable.

In another aspect of the invention there is provided a compound of the formula (1) as defined in herein, or a pharmaceutically acceptable salt and/or solvate thereof, for use as a medicament.

A further aspect of the present invention relates to the compounds of formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, for use in the treatment of diseases, disorders, and conditions in which the H_3 receptor is involved. More specifically, the present invention also concerns the compounds of formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, for use in the treatment of diseases, disorders, and conditions selected from the group consisting of :

- diseases of the central nervous system: sleep disorders, migraine, dyskinesia, stress-induced anxiety, psychotic disorders, epilepsy, Cognition deficiency diseases such as Alzheimer's disease or mild cognitive impairment, depression, mood disorders, schizophrenia, anxiety disorders, attention-deficit

hyperactivity disorder (ADHD), psychotic disorders, obesity, dizziness, vertigo, epilepsy, motion sickness

- inflammatory diseases
- respiratory diseases (adult respiratory distress syndrome, acute respiratory distress syndrome, bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis, chronic sinusitis), allergy, allergy-induced airway responses, allergic rhinitis, viral rhinitis, non-allergic rhinitis, perennial and seasonal rhinitis, nasal congestion, allergic congestion
- Female sexual dysfunction including hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder and sexual pain disorder
- Male sexual dysfunction including male desire disorders, male erectile dysfunction, male orgasmic disorders such as premature ejaculation
- cardiac dysfunctions such as myocardial ischaemia and arrythmia
- diseases of the gastrointestinal tract such as inflammatory bowel disease, Crohn's disease and colitis ulcerosa
- cancer
- hypotension
- pain and
- overactive bladder conditions

The compounds of formula (1) of the invention are particularly suitable for the treatment of allergy, allergy-induced airway responses, allergic rhinitis, viral rhinitis, non-allergic rhinitis, perennial and seasonal rhinitis, nasal congestion, allergic congestion.

A still further aspect of the present invention also relates to the use of the compounds of formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, for the manufacture of a drug being a H_3 ligand. In particular, the present inventions concerns the use of the compounds of formula (1), or pharmaceutically acceptable salts, derived forms or compositions thereof, for the manufacture of a drug for the treatment of H3-mediated diseases and/or conditions, in particular the diseases and/or conditions listed above.

Another aspect of the invention relates to the use of a compound of formula (1), or a pharmaceutically acceptable salt, derived form or composition thereof, for the manufacture of a medicament for the treatment of female sexual dysfunction, including hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder and sexual pain disorder, or for the treatment of male sexual dysfunction including male desire disorders, male erectile dysfunction or male orgasmic disorders such as premature ejaculation.

As a consequence, the present invention provides a particularly interesting method to treat a mammal, including a human being, with an effective amount of a compound of formula (1), or a pharmaceutically acceptable salt, derived form or composition thereof. More precisely, the present invention provides a particularly interesting method for the treatment of a H3-mediated diseases and/or conditions in a

mammal, including a human being, in particular the diseases and/or conditions listed above, comprising administering to said mammal an effective amount of a compound of formula (1), its pharmaceutically acceptable salts and/or derived forms.

EXAMPLES

The following examples illustrate the preparation of phenol and thiophenol derivatives of the formula (1) :

glossary

APCI	atmospheric pressure chemical ionisation
Arbocel®	filter agent
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BOC	*tert*-butoxycarbonyl
br	broad
CDI	carbonyldiimidazole
δ	chemical shift
d	doublet
Δ	heat
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
EDCI	see WSCDI
ESI^+	electrospray ionisation positive scan
ESI^-	electrospray ionisation negative scan
h	hours
HBTU	O-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HOAT	1-hydroxy-7-azabenzotriazole
HOBT	1-hydroxybenzotriazole
HPLC	high pressure liquid chromatography
Hunig's base	Diisopropylethylamine
m/z	mass charge ratio
min	minutes
MS	mass spectrum
NH_3	0.88 ammonia aqueous solution
NMM	*N*-methyl morpholine
NMR	nuclear magnetic resonance
q	quartet

s	singlet
STAB	sodium triacetoxyborohydride
t	triplet
TBME	*tert*-butyl methyl ether
TBTU	2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TosMIC	Tosylmethyl isocyanide
WSCDI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

Intermediate 1: 4-(4-methoxyphenyl)-tetrahydro-2H-pyran-4-carbonitrile

4-Methoxyphenylacetonitrile (10g, 67.9mmol) in DMF (50ml) was added slowly to a suspension of NaH (5.04g, 150mmol) in DMF (50ml) at 0°C under N_2. The reaction was allowed to warm up to room temperature and stirred for 30 min. The reaction was cooled to 0°C and bis(2-chloroethyl)ether (10.7g, 74.7mmol) in DMF (100ml) was added dropwise over 60 min. The reaction was allowed to warm up to room temperature and stirred for 1 hour. The reaction was quenched with water (200ml) and extracted with ethyl acetate (3x300ml). The combined organic extracts were washed with water (2x200ml), brine (200ml), dried over $MgSO_4$, filtered, washed with ethyl acetate and concentrated *in vacuo* to give the title compound (17.2g, 100%).

Intermediate 2: 4-(4-Hydroxy-phenyl)-tetrahydro-pyran-4-carbonitrile

Boron tribromide (1M in DCM, 282ml) was added to a solution of 4-(4-methoxyphenyl)-tetrahydro-2H-pyran-4-carbonitrile (14.7g, 67.9mmol) in DCM (294ml) at 0°C under N_2 keeping the temperature below 5°C. The reaction was allowed to warm to room temperature and stirred for 48hours. The mixture was cooled to -10-0°C with dry ice acetone and quenched with saturated aqueous sodium bicarbonate (294ml). The mixture was allowed to warm to room temperature and stirred for 1hour. The mixture was separated and the aqueous extracted with DCM (3x250ml). The combined organic extracts were dried over $MgSO_4$, filtered, washed with DCM and concentrated *in vacuo* to give the title compound (10.8g, 78%).

Intermediate 3: 4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol

Step 1:

To a stirred suspension of $LiAlH_4$ (79g, 2.08mol, 5eq) in THF (900ml) at 0 to 5°C under an atmosphere of nitrogen was added 4-(4-methoxyphenyl)- tetrahydro-2H-pyran-4-carbonitrile (90g, 0.414mol) in THF (900ml) over a 25 minutes maintaining the temperature at 5 to 10°C. The reaction mixture was allowed to warm to ambient temperature and stirred until complete. Sodium hydroxide (2N, 850ml) was added

dropwise, the resulting solids filtered and washed with THF (2x800ml), the organics concentrated *in vacuo* at 40°C. The residue was dissolved in EtOAc (300ml) and dried over $MgSO_4$, filtered and concentrated *in vacuo* at 40°C to provide {[4-(4-methoxyphenyl)-tetrahydro-2H-pyran-4-yl]methyl}amine as a light yellow oil (92g, quantitative).

Step 2:

To a solution of {[4-(4-methoxyphenyl)-tetrahydro-2H-pyran-4-yl]methyl}amine (60g, 0.271mol) in H_2O (444mL) and AcOH (213ml) was charged formaldehyde (37%ww solution in H_2O, 408 mL) and the mixture cooled to 0 to 5 °C. Sodium triacetoxyborohydride (345g, 1.628mol, 6eq) was added portion wise while maintaining the temperature below 12°C. The mixture was stirred at ambient temperature until complete. Sodium hydroxide (2M, 1000ml) was added slowly and the mixture extracted with DCM (4x250ml). The organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* at 30°C to provide {[4-(4-methoxyphenyl)-tetrahydro-2H-pyran-4-yl]methyl}dimethylamine as a yellow oil (53.5g, 80%).

Step 3:

To a suspension of Sodium thiomethoxide (49.2g, 0.702mol, 5eq) in DMF (140ml) was added {[4-(4methoxyphenyl)-tetrahydro-2H-pyran-4-yl]methyl}dimethylamine (35g, 0.140mol) and the resulting mixture was heated to 130°C. Once complete, allowed to cool to ambient temperature and saturated aqueous NH_4Cl (525ml) was added. The resultant was extracted with EtOAc (3x500ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* at 35°C to provide 4-(4-dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (Intermediate 3) as a yellow solid (35.7g, 106%) containing residual DMF and EtOAc.

Intermediate 4: 3-(4-[(dimethylamino)methyl]tetrahydro-pyran-4-yl)phenol

Step 1:

3-Methoxyphenylacetonitrile (10g, 67.9mmol) in DMF (50ml) was added slowly to a suspension of NaH (5.04g, 150mmol) in DMF (50ml) at 0°C under N_2. The reaction was allowed to warm to room temperature and stirred for 30mns. The reaction was cooled to 0°C and bis(2-chloroethyl)ether (10.7g, 74.7mmol) in DMF (100ml) was added dropwise over 60 min. The reaction was allowed to warm to room temperature and stirred for 1hour. The reaction was quenched with water (500ml) and extracted with ethyl acetate (3x100ml). The combined organic extracts were washed with brine (3x50ml), dried over $MgSO_4$, filtered, washed with ethyl acetate and concentrated *in vacuo*. The crude mixture was purified by column chromatography, eluting with heptane increasing the polarity to heptane:ethyl acetate (90 :10), to give 4-(3-methoxyphenyl)tetrahydro-pyran-4-carbonitrile (4.1g, 28%).

Step 2:

To a stirred suspension of $LiAlH_4$ (3.7 g, 98.7 mmol) in diethyl ether (100 mL) cooled at 0°C was added dropwise a solution of 4-(3-methoxyphenyl)-tetrahydro-pyran-4-carbonitrile (4.2 g, 19.3 mmol) in diethyl ether (100 mL). After being stirred at room temperature for 30 min, the reaction mixture was refluxed for another 15 min. The mixture was cooled to 10°C and water, sodium hydroxide (15% w/v in water, 0.48 mL) and water again were successively added dropwise. After being stirred for 15 min at room temperature, the mixture was filtered over diatomaceous earth and concentrated. The residue was

50

purified with flash chromatography (DCM/MeOH: 95/5) to provide [4-(3-methoxyphenyl)tetrahydro-pyran-4-yl]methylamine (4 g, 94%).

Step 3:

A mixture of [4-(3-methoxyphenyl)tetrahydro-pyran-4-yl]methylamine (0.51 g, 2.3 mmol), acetic acid (0.535 mL, 9.2 mmol), sodium triacetoxyborohydride (0.974 g, 4.6 mmol), 37% solution of formaldehyde in water (0.55 mL) and DCM (40 mL) was stirred 72 h at ambient temperature. The organic phase was washed twice with water. Concentrated NaOH was added to the aqueous phase (pH 12) and the mixture was extracted twice with dichloromethane. The organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide N-[[4-(3-methoxyphenyl)tetrahydro-pyran-4-yl]methyl]-N,N-dimethylamine as an oil (0.35 g, 61%).

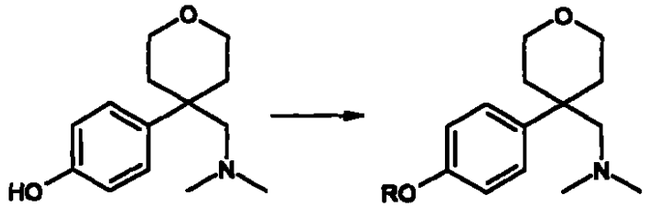
Step 4:

To a suspension of Sodium thiomethoxide (0.42 g, 6 mmol) in DMF (1.2 mL) was added N-[[4-(3-methoxyphenyl)tetrahydro-pyran-4-yl]methyl]-N,N-dimethylamine (0.3 g, 1.2 mmol) and the resulting mixture was heated to 65°C for 7 h, allowed to cool to ambient temperature and quenched with saturated aqueous NH_4Cl (6 mL). The mixture was extracted with DCM, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide 0.25 g of crude product. A mixture of the crude and HBr (3 mL) was heated to reflux for 1 h. After cooling, water was added to quench the reaction and the mixture was basified with $NaHCO_3$ and extracted with DCM. The organic extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (DCM / MeOH (10% NH_3)) to provide 3-{4-[(dimethylamino)methyl]tetrahydro-pyran-4-yl}phenol (0.100 g, 35.5%).

<u>General procedure A for the synthesis of chlorides (R-R^{La} wherein R^{La} is chloride):</u>

Amine (1eq.) was charged to a reaction flask followed by acetone (3vol or 20vol), 5M NaOH solution (1.2eq.) and 1-bromo-3-chloropropane (1.5 eq. or 3eq.). The reaction was stirred overnight at room temperature. The phases were separated and the acetone layer concentrated *in vacuo*. The aqueous was acidified with 2M HCl solution to pH 1 (~10vol). The concentrate was diluted with TBME (30vol) and washed with water (15vol). The aqueous was extracted with TBME (2 x 15ml). The combined TBME was washed with 2M HCl solution (15ml) and combined with the first acidic phase. The combined acidic layers were washed with TBME (15vol) and basified to pH 14 with 4M NaOH solution (~40ml). The aqueous was extracted with TBME (3 x 30ml). The combined organic layers were dried over $MgSO_4$, filtered, washed with TBME (5vol) and concentrated *in vacuo* to give the required chloride.

<u>General procedure B:</u>



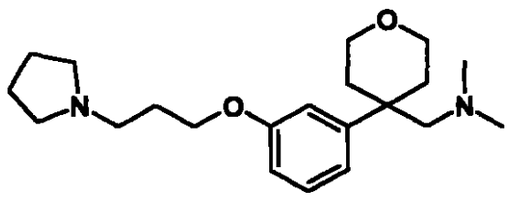
4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (500mg, 2.13mmol), chloride (378mg, 2,13mmol), DMF (10ml), water (17ml) and K_2CO_3 (1.18g, 8.52mmol) was heated to 130°C. Cooled to

ambient temperature, water (40ml) added, extracted with EtOAc (3x25ml) and the combined organic extracts washed with water (2x25ml). The organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* at 35°C. Purification of the crude material by chromatography on silica, *eluant* (4% MeOH, 1% NH_3, in DCM) provided the title compounds.

Intermediate 5: 1-(3-Chloro-propyl)-pyrrolidine

Pyrrolidine (10g, 0.14mol), acetone (28ml), 5M NaOH solution (21ml) and 1-bromo-3-chloropropane (24.4g, 0.15mol) were stirred together under N_2 for 8hours. The organic layer was separated and concentrated *in vacuo*. The crude product was purified by vacuum distillation (b.p. 90°C/30mbar) to give the title compound (11.7g, 57%) as a colourless oil.

Example 1: Dimethyl-[4-[3-(3-pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-amine



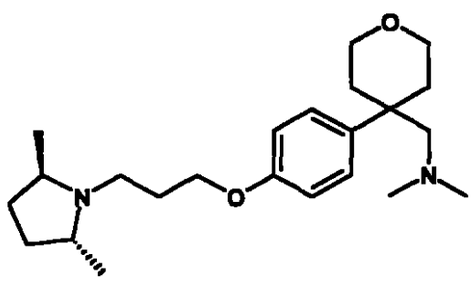
Alkylation of 3-[4-(dimethylamino)methyltetrahydro-2H-pyran-4-yl]phenol (0.1 g, 0.425 mmol) with 1-(3-chloropropyl)pyrrolidine (0.125 g, 0.85 mmol) according to general procedure B gave the desired compound after purification by flash chromatography (0.030 g, 20%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.27-7.18 (m, 1H), 6.92-6.84(m, 2H), 6.75 (dd, 1H), 4.05 (t, 2H), 3.8-3.7 (m, 2H), 3.55 (t, 2H), 2.85 (t, 2H), 2.6-2.5 (m, 4H), 2.4(s, 2H), 2.15-1.85 (m, 6H), 2.0 (s, 6H), 1.85-1.75 (m, 4H).

Intermediate 6: 1-(3-Chloro-propyl)-2(R),5(R)-trans-dimethyl-pyrrolidine

2(R),5(R)-*trans*-Dimethyl-pyrrolidine (0.75g, 7.58mmol), acetone (15ml, 20vol), 5M NaOH solution (1.8ml, 1.2eq.) and 1-bromo-3-chloropropane (3.57g, 22.7mmol, 3eq.) were reacted together according to general procedure A to give the title compound (0.5g, 38%) as a yellow oil.

Example 2: (4-[4-[3-(2,5-Dimethylpyrrolidin-1-yl)propoxy]phenyl]tetra-hydro-pyran-4-ylmethyl)dimethylamine



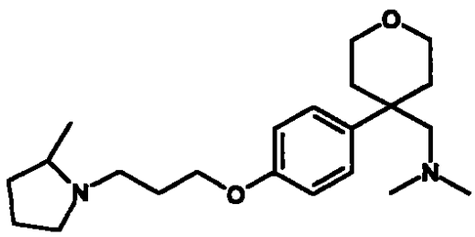
4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (330mg, 1.43mmol), 1-(3-chloro-propyl)-2,5-*trans*-dimethyl-pyrrolidine (221mg, 1.26mmol), DMF (7.8ml) and K_2CO_3 (790mg, 5.72mmol) were reacted

together according to general procedure B. The isolated material was subjected to chromatography on silica, eluant 95:4:1 (DCM, MeOH, NH_3) to give the title compound as a yellow oil (180mg, 34%).
^{1}H NMR (400MHz, $CDCl_3$) δ7.20 (d, 2H), 6.87 (d, 2H), 4.08-3.96 (m, 2H), 3.79-3.70 (m, 2H), 3.69-3.49 (m, 2H), 3.11-3.00 (m, 2H), 2.77 (m, 1H), 2.54 (m, 1H), 2.40 (s, 2H), 2.14-1.81 (m, 8H), 1.98 (s, 6H), 1.44-1.31 (m, 2H), 0.97 (d, 6H).

Intermediate 7: 1-(3-Chloro-propyl)-2-methyl-pyrrolidine

2-Methylpyrrolidine (0.9g, 10.6mmol), acetone (18ml, 20vol), 5M NaOH solution (2.50ml) and 1-bromo-3-chloropropane (5g, 31.8mmol, 3eq) were reacted together according to general procedure A to give the title compound (1g, 59%) as a pale yellow oil.

Example 3: Dimethyl-(4-{4-[3-(2-methyl-pyrrolidin-1-yl)-propoxy]-phenyl}-tetrahydro-pyran-4-ylmethyl)-amine



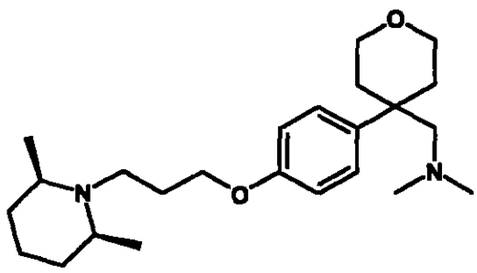
4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (500mg, 2.13mmol), 1-(3-chloro-propyl)-2-methyl-pyrrolidine (344mg, 2,13mmol), DMF (10ml) and K_2CO_3 (1.18g, 8.52mmol) were reacted together according to general procedure B. The isolated material was subjected to chromatography on silica, eluant 95:4:1 (DCM, MeOH, NH_3) to give the title compound as a yellow oil (120mg, 16%).
^{1}H NMR (400MHz, $CDCl_3$) δ7.20 (d, 2H), 6.87 (d, 2H), 4.08-3.96 (m, 2H), 3.75 (dt, 2H), 3.55 (td, 2H), 3.18 (td, 1H), 2.98 (m, 1H), 2.40 (s, 2H), 2.29 (m, 1H), 2.20 (m, 1H), 2.16-1.62 (m, 10H), 1.96 (s, 6H), 1.42 (m, 1H), 1.09 (d, 3H).

Intermediate 8: 1-(3-Chloro-propyl)-2,6-cis-dimethyl-piperidine

Step 1:
2,6-*cis*-Dimethyl-piperidine (1.0g, 8.83mmol), K_2CO_3 (1.52g, 1.25eq.) and 3-bromopropanol (6.14g, 44.2mmol, 4vol) were reacted together at 100°C for 2hours. The reaction was allowed to cool to room temperature, diluted with DCM (20ml) and quenched with 2M HCl solution (20ml). The aqueous was extracted with DCM (2 x 20ml) and basified to pH 14 with 2M NaOH solution (~15ml). The aqueous was extracted with DCM (3 x 20ml). The combined DCM layers were dried over $MgSO_4$, filtered washed with DCM and concentrated *in vacuo* to give 1-(propan-1'-ol)-2,6-*cis*-dimethyl-piperidine (1.22g, 81%) as a pale yellow oil.
Step 2:
1-(Propan-1'-ol)-2,6-*cis*-dimethyl-piperidine (1.22g, 7.12mmol) was dissolved in DCM (24ml) and cooled to 0-5°C under N_2. Thionyl chloride (1.04ml, 14.25mmol) was added dropwise. The reaction was allowed to

warm to room temperature and stirred for 30mins. The reaction was quenched with 2M HCl solution (25ml). The aqueous was extracted with DCM (25ml) and basified to pH 14 with 5M NaOH solution (~25ml). The aqueous was extracted with TBME (3 x 25ml). The combined organic layers were dried over $MgSO_4$, filtered washed with TBME and concentrated *in vacuo* to give the title compound (1.26g, 93%) as a yellow oil.

Example 4: (4-[4-(3-(2,6-Dimethylpiperidin-1-yl)propoxy)phenyl]tetra-hydro-pyran-4-ylmethyl)dimethyl-amine



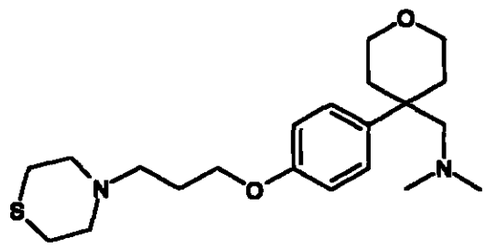
4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (500mg, 2.13mmol), 1-(3-chloro-propyl)-2,6-cis-dimethyl-piperidine (410mg, 2,13mmol), DMF (10ml) and K_2CO_3 (1.18g, 8.52mmol) were reacted together according to general procedure B. The isolated material was subjected to chromatography on silica, eluant 95:4:1 (DCM, MeOH, NH_3) to give the title compound as a yellow oil (280mg, 33.9%).

^1H NMR (400MHz, $CDCl_3$) δ 7.20 (d, 2H), 6.86 (d, 2H), 3.93 (t, 2H), 3.75 (dt, 2H), 3.55 (td, 2H), 2.95 (t, 2H), 2.51-2.36 (m, 2H), 2.40 (s, 2H), 2.14-2.04 (m, 2H), 1.98 (s, 6H), 1.93-1.82 (m, 4H), 1.74-1.51 (m, 3H), 1.41-1.21 (m, 3H), 1.13 (d, 6H).

Intermediate 9: 4-(3-Chloro-propyl)-thiomorpholine

Thiomorpholine (5g, 49mmol), acetone (15ml, 3vol), 5M NaOH solution (11.8ml) and 1-bromo-3-chloropropane (11.6g, 73.5mmol, 1.5eq.) were reacted together according to general procedure A to give the title compound (8.5g, 98%) as a pale yellow oil.

Example 5: Dimethyl-[4-[4-(3-thiomorpholin-4-yl-propoxy)-phenyl]tetra-hydro-pyran-4-ylmethyl]-amine

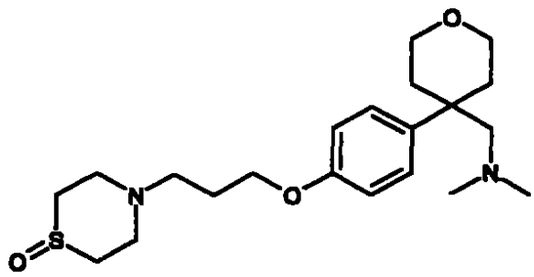


4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (1000mg, 4.25mmol), 4-(3-chloro-propyl)-thiomorpholine (764mg, 2,13mmol), DMF (20ml), and K_2CO_3 (2,34g, 17mmol) were reacted together

according to general procedure B. The isolated material was subjected to chromatography on silica, eluant DCM:MeOH:NH_3 (95:5:1) to give the title compound (320mg, 20%).

^{1}H NMR (400MHz, $CDCl_3$) δ7.20 (d, 2H), 6.86 (d, 2H), 3.99 (t, 2H), 3.75 (dt, 2H), 3.55 (td, 2H), 2.79-2.64 (m, 8H), 2.55 (t, 2H), 2.40 (s, 2H), 2.16-2.04 (m, 2H), 2.01-1.82 (m, 4H), 1.97 (s, 6H).

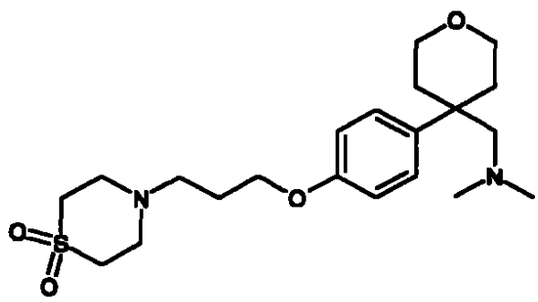
Example 6: Dimethyl-[4-[4-[3-(1-oxothiomorpholin-4-yl)propoxy]phenyl]-tetrahydropyran-4-ylmethyl]amine



Dimethyl-[4-[4-(3-thiomorpholin-4-ylpropoxy)phenyl]tetrahydro-pyran-4-ylmethyl]amine (300mg, 0.792mmol) and TFA (0.99ml) were cooled to 0 to 5 °C and trifluoro-peracetic acid (4M, 0.77ml) [4M solution prepared by the addition of 27.5% H_2O_2 (0.94ml) to TFA (1.56ml)] was added and the reaction stirred for six hours at 0 to 5°C. The mixture was diluted with DCM (8ml), basified with NaOH (2M, 8ml) and extracted with DCM (2x20ml). The DCM extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* at 35°C. Purification by chromatography on silica, eluant DCM:MeOH:NH_3 (96:4:1) provided the title compound (200mg, 61%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ7.21 (d, 2H), 6.86 (d, 2H), 4.01 (t, 2H), 3.75 (dt, 2H), 3.55 (td, 2H), 3.15-3.02 (m, 2H), 2.93-2.79 (m, 4H), 2.72 (dt, 2H), 2.64 (t, 2H), 2.40 (s, 2H), 2.16-1.82 (m, 6H), 1.97 (s, 6H).

Example 7: (4-[4-[3-(1,1-Dioxo-thiomorpholin-4-yl)propoxy]phenyl]tetra-hydro-pyran-4-ylmethyl)dimethyl-amine



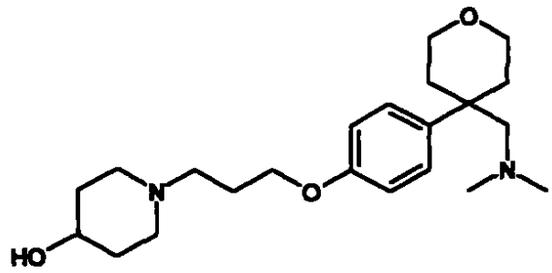
Dimethyl-[4-[4-(3-thiomorpholin-4-ylpropoxy)phenyl]tetrahydro-pyran-4-ylmethyl]amine (300mg, 0.792mmol) and TFA (0.99ml) were cooled to 0 to 5°C and trifluoro-peracetic acid (4M, 0.77ml) was added and the reaction allowed to warm to ambient temperature overnight. The mixture was diluted with DCM (8ml), basified with NaOH (2M, 8ml) and extracted with DCM (2x20ml). The DCM extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* at 35°C. Purification by chromatography on silica, eluant DCM:MeOH:NH_3 (96:4:1) provided the title compound (151mg, 48%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ7.22 (d, 2H), 6.86 (d, 2H), 4.01 (t, 2H), 3.75 (dt, 2H), 3.55 (td, 2H), 3.10-2.97 (m, 8H), 2.72 (t, 2H), 2.40 (s, 2H), 2.14-1.82 (m, 6H), 1.97 (s, 6H).

Intermediate 10: 1-(3-Chloro-propyl)-piperidin-4-ol

4-Hydroxypiperidine (3g, 30mmol), acetone (60ml, 20vol), 5M NaOH solution (7.2ml) and 1-bromo-3-chloropropane (14.2g, 90mmol, 3eq.) were reacted together according to general procedure A to give the title compound (1.5g, 28%) as a pale yellow oil.

Example 8: 1-(3-[4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenoxy]-propyl)-piperidin-4-ol



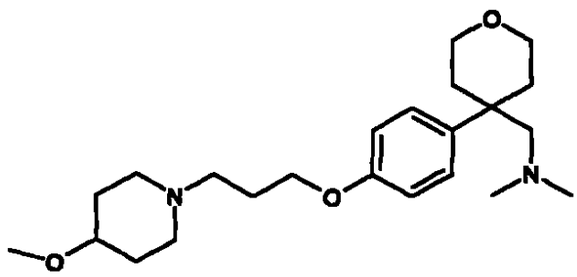
4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (500mg, 2.13mmol), 1-(3-chloro-propyl)-piperidin-4-ol (378mg, 2,13mmol), DMF (10ml) and K_2CO_3 (1.18g, 8.52mmol) were reacted together according to general procedure B. The isolated material was dissolved in EtOAc (30ml), washed with NaOH (2M, 2x20ml) and water (25ml), dried over $MgSO_4$ filtered and concentrated in vacuo at 35°C to give the title compound (411mg, 51%).

^{1}H NMR (400MHz, $CDCl_3$) δ7.20 (d, 2H), 6.86 (d, 2H), 4.00 (t, 2H), 3.80-3.65 (m, 3H), 3.56 (td, 2H), 2.85-2.73 (m, 2H), 2.62 (t, 2H), 2.40 (s, 2H), 2.22-1.82 (m, 10H), 1.97 (s, 6H), 1.66-1.54 (m, 2H), 1.52 (br s, 1H).

Intermediate 11: 1-(3-Chloro-propyl)-4-methoxy-piperidine

4-Methoxy-piperidine (1.5g, 13mmol), acetone (30ml, 20vol), 5M NaOH solution (3.13ml) and 1-bromo-3-chloropropane (6.14g, 39mmol, 3eq.) were reacted together according to general procedure A to give the title compound (1.5g, 60%) as a pale yellow oil.

Example 9: (4-{4-[3-(4-Methoxy-piperidin-1-yl)-propoxy]-phenyl}-tetrahydro-pyran-4-ylmethyl)-dimethyl-amine



4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (500mg, 2.13mmol), 1-(3-chloro-propyl)-4-methoxy-piperidine (410mg, 2,13mmol), DMF (10ml) and K_2CO_3 (1.18g, 8.52mmol) were reacted together

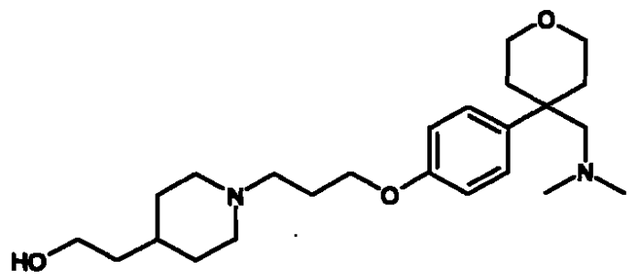
according to general procedure B. The isolated material was subjected to chromatography on silica, eluant 95:4:1 (DCM: MeOH: NH_3) to give the title compound as a yellow oil (415mg, 50%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.20 (d, 2H), 6.86 (d, 2H), 4.00 (t, 2H), 3.75 (dt, 2H), 3.55 (td, 2H), 3.34 (s, 3H), 3.22 (m, 1H), 2.83-2.71 (m, 2H), 2.61 (t, 2H), 2.40 (s, 2H), 2.23-1.81 (m, 10H), 1.97 (s, 6H), 1.67-1.53 (m, 2H).

Intermediate 12: 2-[1-(3-Chloro-propyl)-piperidin-4-yl]-ethanol

4-Piperidine ethanol (0.9g, 7.5mmol), acetone (18ml, 20vol), 5M NaOH solution (1.8ml) and 1-bromo-3-chloropropane (3.54g, 22.5mmol, 3eq.) were reacted together according to general procedure A to give the title compound (0.6g, 37%) as an orange oil.

Example 10: 2-(1-{3-[4-(4-Dimethylaminomethyltetrahydropyran-4-yl)phenoxy]propyl}piperidin-4-yl)ethanol



4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (288mg, 1.22mmol), 2-[1-(3-chloro-propyl)-piperidin-4-yl]-ethanol (252mg, 1.22mmol), DMF (8ml) and K_2CO_3 (674mg, 4.88mmol) were reacted together according to general procedure B. Purification by chromatography on silica, eluant DCM:MeOH:NH_3 (96:4:1) provided the title compound (180mg, 36%) as an off white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.20 (d, 2H), 6.86 (d, 2H), 3.99 (t, 2H), 3.75 (dt, 2H), 3.70 (t, 2H), 3.55 (td, 2H), 2.98-2.88 (m, 2H), 2.49 (t, 2H), 2.40 (s, 2H), 2.14-1.82 (m, 6H), 1.97 (s, 6H), 1.75-1.15 (m, 10H).

Intermediate 13: 1-(3-Chloro-propyl)-4-(2-methoxy-ethyl)-piperidine

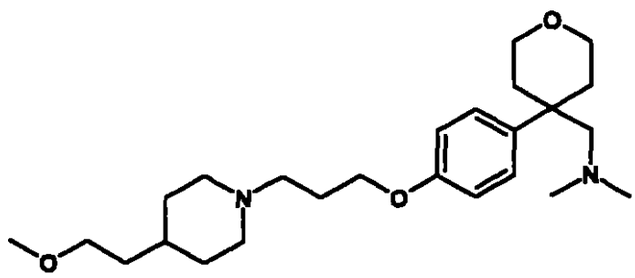
Step 1:

N-Boc-4-(2-hydroxy-ethyl)-piperidine (5g, 21.8mmol) in THF (25ml) was added to a suspension of NaH (1.47g, 43.7mmol) in THF (75ml) at 0°C under N_2. The reaction was stirred for 1hour at 0°C and MeI (2.72ml, 43.7mmol) added slowly. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water (100ml) and extracted with DCM (3 x 100ml). The combined DCM layers were dried over $MgSO_4$, filtered, washed with DCM and concentrated *in vacuo*. The crude reaction (7.5g) was treated with 3M HCl solution in EtOH (150ml) for 12hours. The reaction was concentrated *in vacuo* and azeotroped with toluene (2 x 150ml) to give 4-(2-methoxy-ethyl)-piperidine hydrochloride (3.5g, 89%) as a pale yellow solid.

Step 2:

4-(2-Methoxy-ethyl)-piperidine hydrochloride (1.5g, 8.4mmol), acetone (30ml, 20vol), 5M NaOH solution (6.03ml, 3.6eq.) and 1-bromo-3-chloropropane (3.98g, 25.1mmol, 3eq.) were reacted together according to general procedure A to give the title compound (1.6g, 88%) as a pale yellow oil.

Example 11: [4-(4-[3-[4-(2-Methoxy-ethyl)-piperidin-1-yl]-propoxy]-phenyl)-tetrahydro-pyran-4-ylmethyl]-dimethyl-amine



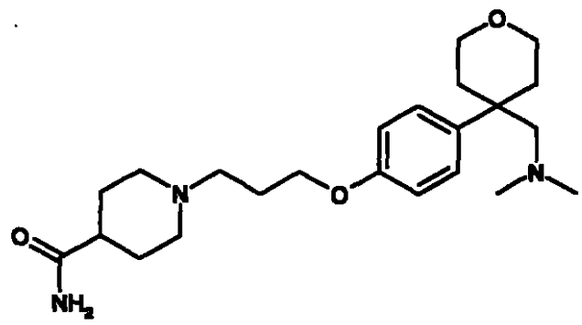
4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (500mg, 2.13mmol), 1-(3-chloro-propyl)-4-(2-methoxy-ethyl)-piperidine (466mg, 2,13mmol), DMF (10ml) and K_2CO_3 (1.18g, 8.52mmol) were reacted together according to general procedure B. Purification by chromatography on silica, eluant DCM:MeOH:NH_3 (96:4:1) provided the title compound (409mg, 46%) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.20 (d, 2H), 6.86 (d, 2H), 3.99 (t, 2H), 3.75 (dt, 2H), 3.55 (td, 2H), 3.41 (t, 2H), 3.33 (s, 3H), 2.97-2.86 (m, 2H), 2.49 (t, 2H), 2.40 (s, 2H), 2.15-1.78 (m, 8H), 1.97 (s, 6H), 1.74-1.17 (m, 7H).

Intermediate 14: 1-(3-Chloro-propyl)-piperidine-4-carboxylic acid amide

Piperidine-4-carboxylic acid amide (0.5g, 3.90mmol), acetone (1.5ml, 3vol), 5M NaOH solution (1.20ml, 1.2eq.) and 1-bromo-3-chloropropane (0.50ml, 5.04mmol, 1eq.) were reacted together according to general procedure A to give the title compound (0.16g, 20%) as a pale yellow oil.

Example 12: 1-[3-[4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenoxy]-propyl]-piperidine-4-carboxylic acid amide



4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (500mg, 2.13mmol), 1-(3-chloro-propyl)-piperidine-4-carboxylic acid amide (438mg, 2,13mmol), DMF (10ml) and K_2CO_3 (1.18g, 8.52mmol) were reacted together according to general procedure B. The isolated material was subjected to chromatography on silica, eluant 95:4:1 (DCM: MeOH: NH_3) to give the title compound as a white solid (175mg, 20%).

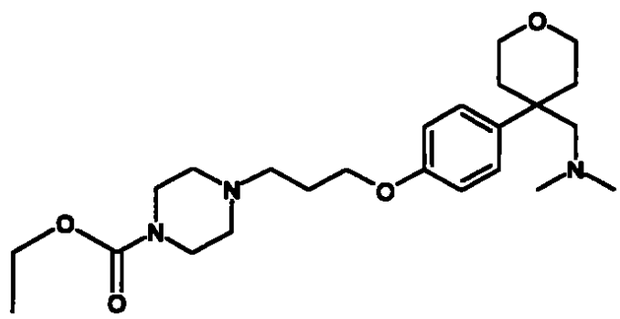
^{1}H NMR (400MHz, $CDCl_3$) δ 7.21 (d, 2H), 6.86 (d, 2H), 5.44 (br s, 1H), 5.25 (br s, 1H), 4.00 (t, 2H), 3.75 (dt, 2H), 3.55 (td, 2H), 3.03-2.93 (m, 2H), 2.51 (t, 2H), 2.40 (s, 2H), 2.22-1.86 (m, 13H), 1.97 (s, 6H).

58

Intermediate 15: 4-(3-Chloro-propyl)-piperazine-1-carboxylic acid ethyl ester

Piperazine-1-carboxylic acid ethyl ester (3.0g, 18.9mmol), K_2CO_3 (2.8g, 1.1eq.), DMF (30ml, 10vol) and 1-bromo-3-chloropropane (1.8ml, 18.9mmol, 1eq.) were reacted together at room temperature overnight. The reaction was quenched with water (100ml) and extracted with DCM (3 x 50ml). The combined DCM extracts were dried over $MgSO_4$, filtered washed with DCM and concentrated *in vacuo* to give the title compound (3.1g, 70%) as a pale yellow oil.

Example 13: {3-[4-(4-Dimethylaminomethyltetrahydropyran-4-yl)phenoxy]-propyl}piperazine-1-carboxylic acid ethyl ester



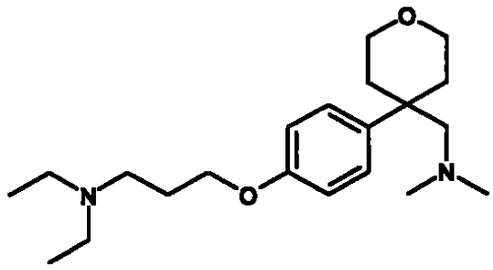
4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (500mg, 2.13mmol), 4-(3-chloro-propyl)-piperazine-1-carboxylic acid ethyl ester (499mg, 2,13mmol), DMF (10ml) and K_2CO_3 (1.18g, 8.52mmol) were reacted together according to general procedure B. Purification by chromatography on silica, eluant (10%MeOH in DCM) the title compound (276mg, 26%).

^{1}H NMR (400MHz, $CDCl_3$) δ7.21 (d, 2H), 6.86 (d, 2H), 4.14 (q, 2H), 4.01 (t, 2H), 3.75 (dt, 2H), 3.60-3.42 (m, 6H), 2.54 (t, 2H), 2.47-2.36 (m, 4H), 2.40 (s, 2H), 2.16-1.82 (m, 6H), 1.97 (s, 6H), 1.26 (t, 3H).

Intermediate 16 : (3-Chloro-propyl)-diethyl-amine

Diethyl-amine (7.27ml, 70mmol), acetone (15ml, 3vol), 5M NaOH solution (16.8ml, 1.2eq.) and 1-bromo-3-chloropropane (16.5g, 105mmol, 1.5eq.) were reacted together according to general procedure A to give the title compound (6.2g, 59%) as a colourless oil.

Example 14: {3-[4-(4-Dimethylaminomethyltetrahydropyran-4-yl)phenoxy]-propyl}diethyl-amine



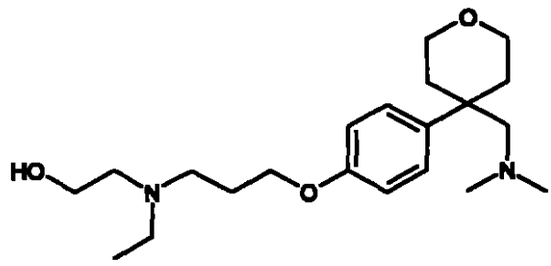
4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (500mg, 2.13mmol), (3-chloro-propyl)-diethyl-amine (319mg, 2,13mmol), DMF (10ml) and K_2CO_3 (1.18g, 8.52mmol) were reacted together according to general procedure B. Purification by chromatography on silica, eluant (3%EtOH: 1%NH_3 in DCM) gave the title compound as a pale yellow clear oil (160mg, 22%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.20 (d, 2H), 6.88 (d, 2H), 4.00 (t, 2H), 3.75 (dt, 2H), 3.55 (td, 2H), 2.61 (t, 2H), 2.54 (q, 4H), 2.40 (s, 2H), 2.15-1.82 (m, 6H), 1.97 (s, 6H), 1.02 (t, 6H).

Intermediate 17: 2-[(3-Chloro-propyl)-ethyl-amino]-ethanol

2-Ethylamino ethanol (6.2g, 70mmol), acetone (18ml, 3vol), 5M NaOH solution (16.8ml, 1.2eq.) and 1-bromo-3-chloropropane (16.5g, 105mmol, 1.5eq.) were reacted together according to general procedure A to give the title compound (4.5g, 39%) as a colourless oil.

Example 16: 2-{(3-[4-(4-Dimethylaminomethyltetrahydropyran-4-yl)-phenoxy]propyl)ethylamino} ethanol

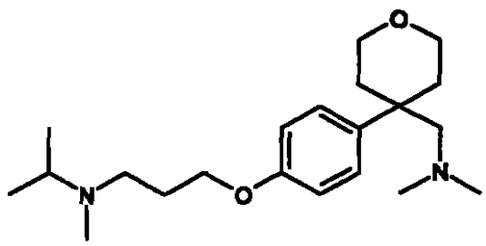


4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (500mg, 2.13mmol), 2-[(3-chloro-propyl)-ethyl-amino]-ethanol (353mg, 2,13mmol), DMF (10ml) and K_2CO_3 (1.18g, 8.52mmol) were reacted together according to general procedure B. The isolated material was subjected to chromatography on silica, eluant 95:4:1 (DCM: MeOH: NH_3) to give the title compound as a white solid (160mg, 19%).
^{1}H NMR (400MHz, $CDCl_3$) δ 7.21 (d, 2H), 6.86 (d, 2H), 4.00 (t, 2H), 3.75 (dt, 2H), 3.60-3.49 (m, 4H), 2.68 (t, 2H), 2.62 (t, 2H), 2.59 (q, 2H), 2.40 (s, 2H), 2.14-1.82 (m, 6H), 1.97 (s, 6H), 1.62 (br s, 1H), 1.03 (t, 3H).

Intermediate 18: (3-Chloro-propyl)-isopropyl-methyl-amine

Isopropylmethylamine (4g, 56mmol), acetone (12ml, 3vol), 5M NaOH solution (13.44ml, 1.2eq.) and 1-bromo-3-chloropropane (13.22g, 84mmol, 1.5eq.) were reacted together according to general procedure A to give the title compound (4.8g, 66%) as a colourless oil.

Example 16: {3-[4-(4-Dimethylaminomethyltetrahydropyran-4-yl)phenoxy]-propyl} isopropylmethylamine



4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (500mg, 2.13mmol), (3-chloro-propyl)-isopropyl-methyl-amine (318mg, 2,13mmol), DMF (10ml) and K_2CO_3 (1.18g, 8.52mmol) were reacted together according to general procedure B. Purification by chromatography on silica, eluant DCM:MeOH:NH_3 (96:3:1) provided the title compound (200mg, 43%) as a white solid.

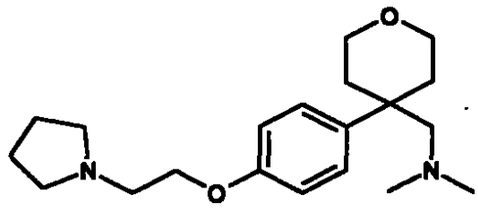
60

^{1}H NMR (400MHz, $CDCl_3$) δ7.20 (d, 2H), 6.87 (d, 2H), 4.00 (t, 2H), 3.75 (dt, 2H), 3.55 (td, 2H), 2.83 (sep, 1H), 2.55 (t, 2H), 2.40 (s, 2H), 2.22 (s, 3H), 2.14-2.05 (m, 2H), 1.96 (s, 6H), 2.00-1.82 (m, 4H), 1.00 (d, 6H).

Intermediate 19: 1-(2-chloro-ethyl)-pyrrolidine

Pyrrolidine (10.4g, 0.15mol), acetone (200ml), 5M NaOH solution (35ml) and 1-bromo-2-chloroethane (62.9g, 0.44mol) were reacted together according to general procedure A. The crude mixture was purified by column chromatography eluting with ethyl acetate to give the title compound (2.0g, 10%) as a pale yellow oil.

Example 17: Dimethyl-[4-[4-(2-pyrrolidin-1-ylethoxy)phenyl]tetrahydro-pyran-4-ylmethyl]-amine



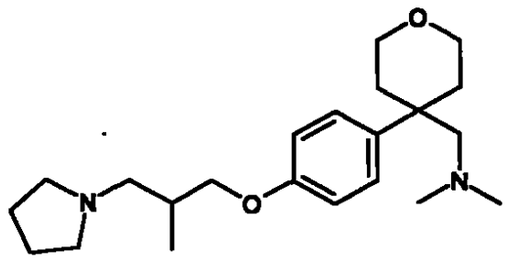
4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (389mg, 1.65mmol), 1-(2-chloro-ethyl)-pyrrolidine (210mg, 1.57mmol), DMF (4.5ml) and K_2CO_3 (885g, 6.40mmol) was heated to 130°C for 30 minutes. The mixture was cooled to ambient temperature; water (9ml) was added and the mixture was extracted with EtOAc (3 x 4.5ml). The organic phase was washed with brine (10ml), NaOH solution (2M, 10ml) and water (10ml). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* at 35°C and the residue subjected to chromatography on silica eluting with DCM:MeOH:NH3 (98:1:1) to give the title compound as a white solid (150mg, 27%).

^{1}H NMR (400MHz, $CDCl_3$) δ7.21 (d, 2H), 6.89 (d, 2H), 4.10 (t, 2H), 3.75 (dt, 2H), 3.55 (td, 2H), 2.89 (t, 2H), 2.67-2.58 (m, 4H), 2.40 (s, 2H), 2.13-2.05 (m, 2H), 1.97 (s, 6H), 1.86 (ddd, 2H), 1.84-1.77 (m, 4H).

Intermediate 20: 1-(3-Chloro-2-methyl-propyl)-pyrrolidine

Pyrrolidine (3.0g, 42mmol), acetone (80ml), 5M NaOH solution (10ml) and 1-bromo-3-chloro-2-methyl-propane (21.7g, 0.13mol) were reacted together according to general procedure A to give the title compound (3.9g, 58%) as a pale yellow oil.

Example 18: Dimethyl-[4-[4-(2-methyl-3-pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-amine



4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (0.91g, 3.87mmol), 1-(3-chloro-2-methyl-propyl)-pyrrolidine (500mg, 3.10mmol), DMF (5ml) and K_2CO_3 (2.14g, 15.50mmol) were reacted together according to general procedure B. The organic phase was washed with 2M NaOH (3 x 20ml), water (2 x 20ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* at 35°C. The crude material was subjected to chromatography on silica eluting with DCM :MeOH :NH_3 (97 :2 :1) to provide the title compound (464mg, 42%) as a pale yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.20 (d, 2H), 6.88 (d, 2H), 4.00 (dd, 1H), 3.80-3.70 (m, 3H), 3.55 (td, 2H), 2.59-2.43 (m, 5H), 2.40 (s, 2H), 2.33 (dd, 1H), 2.21-2.04 (m, 3H), 1.97 (s, 6H), 1.88 (ddd, 2H), 1.82-1.70 (m, 4H), 1.08 (d, 3H).

Intermediate 21: Methanesulfonic acid 1-isopropyl-piperidin-4-yl ester

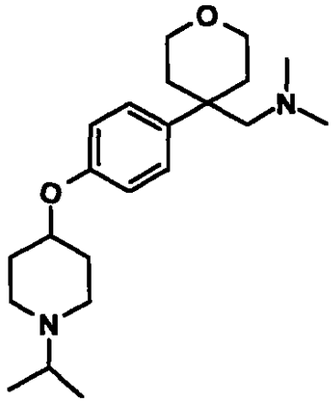
Step 1:

4-Hydroxypiperidine (2.13g, 21.1mmol), K_2CO_3 (5.83g, 2eq.), 2-bromopropane (11.2g, 91mmol, 4.3eq.) and MeOH (21.3ml) were refluxed together overnight. The reaction was allowed to cool to room temperature and quenched with 2M HCl solution (40ml) and extracted with TBME (40ml). The aqueous phase was basified to pH 14 with 2M NaOH solution and extracted with DCM (9 x 50ml). The combined organic extracts were dried over $MgSO_4$, filtered, washed with DCM and concentrated *in vacuo* to give 1-isopropyl-4-hydroxypiperidine (2.41g, 80%) as a pale yellow oil.

Step 2:

1-Isopropyl-4-hydroxypiperidine (1g, 6.98mmol), DCM (10ml) and triethylamine (1.08ml, 7.68mmol) were cooled to 0-5°C and mesyl chloride (0.54ml, 6.98mmol) was added dropwise under N_2. The reaction was allowed to warm to room temperature and stirred for 1hour. The reaction was quenched with sat. $NaHCO_3$ (20ml) and the aqueous phase extracted with DCM (2 x 5ml). The combined organic extracts were dried over $MgSO_4$, filtered, washed with DCM and concentrated *in vacuo* to give the title compound (1.55g, 100%) as a pale yellow oil.

Example 19: [4-[4-(1-Isopropylpiperidin-4-yloxy)phenyl]tetrahydropyran-4-ylmethyl]dimethyl-amine



4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (532mg, 2.26mmol) in DMF (2ml) was added to a solution of NaH (100mg, 2.5mmol) in DMF (2ml) at room temperature under N_2. The reaction was stirred for 1 hr and a solution of methanesulfonic acid 1-isopropyl-piperidin-4-yl ester (400mg, 1.81mmol) in DMF (1.3ml) was slowly added. The reaction was heated to 75°C and stirred for 6hrs. The reaction was

allowed to cool to room temperature and diluted with TBME (20ml), water (10ml) and 5M NaOH solution (10ml). The organic layer was washed with 2.5M NaOH (2 x 20ml), brine (2 x 20ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude reaction was purified by column chromatography, eluting with DCM :MeOH : NH_3 (98 :1 :1) to give the title compound as a white crystalline solid (113mg, 17%).

^1H NMR (400MHz, $CDCl_3$) δ7.20 (d, 2H), 6.87 (d, 2H), 4.27 (m, 1H), 3.75 (dt, 2H), 3.55 (td, 2H), 2.85-2.68 (m, 3H), 2.45-2.32 (m, 2H), 2.40 (s, 2H), 2.14-1.94 (m, 4H), 1.96 (s, 6H), 1.93-1.75 (m, 4H), 1.06 (d, 6H).

Intermediate 22: Methanesulfonic acid 1-cyclopentyl-piperidin-4-yl ester

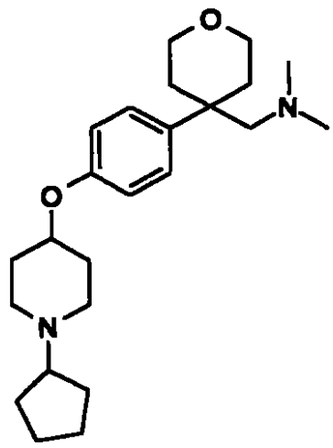
Step 1:

4-Hydroxypiperidine (2.08g, 21.2mmol), K_2CO_3 (5.86g, 2eq.), cyclopentylbromide (11.51g, 77.6mmol, 3.7eq.) and MeOH (20.8ml) were refluxed together overnight. The reaction was allowed to cool to room temperature and quenched with 2M HCl solution (40ml) and extracted with TBME (40ml). The aqueous phase was basified to pH 14 with a 2M NaOH solution and extracted with DCM (4 x 50ml). The combined organic extracts were dried over $MgSO_4$, filtered, washed with DCM and concentrated *in vacuo* to give 1-cyclopentyl-4-hydroxypiperidine (2.55g, 71%) as a pale yellow oil.

Step 2:

1-Cyclopentyl-4-hydroxypiperidine (1g, 5.91mmol), DCM (10ml) and triethylamine (0.91ml, 6.5mmol) were cooled to 0-5°C and mesyl chloride (0.46ml, 5.91mmol) was added dropwise under N_2. The reaction was allowed to warm to room temperature and stirred for 1hour. The reaction was quenched with sat. $NaHCO_3$ (20ml) and the aqueous phase extracted with DCM (2 x 5ml). The combined organic extracts were dried over $MgSO_4$, filtered, washed with DCM and concentrated *in vacuo* to give the title compound (1.38g, 95%) as a pale yellow oil.

Example 20: [4-[4-(1-Cyclopentylpiperidin-4-yloxy)phenyl]tetrahydropyran-4-ylmethyl]dimethylamine

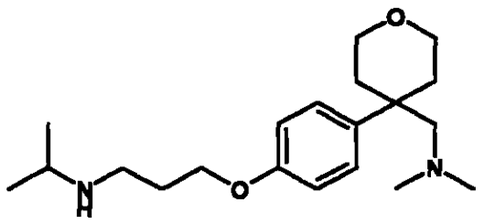


4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (487mg, 2.07mmol) in DMF (2ml) was added to a solution of NaH (100mg, 2.5mmol) in DMF (2ml) at room temperature under N_2. The reaction was stirred for 1 hr and a solution of methanesulfonic acid 1-cyclopentyl-piperidin-4-yl ester (409mg, 1.65mmol) in DMF (1.5ml) was slowly added. The reaction was heated to 75°C and stirred for 6hrs. The reaction was allowed to cool to room temperature and diluted with TBME (20ml), water (10ml) and 5M NaOH solution

(10ml). The organic layer was washed with 2.5M NaOH (2 x 20ml), brine (2 x 20ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude reaction was purified by column chromatography, eluting with DCM :MeOH : NH_3 (98 :1 :1) to give the title compound as a white solid (78mg, 12%).

^1H NMR (400MHz, $CDCl_3$) δ7.20 (d, 2H), 6.87 (d, 2H), 4.28 (m, 1H), 3.75 (dt, 2H), 3.55 (td, 2H), 2.89-2.76 (m, 2H), 2.52 (p, 1H), 2.40 (s, 2H), 2.37-2.25 (m, 2H), 2.14-1.94 (m, 4H), 1.96 (s, 6H), 1.93-1.77 (m, 6H), 1.76-1.34 (m, 6H).

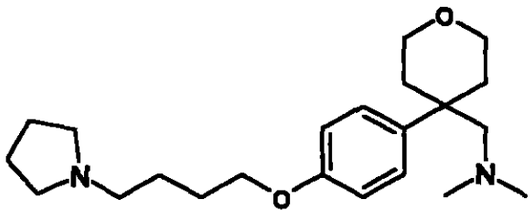
Example 21: (3-[4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenoxy]-propyl)-isopropyl-amine



4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (730mg, 3.10mmol), 3-chloro-1-bromopropane (980mg, 6.20mmol), DMF (10ml) and K_2CO_3 (1.72g, 12.40mmol) were reacted together according to general procedure B. Purification by chromatography on silica, eluant DCM:MeOH (20: 1) provided a mixture of bromo and chloro phenoxy ether (250mg) which was used in the next stage. The mixture (250mg) was refluxed with isopropyl amine (34°C) (10ml, 40vol) for 7 days. The reaction was concentrated *in vacuo* and partitioned between 2M NaOH (10ml) and DCM (10ml). The aqueous phase was extracted with DCM (3 x 10mL). The combined DCM layers were dried over $MgSO_4$, filtered, washed with DCM and concentrated *in vacuo*. Purification by chromatography on silica, eluant DCM :MeOH :NH_3 (95 :5 :0) increasing gradually to DCM :MeOH :NH_3 (90 :9 :1) gave the title compound as a pale yellow solid (180mg, 17% over the 2 steps).

^1H NMR (400MHz, $CDCl_3$) δ7.20 (d, 2H), 6.88 (d, 2H), 4.03 (t, 2H), 3.75 (dt, 2H), 3.59-3.50 (m, 2H), 2.89-2.76 (m, 3H), 2.40 (s, 2H), 2.15-2.05 (m, 2H), 2.03-1.93 (m, 2H), 1.96 (s, 6H), 1.88 (ddd, 2H), 1.49 (br s, 1H), 1.07 (d, 6H).

Example 22: Dimethyl-[4-[4-(4-pyrrolidin-1-yl-butoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-amine

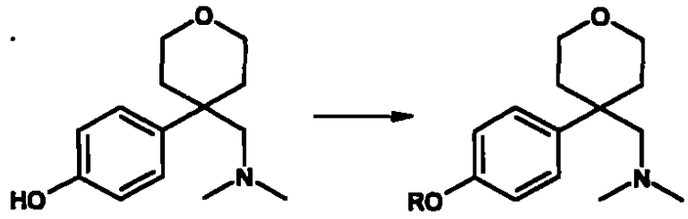


4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (1.5g, 6.38mmol), 1-bromo-4-chlorobutane (1.5ml, 12.77mmol), DMF (20ml) and K_2CO_3 (3.5g, 25.53mmol) were reacted together according to general procedure B. Purification of a fraction of the crude (900mg) by chromatography on alumina, eluant ethyl acetate:heptanes (12: 88) provided a mixture of bromo and chloro phenoxy ether (220mg) which was used in the next stage. The purified mixture (220mg, 0.68mmol) and pyrrolidine (0.17ml, 2.03mmol) were refluxed in EtOH (3ml, 15vol) overnight. The reaction was concentrated *in vacuo* and

partitioned between 2M NaOH (10ml) and ethyl acetate (10ml). The aqueous was extracted with ethyl acetate (3 x 5mL). The combined ethyl acetate layers were washed with brine (3 x 5ml), dried over $MgSO_4$, filtered, washed with ethyl acetate and concentrated *in vacuo*. Purification by chromatography on silica, eluant 95:3:2 (DCM: MeOH: NH_3) followed by a second column eluting with DCM :MeOH :NH_3 (96.5 :3 :0.5), gave the title compound as a colourless oil (134mg, 55%).

^{1}H NMR (400MHz, $CDCl_3$) δ7.21 (d, 2H), 6.86 (d, 2H), 3.97 (t, 2H), 3.75 (dt, 2H), 3.59-3.50 (m, 2H), 2.57-2.45 (m, 6H), 2.40 (s, 2H), 2.14-2.05 (m, 2H), 1.98 (s, 6H), 1.92-1.85 (m, 10H).

General procedure C:

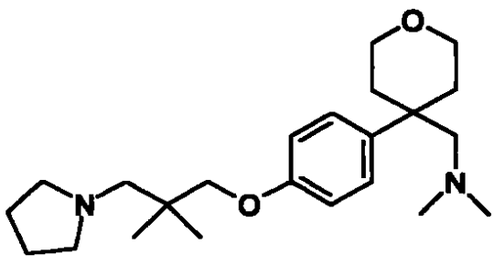


4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (1eq.), alcohol (R-OH) (0.8eq.) and PPh_3 (1eq.) were mixed together in THF (10vol) and cooled to 0°C under N_2. DIAD (1eq.) in THF (10vol) was added slowly to the reaction and allowed to warm to room temperature overnight. The reaction was quenched with 2M HCl solution (10vol) and extracted with ethyl acetate (3 x 10vol). The aqueous phase was basified to pH 14 with NaOH (~30vol) and extracted with ethyl acetate (3 x 10vol). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* at 35°C. Purification of the crude material by chromatography on silica, eluant (10%MeOH in DCM) provided the title compounds.

Intermediate 23: 2,2-Dimethyl-3-pyrrolidin-1-yl-propan-1-ol

Pyrrolidine (1.82g, 25mmol), K_2CO_3 (3.0g, 1.04eq.), 3-bromo-2,2-dimethyl-propan-1-ol (8.45g, 50mmol, 2eq.) were heated together at 90°C overnight. The reaction was allowed to cool to room temperature and quenched with 2M HCl solution (50ml) and extracted with TBME (3 x 50ml). The aqueous phase was basified to pH 14 with 2M NaOH solution and extracted with DCM (3 x 50ml). The combined organic extracts were dried over $MgSO_4$, filtered, washed with DCM and concentrated *in vacuo* to give the title compound (1.03g, 26%) as a pale yellow oil.

Example 23: (4-[4-(2,2-Dimethyl-3-pyrrolidin-1-yl-propoxy)-phenyl]-tetra-hydropyran-4-ylmethyl)-dimethyl-amine



4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (0.28g, 1.19mmol), 2,2-dimethyl-3-pyrrolidin-1-yl-propan-1-ol (0.15g, 0.96mmol), PPh_3 (0.31g, 1.19mmol), THF (3ml) and DIAD (0.24ml, 1.19mmol) were

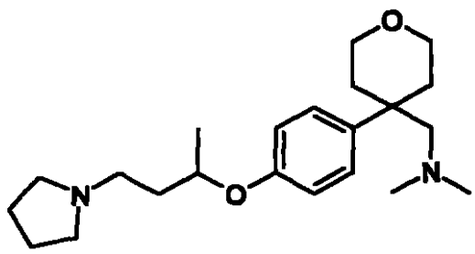
reacted together according to general procedure C. The crude material was subjected to chromatography on silica eluting with DCM :MeOH :NH_3 (97 :2 :1) to provide the title compound (85mg, 24%) as an off-white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.23 (d, 2H), 6.91 (d, 2H), 3.84-3.69 (m, 4H), 3.69-3.54 (m, 2H), 2.67-2.56 (m, 4H), 2.50 (s, 2H), 2.44 (s, 2H), 2.18-2.08 (m, 2H), 2.01 (s, 6H), 1.92 (ddd, 2H), 1.79-1.67 (m, 4H), 1.04 (s, 6H).

Intermediate 24: 4-Pyrrolidin-1-yl-butan-2-ol

Pyrrolidine (2ml, 24mmol), THF (20ml) and methyl vinylketone (2.5ml, 31mmol) were mixed together and stirred overnight. $NaBH_4$ (1.17g, 31mmol) was added to the reaction mixture and stirred for 3hours. The reaction was quenched with water (20ml) and extracted with TBME (2 x 20ml). The combined organic extracts were dried over $MgSO_4$, filtered, washed with TBME and concentrated *in vacuo*. The crude product was purified by column chromatography, eluting with DCM :MeOH :NH_3 (94 :5 :1), to give the title compound as a pale yellow oil (1.3g, 38%).

Example 24: Dimethyl-[4-[4-(1-methyl-3-pyrrolidin-1-ylpropoxy)phenyl]-tetrahydropyran-4-ylmethyl]amine



4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (1.03g, 4.40mmol), 4-pyrrolidin-1-yl-butan-2-ol (0.5g, 3.50mmol), PPh_3 (1.15g, 4.40mmol), THF (10ml) and DIAD (0.86ml, 4.40mmol) were reacted together according to general procedure C. The crude product was purified by preparative HPLC, eluting with acetonitrile/water/0.1%TFA as a gradient, to give the title compound as a yellow oil (125mg, 10%).

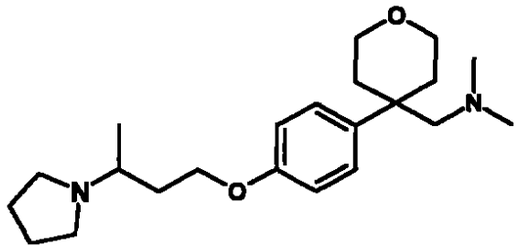
^{1}H NMR (400MHz, $CDCl_3$) δ 7.19 (d, 2H), 6.86 (d, 2H), 4.43 (m, 1H), 3.75 (dt, 2H), 3.60-3.51 (m, 2H), 2.67-2.46 (m, 6H), 2.40 (s, 2H), 2.14-2.04 (m, 2H), 1.97 (s, 6H), 1.93-1.73 (m, 8H), 1.31 (d, 3H).

Intermediate 25: 3-Pyrrolidin-1-yl-butan-1-ol

Pyrrolidine (28.15g, 0.4mol), toluene (200ml), catalytic *p*-TsOH (200mg) and ethyl acetoacetate (20g, 0.15mol) were refluxed together in a Dean-Stark apparatus under N_2 for 3hours. The reaction was cooled to room temperature and concentrated *in vacuo*. $NaBH_4$ (3.1g, 82mmol) was dissolved in MeOH (50ml) and cooled to 0-5°C. A portion of the previous crude reaction (5g, 27mmol) in MeOH (25ml) was added to the reaction mixture and stirred for 72hours. The reaction was quenched with an aqueous solution of NaOH (1%w/w, 50ml) and concentrated *in vacuo*. The aqueous phase was extracted with TBME (3 x 50ml). The combined organic extracts were dried over $MgSO_4$, filtered, washed with TBME and concentrated *in vacuo* to give a mixture of the title compound, 3-pyrrolidin-1-yl-butanoic acid ethyl ester and residual TBME (3.5g). The mixture (3.5g) in THF (20ml) was added to a solution of $LiALH_4$ (1M in THF, 33.5ml, 33.5mmol) at 0-5°C under N_2. The reaction was allowed to warm to room temperature and

stirred for 3hours. The reaction was quenched with an aqueous solution of NaOH (1%w/w, 50ml) at 0-5°C, filtered and washed with THF (3 x 20ml). The combined organic layers were dried over $MgSO_4$, filtered, washed with THF and concentrated *in vacuo* to give the title compound as a yellow oil (2g, 73%).

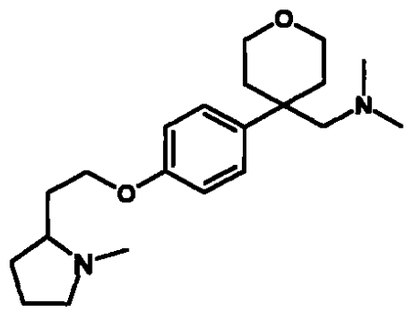
Example 25: Dimethyl-[4-[4-(3-pyrrolidin-1-yl-butoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-amine



4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (925mg, 3.93mmol), 3-pyrrolidin-1-yl-butan-1-ol (450mg, 3.14mmol), PPh_3 (1.03g, 3.93mmol), THF (9ml) and DIAD (0.77ml, 3.93mmol) were reacted together according to general procedure C. The crude material was subjected to chromatography on silica eluting with DCM :MeOH (99.5 :0.5) to provide the title compound (268mg, 24%) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.21 (d, 2H), 6.88 (d, 2H), 4.11-3.97 (m, 2H), 3.75 (dt, 2H), 3.55 (td, 2H), 2.66-2.52 (m, 5H), 2.40 (s, 2H), 2.19-2.05 (m, 3H), 1.96 (s, 6H), 1.83-1.70 (m, 7H), 1.16 (d, 3H).

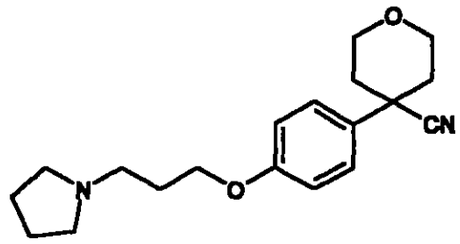
Example 26: Dimethyl-[4-[4-[2-(1-methylpyrrolidin-2-yl)ethoxy]phenyl]-tetrahydropyran-4-ylmethyl]amine



4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (405mg, 1.72mmol), 2-(1-methyl-pyrrolidin-2-yl)-ethanol (178mg, 1.38mmol), PPh_3 (451mg, 1.72mmol), THF (8ml) and DIAD (348mg, 1.72mmol) were reacted together according to general procedure C. The crude product was subjected to chromatography on alumina eluting with ethyl acetate :heptane (50 :50) to provide the title compound (130mg, 27%) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$) δ7.21 (d, 2H), 6.87 (d, 2H), 4.09-3.95 (m, 2H), 3.75 (dt, 2H), 3.55 (td, 2H), 3.09 (m, 1H), 2.40 (s, 2H), 2.35 (s, 3H), 2.30-1.99 (m, 6H), 1.96 (s, 6H), 1.93-1.63 (m, 6H).

Example 27: 4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-carbonitrile



4-(4-Hydroxy-phenyl)-tetrahydro-pyran-4-carbonitrile (2g, 9.88mmol), 1-(3-chloro-propyl)-pyrrolidine (2.33g, 15.78mmol), DMF (40ml) and K_2CO_3 (5.45g, 39.44mmol) were reacted together according to general procedure E. The crude reaction product was diluted with 2M HCl solution (200ml) and washed with ethyl acetate (3 x 50ml). The aqueous phase was basified to pH 14 with 2M NaOH (200ml) and extracted with ethyl acetate (4 x 50ml). The combined organic extracts were dried over $MgSO_4$, filtered, washed with ethyl acetate and concentrated *in vacuo* to give a white solid. The solid was slurried in TBME (15ml) and heptane (15ml), filtered, washed with heptane (8ml) and dried on the filter for 2 hours to give the title compound as a white solid (1.6g, 53%).

^{1}H NMR (400MHz, DMSO-d_6) δ7.43 (d, 2H), 6.99 (d, 2H), 4.08-3.94 (m, 4H), 3.84 (dt, 2H), 2.57-2.47 (m, 2H), 2.46-2.36 (m, 4H), 2.12-1.94 (m, 4H), 1.87 (p, 2H), 1.73-1.62 (m, 4H).

Alternatively, 4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-carbonitrile can be prepared by the following steps:

Step 1:

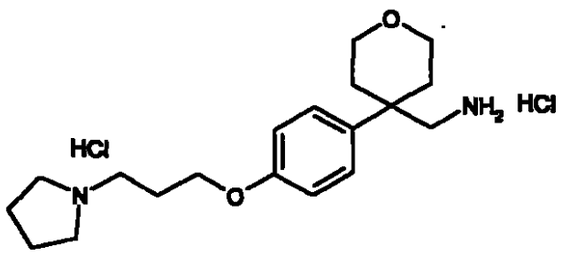
4-Hydroxybenzylcyanide (20 g, 0.15 mol) was dissolved in DMF (500 mL) and then K_2CO_3 (41.4 g, 0.3 mol) and NaI (7.8 g, 0.052 mol) were added followed by dropwise addition of 3-(1-pyrrolidine)-propylchloride (26.5 g, 0.16 mol) at 80 ^{0}C. Heating was continued at 90 ^{0}C for 3 h and then the mixture was heated overnight at 60 ^{0}C. 3-(1-Pyrrolidine)-propylchloride (10 g, 0.067 mol) was again added as the reaction was not complete and heating was continued for a further 6 h. The reaction mixture was concentrated and taken up in EtOAc. The organic layer was washed with water, finally with brine. Crude [4-(3-pyrrolidin-1-ylpropoxy)phenyl]acetonitrile was purified by DCM/MeOH 9.5/0.5 over a silica gel column. Yield: 25.5g (70 %).

^{1} H-NMR (400 MHz, $CDCl_3$) δ 1.77 (m, 4H); 1.98 (m, 2H); 2.50 (m, 4H); 2.59 (t, 2H); 3.66 (s, 2H); 4.00 (t, 2H); 6.87(d, 2H); 7.19(d, 2H).

Step 2:

NaH (14.6 g, 0.61 mol) was suspended in DMF (100 mL). [4-(3-Pyrrolidin-1-ylpropoxy)phenyl]acetonitrile (25.5 g, 0.10 mol) was dissolved in DMF (100 mL) and added dropwise to the ice-cooled suspension of NaH. The reaction mixture was stirred at room temperature for 30 min followed by dropwise addition of 2-bromoethylether (36.2 g, 0.16 mol) in DMF (200 mL) in ice-cold condition. The reaction mixture was poured into ice-cold water. The solid was filtered, washed with water, dried and the resulting solid was washed with 5 % EtOAc in hexane to give the title compound (22 g, 67 %).

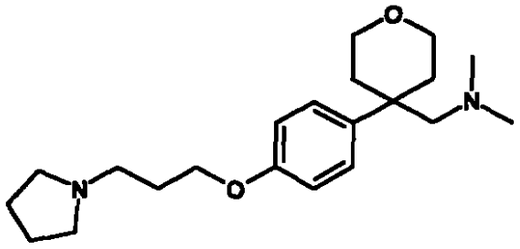
Example 28: {4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine dihydrochloride



To a stirred suspension of $LiAlH_4$ (1.81g, 47.7mmol, 5eq) in Et_2O/DCM (1:1, 30mL) at 0 to 5°C under a nitrogen atmosphere was added 4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-carbonitrile (3g, 9.55 mmol) in Et_2O/DCM (1:1, 30mL) over 15 minutes maintaining the temperature at 5 to 10°C. The reaction mixture was allowed to warm up to ambient temperature and stirred until complete. Sodium hydroxide (2N, 15mL) was added dropwise and the resulting solids were filtered, washed with Et_2O/DCM (1:1, 6 x 50mL) and concentrated *in vacuo* at 40°C. A portion of the crude product from the above reaction (0.5 g, 1.57 mmol) was dissolved in dioxane (5mL) and 4M HCl in dioxane (1.18mL) added under N_2. The reaction was stirred for 3 hours and filtered under a blanket of N_2 (hygroscopic), washed with TBME and dried in the oven at 40°C to give the title compound as a white solid (0.5g, 81%).

^{1}H NMR (400MHz, DMSO-d_6) δ 11.24 (br s, 1H), 8.00 (br s, 3H), 7.33 (d, 2H), 6.98 (d, 2H), 4.08 (t, 2H), 3.76-3.63 (m, 2H), 3.60-3.46 (m, 2H), 3.45-3.18 (m, 4H), 3.07-2.87 (m, 4H), 2.25-1.77 (m, 10H).

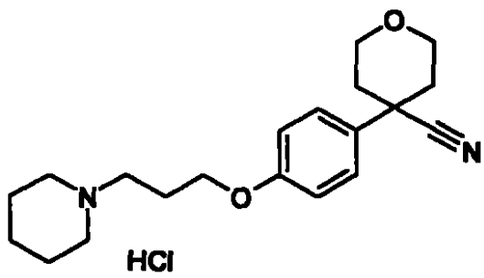
Example 29: Dimethyl-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]-tetrahydro-pyran-4-ylmethyl]amine



To a mixture of {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (2.5g, 7.86 mmol), acetic acid (6ml), and water (12.5ml) was added formaldehyde (11.5ml) and stirred for 15 minutes. STAB (10g, 4.72mmol) was added portionwise and stirred for one hour. Sodium hydroxide (2M, 100ml) was added slowly to attain a pH of 9. The resulting mixture was extracted with DCM (3x100ml) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* at 35°C. The crude mixture was purified by column chromatography on silica eluting with DCM:MeOH:NH_3 (95:4:1) to give the title compound as a white solid (1.09g, 40%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.21 (d, 2H), 6.87 (d, 2H), 4.02 (t, 2H), 3.75 (dt, 2H), 3.55 (td, 2H), 2.65 (t, 2H), 2.56 (br s, 4H), 2.40 (s, 2H), 2.15-1.74 (m, 10H), 1.97 (s, 6H).

Example 30: 4-[4-(3-Piperidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-carbonitrile

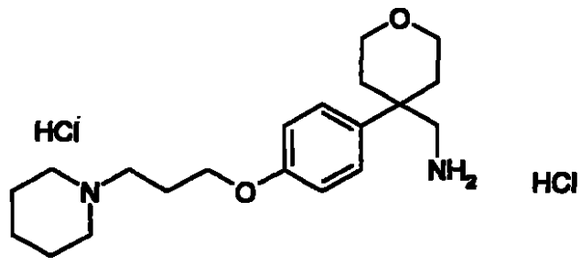


A mixture of 4-(4-hydroxyphenyl)tetrahydro-2H-pyran-4-carbonitrile (1.0 g, 5 mmol), 1-(3-chloropropyl)piperidine (1.2 g, 7.5 mmol) obtained following the procedure described in the *Patent DD 60557*, cesium carbonate (2.4g, 7.5 mmol), KI (1.2 g, 7.5 mmol) in DMF (50 mL) was heated to 70°C overnight. After DMF removal under reduced pressure, the residue was quenched with water and extracted with DCM. The organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (50 g silica gel, DCM / MeOH) to provide the title compound (1.45 g, 88%).

The hydrochloride salt as analytical sample was prepared with ether/HCl 2M in dichloromethane and crystallization in ether.

^{1}H NMR (500MHz, $CDCl_3$) δ 12.14 (bs, 1H), 7.32 (d, 2H), 6.83(d,2H), 4.07 –3.97 (m, 4H), 3.85 –3.78 (m, 2H), 3.57-3.48 (m, 2H), 3.14-3.07 (m, 2H), 2.67 – 2.56 (m, 2H), 2.45 – 2.36 (m, 2H), 2.32 – 2.19 (m, 2H), 2.06 – 1.92 (m, 4H), 1.90-1.75 (m, 4H), 1.43-1.32 (m, 1H).

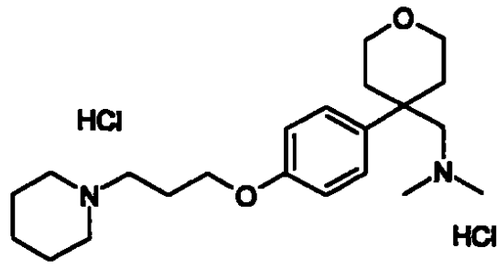
Example 31: [4-[4-(3-Piperidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl] methylamine dihydrochloride



A mixture of 4-[4-(3-piperidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-carbonitrile (1.45 g, 4.4 mmol), isopropanol (12 mL), concentrated HCl (350µL), and PtO_2 (115 mg) was stirred and hydrogenated to 50°C overnight at atmospheric pressure. The mixture was filtrated over diatomaceous earth and concentrated. The residue was dissolved in DCM /MeOH mixture and washed with NaOH (1M). The organic layers were dried over Na_2SO_4, filtered and concentrated, purified by flash chromatography (10 g silica gel, DCM/ MeOH (10% NH_3)) to provide the title compound as free base (0.650 g, 44.5%). This was then converted to the dihydrochloride salt.

^{1}H NMR (400MHz, DMSO-D6) δ 10.66 (bs, 1H), 7.74 (bs, 3H), 7.32 (d, 2H), 6.97 (d, 2H), 4.07 (t, 2H), 3.73-3.65 (m, 2H), 3.47-3.28 (m, 4H), 3.18-3.10 (m, 2H), 2.98-2.81 (m, 4H), 2.25-2.16 (m, 2H), 2.14-2.06 (m, 2H), 1.90-1.67 (m, 7H), 1.44-1.31 (m, 1H).

Example 32: Dimethyl-[4-[4-(3-piperidin-1-ylpropoxy)phenyl]tetrahydro-pyran-4-ylmethyl]amine dihydrochloride



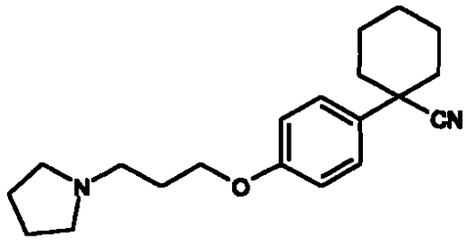
To (0.50 g, 1.5 mmol) of {4-[4-(3-Piperidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine dihydrochloride was added 1.5 mL of formaldehyde (37% w/w solution in H_2O). 1.9 mL of formic acid was added and the mixture was heated to 100°C for 1.5 h. After cooling, water was added and the mixture extracted with ether. NaOH was added to the aqueous phase and the mixture extracted 3 times with ether. The organic extracts were washed with brine, dried over Na_2SO_4 filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (25 g silica gel, DCM/ MeOH/ 10% NH_3). This was then converted to the dihydrochloride salt.

^{1}H NMR (400MHz, DMSO-D6) δ 10.63 (bs, 1H), 9.73 (bs, 1H), 7.43 (d, 2H), 6.99(d, 2H), 4.11-4.03 (t, 2H), 3.76-3.67 (m, 2H), 3.47-3.29 (m, 7H), 3.19-3.11 (m, 2H), 2.92-2.81 (m, 2H), 2.41-2.35 (m, 6H), 2.32-2.16 (m, 4H), 1.95-1.66 (m, 7H), 1.45-1.32 (m, 1H).

Intermediate 28: 1-(4-hydroxyphényl)cyclohexanecarbonitrile

To a solution of 1-(4-methoxyphenyl)cyclohexanecarbonitrile (2 g, 9.29 mmol) in DCM (40 mL) at 0°C under N_2 was added dropwise BBr_3 (2.63 mL, 27.87 mmol). The reaction was allowed to warm to room temperature and stirred for 48hours. The mixture was stirred for 3 hours at 0°C and quenched with water (30 mL). The mixture was separated and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$ then water. The combined organic extracts were dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by column chromatography on silica gel eluting with DCM:acetone (97:3) to give the title compound (1.71 g, 91%).

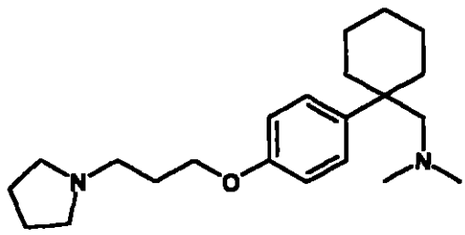
Example 33: 1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexanecarbonitrile



1-(4-Hydroxyphenyl)cyclohexanecarbonitrile (1.70 g, 8.45 mmol), 1-(3-chloro-propyl)-pyrrolidine (1.87 g, 12.67 mmol), acetone (50 mL), sodium iodide (0.444 g, 2.96 mmol) and K_2CO_3 (5.45g, 39.44 mmol) were heated to 50°C overnight. The solvent was evaporated and the crude product was taken into DCM, washed with 0.5N NaOH , extracted with 0.5N HCl solution and washed with DCM. The aqueous layer was basified with 0.5N NaOH and extracted with DCM. The combined organic extracts were dried over

Na_2SO_4, filtered, washed with DCM and concentrated *in vacuo* to give a yellowish solid. The solid was slurried in ether, filtered, washed with ether to give the title compound as a white solid (1.34 g, 51%).
^1H NMR (400MHz, $CDCl_3$) δ 7.30 (d, 2H), 6.83 (d, 2H), 3.95 (t, 2H), 2.64 (t, 2H), 2.44 (m, 4H), 2.08 (m, 2H), 1.92 (m, 2H), 1.84-1.58 (m, 12H).

Example 34: N-{(1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl)methyl}-N,N-dimethylamine



Step 1:
To a stirred suspension of $LiAlH_4$ (0.607 g, 16 mmol) in diethyl ether (15 mL) cooled at 0°C was added dropwise a solution of 1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexanecarbonitrile (1 g, 3.2 *mmol*) in diethyl ether (10 mL). After being stirred at room temperature for 30 min, the reaction mixture was refluxed for another 30 min. The mixture was cooled to 0°C and water (1.38 mL), a 5N aqueous solution of sodium hydroxide (1.38 mL) and water (5.52 mL) again were successively added dropwise. After being stirred for 15 min at room temperature, the mixture was filtered over diatomaceous earth and concentrated. The crude {1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl}methylamine (0.961 g, 95%) was used in the next step without further purification.

Step 2:
To {1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl}methylamine (0.96 g, 3 mmol) was added formic acid (5 mL) followed by formaldehyde (37% w/w solution in H_2O, 0.915 mL, 33 mmol). The mixture was refluxed for 3 h and allowed to stir overnight at room temperature. It was then diluted with DCM, basified to pH 12 with an aqueous solution of NaOH and the mixture was extracted with DCM. The organic extracts were dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by column chromatography on silica gel eluting with a gradient of DCM:MeOH:NH_3 (from 99:0:1 to 90:10:1) to provide the title compound (0.447 g, 43%) as an oil.
^1H NMR (400MHz, $CDCl_3$) δ 7.18 (d, 2H), 6.78 (d, 2H), 3.94 (t, 2H), 2.56 (t, 2H), 2.45 (m, 4H), 2.22 (m, 2H), 2.06-1.86 (m, 10H), 1.72 (m, 4H), 1.58-1.19 (m, 8H).

Intermediate 27: 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carbaldehyde

Step 1:
A solution of 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbonitrile (20g, 0.0636mol) in concentrated hydrochloric acid (200ml, 10vol) was heated and stirred at *reflux* for 16h after which time LC/LCMS analysis showed the reaction had stalled at 85-90% conversion. The solution was evaporated to dryness *in vacuo*, azeotroped with methanol (200ml, 20vol) and toluene (2x 200ml, 2x 20vol) to yield 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carboxylic acid as a beige solid which was used directly (no NMR data recorded).

72

Step 2:

A suspension of 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carboxylic acid (23.5g, 0.0836mol) in methanol (235ml, 10vol) was stirred and cooled to 0 to -5°C under nitrogen. Thionyl chloride (9.3ml, 0.1272mol, 0.40vol) was charged dropwise over 20minutes, maintaining the temperature at -5 to +5°C. The resulting slurry was then heated and stirred at reflux under nitrogen for 16h after which time LC analysis showed 1.4% by area of acid remaining. The solution was evaporated to dryness *in vacuo* at 40°C to give a brown sludge. The sludge was dissolved in ethyl acetate (118ml, 5vol) and water (235ml, 10vol) and the layers separated. The aqueous layer was washed with ethyl acetate (118ml, 5vol) and basified to pH 11 with saturated aqueous potassium carbonate (118ml, 5vol). The product was extracted into dichloromethane (3x 118ml, 3x 5vol) and the combined extracts dried over magnesium sulfate (23g) and concentrated *in vacuo* at 40°C to yield methyl 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carboxylate (21.7g, 98% from the nitrile) as a cream solid.

Step 3:

Anhydrous tetrahydrofuran (141ml, 10vol) was charged rapidly onto stirred and cooled (0-5°C) lithium aluminium hydride (6.2g, 0.1634mol, 0.44wt) under nitrogen. The resulting slurry was cooled to 0-5°C and then a solution of methyl 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carboxylate (14.1g, 0.04058mol) in tetrahydrofuran (99ml, 7vol) was added dropwise over 30 minutes maintaining 0-5°C. On complete addition the reaction was allowed to warm to room temperature over 30 minutes and stirred at 18-25°C for 30 minutes, LC analysis showed the reaction to be complete. The mixture was cooled to 0 to 5°C, a 1:1 mixture of tetrahydrofuran and water (18.6ml, 1.32vol) was added very slowly. The mixture was further quenched with 20% w/v sodium hydroxide solution (6.2ml, 0.44vol) and water (18.6ml, 1.32vol) and the resulting white suspension stirred vigorously for 30 minutes at 18-25°C. The salts were removed by filtration and rinsed with tetrahydrofuran (3x 150ml). The combined filtrates were evaporated to dryness at 40°C to yield {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}methanol (12.1g, 94%) as a white solid.

Step 4:

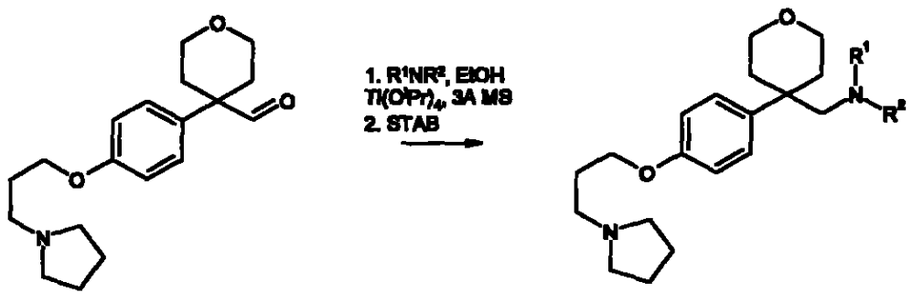
Pyridinium chlorochromate (20.3g, 0.09415mol), 1.69wt) was charged to a stirred suspension of celite (24g, 2wt) and {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}methanol (12.03g, 0.03766mol) in dichloromethane (120ml, 10vol) with stirring. The mixture was stirred at 18-25°C for 3.5 hours after which time LC analysis showed the reaction to be 70% complete. Magnesium sulphate (12g, 1wt) was added and the resulting slurry filtered through a pad of aluminium oxide (activated, basic, Brockmann I, standard grade, ~150 mesh) (481g, 40wt) eluting with 1% methanol/dichloromethane. Clean fractions were combined and evaporated to dryness at 40°C. The resulting brown solid was stirred in *tert*butylmethylether (120ml, 10vol). Undissolved residue was removed by filtration and rinsed with *tert*butylmethylether (3x120ml, 3x 10vol). The combined filtrates were evaporated at 40°C to yield 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbaldehyde (6.0g, 50.2%) as a beige waxy solid.

Alternatively, 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbaldehyde can be prepared as follows:

To a solution of 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carbonitrile (250 mg, 0.79 mmol) in anhydrous toluene (2 mL) at -78°C was added dropwise a 1.5M solution of diisobutyl aluminium hydride in toluene (1.59 mL, 2.38 mmol, 3 equiv). The reaction mixture was stirred for 2 h at -78°C. Ethyl

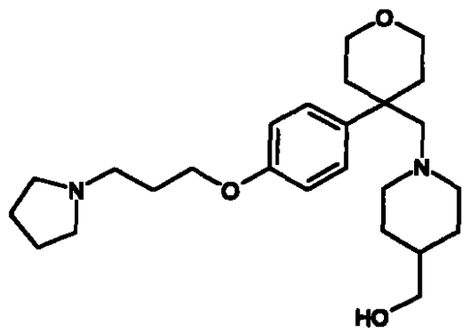
acetate was then added followed by a saturated solution of sodium potassium tartrate and dichloromethane. After stirring at room temperature for 1h, the organic layer was separated. The aqueous layer was extracted three times with dichloromethane. The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure to give an 8:2 mixture of the desired aldehyde and starting nitrile as an orange oil.

General procedure D:



A solution of the 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbaldehyde (700mg, 2.205mmol, 1wt) and secondary amine (NR^1R^2) (4.21mmol) in absolute ethanol (28ml, 40vol) was stirred 18 to 25°C under nitrogen over activated 3Å molecular sieves (700mg, 1wt). Titanium (IV) isopropoxide (3.25ml, 11.025mmol, 4.62vol) was added dropwise over 2 minutes. The resulting solution was stirred at 18 to 25°C under nitrogen for 20 to 24h, over which time precipitation was observed. Sodium triacetoxyborohydride (3.97g, 0.0187mol, 5.67wt) was then added in one portion (Note: not exothermic, but gentle gas evolution was observed) and the reaction was stirred for 1 to 8h until LC analysis showed the reaction to be either complete or stalled at 1-10% aldehyde by area). The reaction mixture was decanted from the sieves and evaporated to dryness *in vacuo* at 40°C. *tert*-Butylmethyl ether (28ml, 40vol), 50% w/v Rochelle's solution (28ml, 40vol) and sat. aqueous potassium carbonate solution (28ml, 40vol) were added and the mixture stirred vigorously for 1 to 2h until two layers were visible (the organic layer was clear, the aqueous cloudy). The layers were separated and the aqueous layer re-extracted with *tert*-butylmethyl ether (28ml, 40vol). The extracts were combined, washed with sat. aqueous sodium chloride solution (28ml, 40vol), dried over magnesium sulfate (700mg, 1wt) and evaporated *in vacuo* at 40°C to yield a viscous oil. The oil was purified by column chromatography on silica (20g, 28.6wt) eluting with DCM(95):MeOH(4):NH_3(1) to remove unreacted aldehyde, alcohol by-product (typically 1-10% by area) and the excess secondary amine to yield the pure product as a viscous oil contaminated by dichloromethane after evaporation. The oil was dissolved in ethanol (5ml, 7.1vol) and evaporated to dryness *in vacuo* at 40°C, then in a vacuum oven at 40°C for 12 to 24h to yield the required tertiary amine product as a viscous oil or waxy solid.

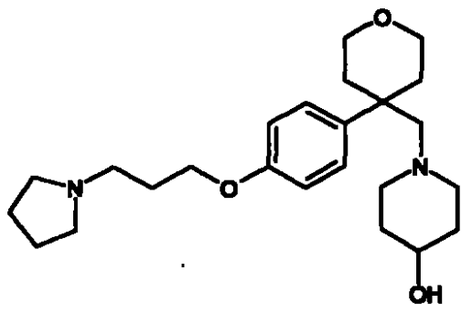
Example 35: (1-[4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl]piperidin-4-yl)-methanol



4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbaldehyde (700mg, 2.205mmol, 1wt), 4-piperidinemethanol (485mg, 4.21mmol), absolute ethanol (28ml, 40vol), activated 3Å molecular sieves (700mg), titanium (IV) isopropoxide (3.25ml, 11.03mmol) and STAB (3.97g, 18.7mmol) was reacted in accordance with the general procedure D. The isolated waxy solid was purified by column chromatography on silica eluting with DCM:MeOH:NH_3 95:4:1 to give the title compound as a colorless oil (820mg, 72%).

^{1}H NMR (400MHz, $CDCl_3$) δ7.20 (d, 2H), 6.85 (d, 2H), 4.02 (t, 2H), 3.75 (dt, 2H), 3.59-3.46 (m, 2H), 3.42 (d, 2H), 2.63 (t, 2H), 2.53 (br s, 4H), 2.39-2.26 (m, 4H), 2.15-1.03 (m, 18H).

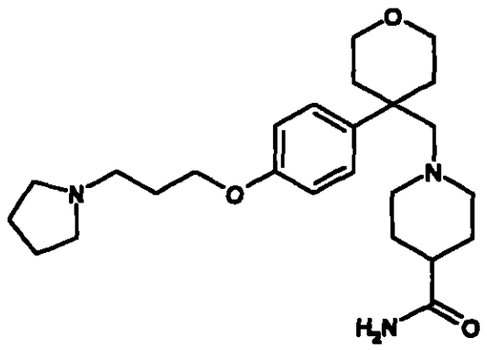
Example 36: 1-[4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl]piperidin-4-ol



4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbaldehyde (420mg, 1.30mmol, 1wt), 4-hydroxypiperidine (268mg, 2.60mmol), absolute ethanol (17ml, 40vol), activated 3Å molecular sieves (420mg), titanium (IV) isopropoxide (1.94ml, 4.62vol) and STAB (2.34g, 11.1mmol) was reacted in accordance with the general procedure D. The isolated waxy solid was purified by preparative HPLC, eluting with acetonitrile/water/0.1%TFA as a gradient, to give the title compound as a white solid (380mg, 73%).

^{1}H NMR (400MHz, $CDCl_3$) δ7.21 (d, 2H), 6.86 (d, 2H), 4.02 (t, 2H), 3.75 (dt, 2H), 3.59-3.47 (m, 2H), 2.63 (t, 2H), 2.53 (br s, 4H), 2.35 (s, 2H), 2.33-2.25 (m, 2H), 2.13-1.96 (m, 6H), 1.93-1.83 (m, 2H), 1.82-1.76 (m, 4H), 1.72-1.59 (m, 3H), 1.47-1.29 (m, 3H).

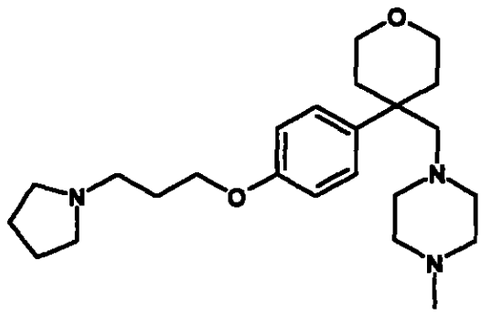
Example 37: 1-[4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-piperidine-4-carboxylic acid amide



4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbaldehyde (500mg, 1.58mmol), isonipecotamide (434mg, 3.03mmol), absolute ethanol (20ml), activated 3Å molecular sieves (500mg), titanium (IV) isopropoxide (2.31ml, 7.88mmol) and STAB (2.84g, 13.6mmol) were reacted in accordance with the general procedure D. The isolated crude product was purified by column chromatography on silica eluting with DCM:MeOH:NH_3 (97:2:1) to give the title compound as a colorless solid (400mg, 59%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.20 (d, 2H), 6.85 (d, 2H), 6.45 (br s, 2H), 4.01 (t, 2H), 3.79-3.69 (m, 2H), 3.57-3.46 (m, 2H), 2.63 (t, 2H), 2.53 (br s, 4H), 2.35 (s, 2H), 2.31 (br s, 1H), 2.14-1.72 (m, 14H), 1.67-1.51 (m, 4H).

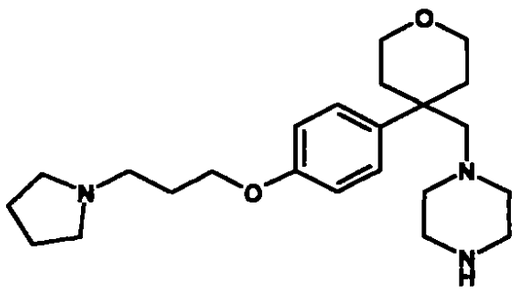
Example 38: 1-Methyl-4-[4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-piperazine



A solution of 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbaldehyde (500mg, 1.58mmol, 1wt), 1-methylpiperazine (300mg, 2.99mmol), absolute ethanol (20ml, 40vol), activated 3Å molecular sieves (500mg), titanium (IV) isopropoxide (2.32ml, 7.83mmol) and STAB (1.43g, 6.73mmol) were reacted in accordance with the general procedure D. The isolated oil was purified by column chromatography on silica (20g, 28.6wt) eluting with DCM(95):MeOH(4):NH_3(1) to give the title compound as a clear viscous oil (360mg, 56%).

^{1}H NMR (400MHz, $CDCl_3$) δ7.21 (d, 2H), 6.86 (d, 2H), 4.02 (t, 2H), 3.75 (dt2H), 3.60-3.47 (m, 2H), 2.63 (t, 2H), 2.53 (br s, 4H), 2.38 (s, 2H), 2.34-2.14 (m, 11H), 2.13-1.73 (m, 10H).

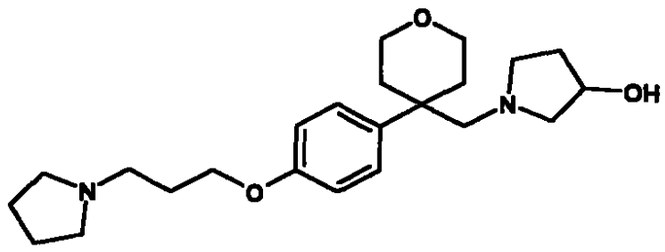
Example 39: 1-[4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl]piperazine



4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbaldehyde (350mg, 1.103mmol), 4-piperazine-1-carboxylic acid *tert*-butyl ester (372mg, 1.98mmol), absolute ethanol (40ml), activated 3Å molecular sieves (350mg), titanium (*IV*) isopropoxide (1.62ml, 5.48mmol) and STAB (2.0g, 9.74mmol) were reacted in accordance with the general procedure D. The isolated crude product was purified by column chromatography on silica eluting with DCM:MeOH:NH_3 (98:1:1) to give a white solid (295mg, 69%). This was re-dissolved in methanol (3.2ml) and 1,4-dioxane (8ml), HCl in dioxane (4M, 1.95ml) was added. The mixture was stirred overnight and concentrated *in vacuo* at 40°C. TBME (13ml) and NaOH (2M aqueous) were added to attain a pH of 12-14. The organic phase was separated and dried over $MgSO_4$ and concentrated *in vacuo* at 35°C. The crude product was subjected to chromatography on silica eluting with DCM:MeOH:NH_3 (94:4:2) to give the title compound as a yellow oil (100mg, 23%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.21 (d, 2H), 6.85 (d, 2H), 4.02 (t, 2H), 3.80-3.70 (m, 2H), 3.58-3.48 (m, 2H), 2.73-2.66 (m, 4H), 2.63 (t, 2H), 2.53 (br s, 4H), 2.34 (s, 2H), 2.17-1.48 (m, 15H).

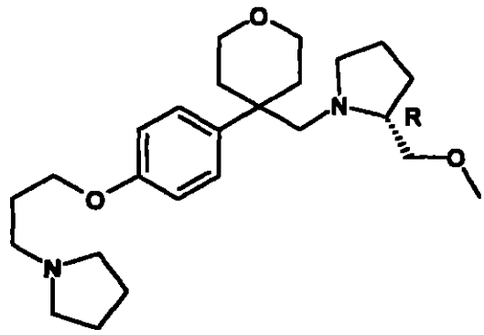
Example 40: 1-[4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl]pyrrolidin-3-ol



4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbaldehyde (350mg, 1.103mmol), 3-pyrrolidinol (200mg, 2.02mmol), absolute ethanol (40ml), activated 3Å molecular sieves (350mg), titanium (IV) isopropoxide (1.62ml, 5.48mmol) and STAB (2.0g, 9.74mmol) were reacted in accordance with the general procedure D. The isolated crude product was purified by column chromatography on silica eluting with DCM:MeOH:NH_3 (97:2:1) to give the title compound as a white solid (390mg, 91%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.20 (d, 2H), 6.87 (d, 2H), 4.10-4.01 (m, 3H), 3.81-3.68 (m, 3H), 3.55 (t, 2H), 2.67-2.48 (m, 9H), 2.26-1.61 (m, 15H).

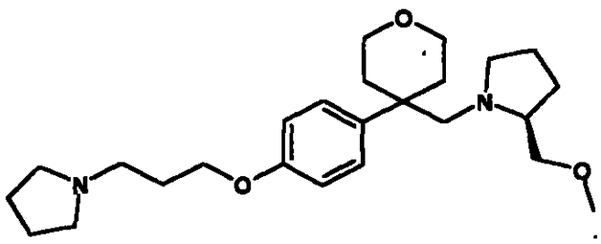
Example 41: (R)-2-Methoxymethyl-1-[4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-pyrrolidine



4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbaldehyde (500mg, 1.575mmol), (R)-2-(methoxymethyl)pyrrolidine (347mg, 4.21mmol), absolute ethanol (20ml), activated 3Å molecular sieves (500mg), titanium (IV) isopropoxide (2.33ml, 7.88mmol) and STAB (2.84g, 13.4mmol) were reacted in accordance with the general procedure D. The isolated waxy solid was purified by column chromatography on silica eluting with DCM:MeOH:NH_3 95:14:1 to give the title compound as a viscous pale yellow oil (390mg, 59%).

^{1}H NMR (400MHz, $CDCl_3$) δ7.18 (d, 2H), 6.86 (d, 2H), 4.02 (t, 2H), 3.85-3.69 (m, 2H), 3.59 (td, 1H), 3.45 (td, 1H), 3.27 (s, 3H), 3.10 (dd, 1H), 3.02 (dd, 1H), 2.94 (d, 1H), 2.63 (t, 2H), 2.58-2.45 (m, 6H), 2.39 (m,1H), 2.21 (m, 1H), 2.07-1.87 (m, 11H), 1.57-1.33 (m, 3H).

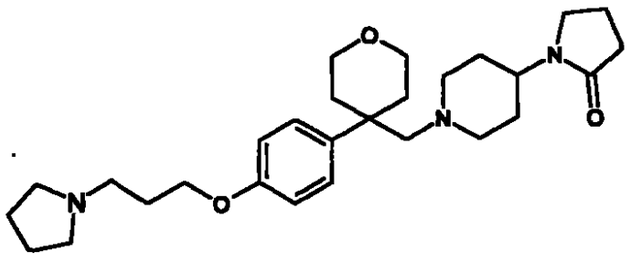
Example 42: (S)-2-Methoxymethyl-1-(4-[4-(3-pyrrolidin-1-ylpropoxy)-phenyl]tetrahydropyran-4-ylmethyl)pyrrolidine



4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbaldehyde (350mg, 1.103mmol), (s)-(+)-2-(methoxymethyl)pyrrolidine (230mg, 2.00mmol), absolute ethanol (40ml), activated 3Å molecular sieves (350mg), titanium (IV) isopropoxide (1.62ml, 5.48mmol) and STAB (2.0g, 9.74mmol) were reacted in accordance with the general procedure D. The isolated crude product was purified by column chromatography on silica eluting with DCM:MeOH:NH_3 (98:1:1) to give the title compound as a white solid (330mg, 72%).

^{1}H NMR (400MHz, $CDCl_3$) δ7.18 (d, 2H), 6.86 (d, 2H), 4.02 (t, 2H), 3.84-3.70 (m, 2H), 3.59 (td, 1H), 3.45 (td, 1H), 3.27 (s, 3H), 3.10 (dd, 1H), 3.02 (dd, 1H), 2.94 (d, 1H), 2.63 (t, 2H), 2.59-2.45 (m, 5H), 2.39 (m,1H), 2.21 (m, 1H), 2.08-1.34 (m, 15H).

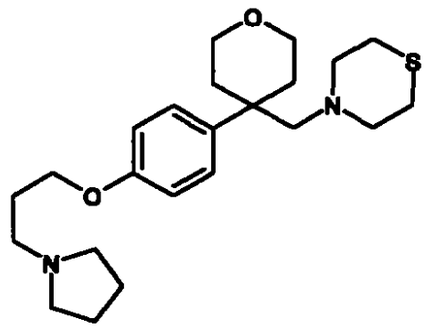
Example 43: 1-(1-[4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl]piperidin-4-yl)pyrrolidin-2-one



4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbaldehyde (400mg, 1.280mmol), 4-(N-2-pyrrolidinone)piperidine hydrochloride (493mg, 4.407mmol), absolute ethanol (16ml), activated 3Å molecular sieves (400mg), titanium (IV) isopropoxide (1.86ml, 6.30mmol) and STAB (2.27g, 10.71mmol) were reacted in accordance with the general procedure D. The isolated waxy solid was purified by column chromatography on silica eluting with DCM(95):MeOH(4):NH_3(1) to give the title compound as a pale yellow oil (133mg, 22%).

^{1}H NMR (400MHz, $CDCl_3$) δ7.20 (d, 2H), 6.86 (d, 2H), 4.02 (t, 2H), 3.83-3.71 (m, 3H), 3.62 (dt, 2H), 3.32 (t, 2H), 2.63 (t, 2H), 2.53 (br s, 4H), 2.41-2.30 (m, 6H), 2.18 (dt, 2H), 2.12-1.36 (m, 16H).

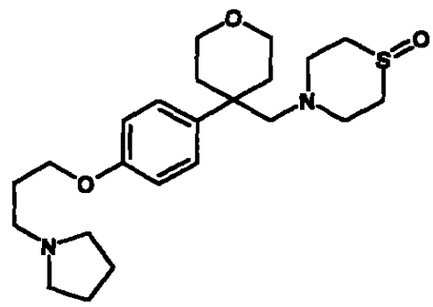
Example 44: 4-[4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-thiomorpholine



4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbaldehyde (1.5g, 4.728mmol, 1wt), thiomorpholine (930mg, 9.027mmol), absolute ethanol (60ml), activated 3Å molecular sieves (1.5g), titanium (IV) isopropoxide (6.97ml, 23.630mmol) and STAB (6.51g, 40.15mmol) were reacted in accordance with the general procedure D. The isolated waxy solid was purified by column chromatography on silica eluting with DCM(95):MeOH(4):NH_3(1) to give the title compound as a pale yellow oil (1.08g, 55%).

^{1}H NMR (400MHz, $CDCl_3$) δ7.20 (d, 2H), 6.86 (d, 2H), 4.02 (t, 2H), 3.75 (dt, 2H), 3.57-3.45 (m, 2H), 2.63 (t, 2H), 2.59-2.39 (m, 12H), 2.36 (s, 2H), 2.14-1.95 (m, 4H), 1.92-1.73 (m, 6H).

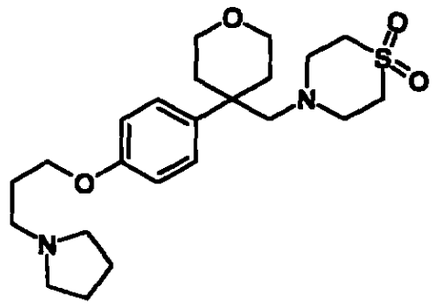
Example 45: 4-[4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl]thiomorpholine-1-oxide



To a solution of 4-[4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-thiomorpholine (200mg, 0.494mmol) in TFA (0.67ml) at 5 to 10°C was added dropwise a solution of trifluoro-peracetic acid [4M solution prepared by the addition of 27.5% H_2O_2 (0.94ml) to TFA (1.56ml)] and stirred at 5 to 10°C for 1 hour. The reaction mixture was diluted with DCM (5ml) and NaOH (5M solution, 4ml) was added to attain pH14. The mixture was extracted with DCM ((2x5ml), the combined DCM extracts were washed with saturated aqueous brine (10ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The isolated yellow oil was purified by column chromatography on silica eluting with DCM(95):MeOH(4):NH_3(1) to give the title compound as a yellow oil (165mg, 79%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.20 (d, 2H), 6.87 (d, 2H), 4.02 (t, 2H), 3.81-3.69 (m, 2H), 3.59-3.43 (m, 2H), 2.99-2.82 (m, 2H), 2.76-2.2.59 (m, 6H), 2.53 (br s, 4H), 2.46 (s, 2H), 2.31-1.73 (m, 12H).

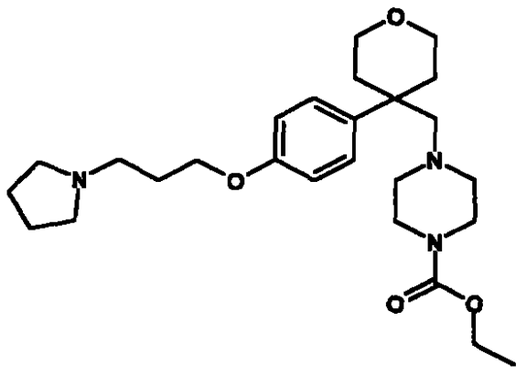
Example 46: 4-[4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-thiomorpholine 1,1-dioxide



To a solution of 4-[4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-thiomorpholine (230mg, 0.56mmol) in TFA (0.77ml) at 0 to 5°C was added dropwise a solution of trifluoro-peracetic acid [4M solution prepared by the addition of 27.5% H_2O_2 (0.94ml) to TFA (1.56ml)]. The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was cooled to 0 to 5°C, diluted with DCM (5ml) and quenched with NaOH (5M solution, 5ml) to attain pH14. The mixture was extracted with DCM (4x5ml), the combined DCM extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The isolated yellow oil was purified by column chromatography on silica eluting with DCM(95):MeOH(4):NH_3(1) to give the title compound as a colourless oil (96.6mg, 39%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.20 (d, 2H), 6.88 (d, 2H), 4.02 (t, 2H), 3.76 (dt, J = 11 and 4Hz, 2H), 3.57-3.45 (m, 2H), 2.89-2.79 (m, 4H), 2.73-2.65 (m, 4H), 2.63 (t, 2H), 2.55 (br s, 4H), 2.53 (s, 2H), 2.22-2.11 (m, 2H), 2.01 (m, 2H), 1.87-1.73 (m, 6H).

Example 47: 4-[4-[4-(3-Pyrrolidin-1-yl-propoxy)phenyl]tetrahydropyran-4-ylmethyl]-piperazine-1-carboxylic acid ethyl ester



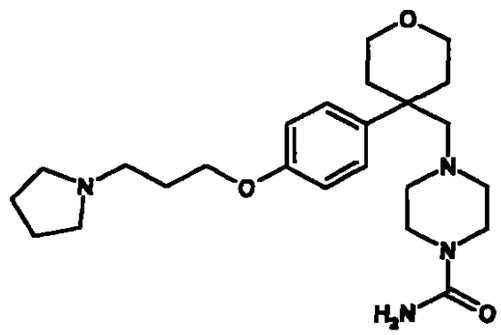
4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbaldehyde (500mg, 1.55mmol), ethyl piperazine-1-carboxylate (471mg, 3.00mmol), absolute ethanol (20ml), activated 3Å molecular sieves (500mg), titanium (IV) isopropoxide (2.31ml, 7.88mmol) and STAB (2.84g, 13.6mmol) were reacted in accordance with the general procedure D. The isolated crude product was purified by column chromatography on silica eluting with DCM:MeOH:NH_3 (97:2:1) to give the title compound as a white solid containing residual 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbaldehyde (350mg). The material was dissolved in DCM (14ml) and PS-AMPS (loading 2.04mmol^{-1}g, 23mg) was added and shaken for 24 hours. The resin was filtered and the solution concentrated *in vacuo* at 30°C, the crude material was subjected to chromatography on silica eluting with DCM:MeOH:NH_3 (97:2:1) to give the title compound as a white solid (130mg, 18%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.20 (d, 2H), 6.86 (d, 2H), 4.08 (q, 2H), 4.02 (t, 2H), 3.79-3.70 (m, 2H), 3.67-3.47 (m, 2H), 3.27 (br s, 4H), 2.63 (t, 2H), 2.53 (br s, 4H), 2.38 (s, 2H), 2.21-1.73 (m, 14H), 1.21 (t, 3H).

Intermediate 28: Piperazine-1-carboxylic acid amide hydrochloride

4-Piperazine-1-carboxylic acid *tert*-butyl ester (1.0g, 5.4mmol), acetic acid (3ml) and water (5ml) were mixed together. Potassium cyanate (2.25g, 27.7mmol) was added portionwise as a solution in water (5ml) and stirred for 4 hours, during which time a solid precipitated. The solid was filtered, re-dissolved in DCM (20ml), dried over $MgSO_4$, filtered, the filter cake washed with DCM (5vol) and concentrated *in vacuo* to give a white solid (0.38g). The white solid (0.38g) was dissolved in methanol (3.8ml) and 1,4-dioxane (0.7ml), 4M HCl in 1,4-dioxane (2.5ml, 10mmol) was added to the reaction and stirred overnight. The reaction was concentrated *in vacuo* to give the title compound (0.28g, 31% over 2 steps) as a white solid.

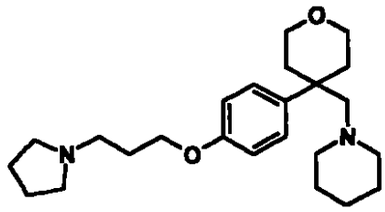
Example 48: 4-[4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl]-piperazine-1-carboxylic acid amide



4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbaldehyde (317mg, 1mmol), piperazine-1-carboxylic acid amide hydrochloride (273mg, 1.85mmol), absolute ethanol (12.7ml), activated 3Å molecular sieves (320mg), Et_3N (0.278ml), titanium (IV) isopropoxide (1.46ml, 5.20mmol) and STAB (1.8g, 8.5mmol) were reacted in accordance with the general procedure D. The isolated crude product was purified by column chromatography on silica eluting with DCM:MeOH:NH_3 (98:1:1) to give the title compound as a off white solid (70mg, 16%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.21 (d, 2H), 6.86 (d, 2H), 4.30 (br s, 2H), 4.02 (t, 2H), 3.80-3.71 (m, 2H), 3.58-3.48 (m, 2H), 3.23-3.15 (m, 4H), 2.63 (t, 2H), 2.53 (br s, 4H), 2.40 (s, 2H), 2.19-1.73 (m, 14H).

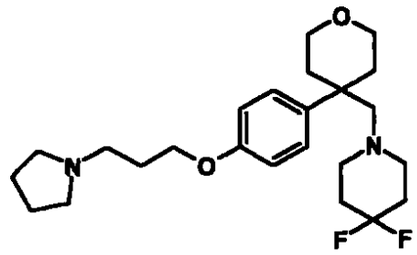
Example 49: 1-[4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl]-piperidine



4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbaldehyde (272 mg, 0.86 mmol), piperidine (0.161 mL, 1.63 mmol), absolute ethanol (11 mL), activated 4Å molecular sieves, titanium (IV) isopropoxide (1.205 mL, 4.28 mmol) and STAB (1.54 g, 7.28 mmol) were reacted in accordance with the general procedure D. The isolated waxy solid was purified by column chromatography on silica eluting with a gradient of DCM:MeOH:NH_3 (from 99:0:1 to 90:9:1) to give the title compound (97.4 mg, 25%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.21(d, 2H), 6.85 (d, 2H), 4.02 (t, 2H), 3.77 –3.72 (m, 2H), 3.64 –3.48 (t, 2H), 2.63 (t, 2H), 2.53 (m, 4H), 2.29 (s, 2H), 2.13-1.87 (m, 10H), 1.79 (quint, 4H), 1.41-1.36 (m, 4H), 1.30-1.26 (m, 2H).

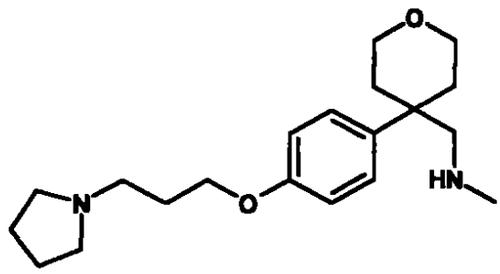
Example 50: 4,4-difluoro-1-[4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetra-hydropyran-4-ylmethyl]-piperidine



4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbaldehyde (260 mg, 0.82 mmol), 4,4-difluoropiperidine hydrochloride (323 mg, 2.05 mmol), absolute ethanol (11 mL), activated 4Å molecular sieves, titanium (IV) isopropoxide (1.209 mL, 4.09 mmol) and STAB (1.475 g, 6.96 mmol) were reacted in accordance with the general procedure D. The isolated waxy solid was purified by reverse phase preparative HPLC on a Xterra column eluting with a gradient of MeCN:H_2O:Et_3N (from 29.9:70:0.1 to 94.9:5:0.1 in 13 min) to give the title compound (26 mg, 6%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.21(d, 2H), 6.88 (d, 2H), 4.02 (t, 2H), 3.77 –3.73 (m, 2H), 3.53 –3.47 (t, 2H), 2.64 (t, 2H), 2.54 (m, 4H), 2.39 (s, 2H), 2.30-2.24 (m, 6H), 2.13 (d, 2H), 2.02 (m, 2H), 1.90-1.71 (m, 6H).

Example 81: methyl-{4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]-tetrahydropyran-4-ylmethyl}amine



Step 1:

To a stirred solution of {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (10.83 g, 34.05 mmol) and triethylamine (10.31 g, 102.16 mmol) in dry dichloromethane at 0 ° C was added dropwise a solution of di-*tert*-butyldicarbonate (9.65 g, 44.27 mmol) in dry dichloromethane. Stirring was continued for another hour at 0 °C and then overnight at room temperature. The reaction mixture was then diluted with dichloromethane, washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure to provide a crude product. The crude product was purified by column chromatography on silica gel (EtOAc-MeOH-Et_3N) to give methyl-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-pyran-4-ylmethyl]carbamic acid *tert*-butyl ester (9.80 g, 69 % yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 9H); 1.75-1.88 (m, 6H); 1.96-2.07 (m, 4H); 2.48-2.56 (m, 4H); 2.61 (t, 2H); 3.28 (d, 2H); 3.51-3.59 (m, 2H); 3.76-3.80 (m, 2H); 4.01 (t, 2H); 4.15 (brm, 1H); 6.89 (d, 2H); 7.16 (d, 2H).

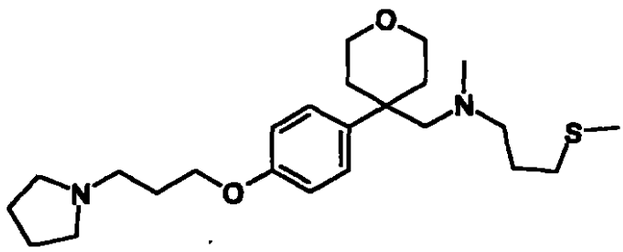
Step 2:

To a stirred solution of $LiAlH_4$ (2.59 g, 68.18 mmol) in dry THF at 0 ° C was added dropwise a solution of methyl-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-pyran-4-ylmethyl]carbamic acid *tert*-butyl ester (9.50 g, 22.72 mmol). The reaction mixture was then brought to room temperature and finally heated to

reflux for 3 h. The reaction mixture was quenched with aqueous NaOH solution and filtered over a short pad of celite, dried over Na_2SO_4 and concentrated under reduced pressure to provide the title compound (7.1 g, 84 % yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71-1.78 (m, 4H); 1.80-1.90 (m, 2H); 1.88-2.02 (m, 2H); 2.06-2.14 (m, 2H); 2.23 (s, 3H); 2.46-2.53 (m, 4H); 2.51-2.63 (m, 4H); 3.47- 3.56 (m, 2H); 3.70-3.77 (m, 2H); 3.99 (t, 2H); 6.86 (d, 2H); 7.17 (d, 2H).

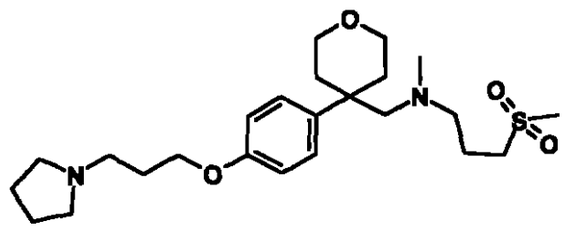
Example 52: methyl-(3-methylsulfanyl-propyl)-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl]amine



To a solution of methyl-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl]amine (200 mg, 0.629 mmol) in dichloroethane (5 mL) under nitrogen atmosphere was added acetic acid (45 mg, 1.258 mmol), triethylamine (76 mg, 1.258 mmol) and 3-(methylthio)propanal (108 mg, 1.04 mmol). The mixture was stirred for 30 min and a solution of $NaHB(OAc)_3$ (238 mg, 1.15 mmol) in dichloroethane (5 mL) was added. After stirring at room temperature overnight, the reaction mixture was filtered over celite, concentrated *in vacuo* and purified by column chromatography on silica gel eluting with DCM:MeOH:NH_3 (94.9:5:0.1) to give the title compound (29 mg, 7%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.19 (d, 2H), 6.86 H), 4.02 (t, 2H), 3.78 - 3.73 (m, 2H), 3.54 - 3.49 (m, 2H), 2.67 (t, 2H), 2.59 (m, 4H), 2.42 (s, 2H), 2.35 (t, 2H), 2.22 (t, 2H), 2.11 - 2.00 (m, 7H), 1.91-1.86 (m, 6H), 1.85- 1.82 (m, 4H), 1.56 (q, 2H).

Example 53: (3-methanesulfonyl-propyl)-methyl-[4-[4-(3-pyrrolidin-1-yl-propoxy)phenyl]tetrahydropyran-4-ylmethyl]amine

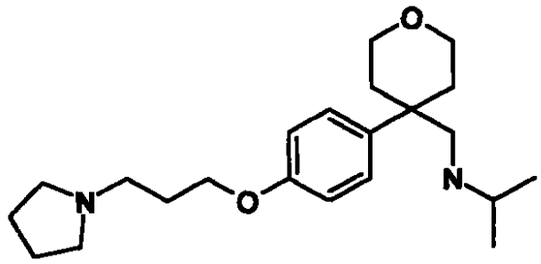


To a solution of methyl-(3-methylsulfanyl-propyl)-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl]amine (170 mg, 0.404 mmol) in DCM (10 mL) under nitrogen atmosphere at 0°C was added TFA (0.240 mL, 3.2 mmol) followed by meta-chloroperbenzoic acid (70% pure, 199 mg, 0.808 mmol). The reaction mixture was stirred overnight allowing it to warm up to room temperature. It was quenched with an aqueous solution of Na_2S2O_3. The organic layer was separated and washed with an aqueous solution of $NaHCO_3$. The organic layer was then dried over sodium sulphate, filtered, concentrated and purified by

column chromatography on silica gel eluting with DCM:MeOH:NH_3 (89.9:10:0.1) to give the title compound.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.18 (d, 2H), 6.88 (d, 2H), 4.03 (t, 2H), 3.78 - 3.73 (m, 2H), 3.53 - 3.48 (m, 2H), 2.82 (s, 3H), 2.69-2.73 (m, 2H), 2.65 (m, 2H), 2.55 (m, 4H), 2.47 (s, 2H), 2.22 (t, 2H), 2.12 - 2.09 (m, 2H), 1.89 – 2.05 (m, 5H), 1.68-1.85 (m, 8H).

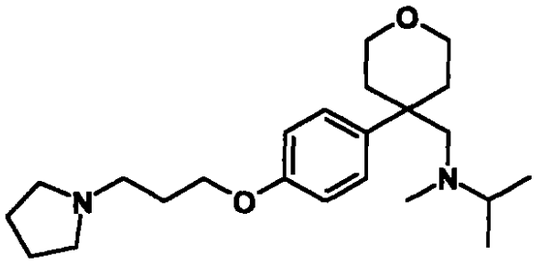
Example 64: Isopropyl-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]-tetrahydro-pyran-4-ylmethyl]amine



To a solution of {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (400 mg, 1.256 mmol) in dichloroethane (10 mL) under nitrogen atmosphere was added acetic acid (180.5 mg, 2.76 mmol), triethylamine (308.4 mg, 2.76 mmol) and acetone (80.2 mg, 1.38 mmol). The mixture was stirred for 1 h at ambient temperature and $NaHB(OAc)_3$ (601 mg, 2.76 mmol) was added. After stirring overnight, the reaction mixture was filtered over celite, concentrated *in vacuo* and purified by column chromatography on silica gel eluting with DCM:MeOH:NH_3 (89:10:1) to give the title compound as an oil (282 mg, 60%).

^{1}H NMR (400 MHz, CDCl3) δ 7.13 (d, 2H), 6.82 (d, 2H), 3.96 (t, 2H), 3.68 (m, 2H), 3.49 (m, 2H), 2.61 (s, 2H), 2.56 (t, 2H), 2.46 (m, 6H), 2.04 (m, 2H), 1.94 (m, 2H), 1.84 (m, 2H), 1.72 (m, 4H), 1.19 (s, 1H), 0.83 (d, 6H).

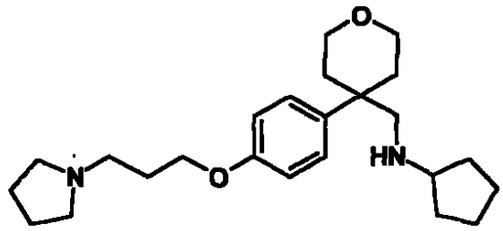
Example 65: Isopropyl-methyl-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]-tetrahydropyran-4-ylmethyl]amine



To Isopropyl-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl]-amine (258 mg, 0.71 mmol) was added formaldehyde (37% w/w solution in H_2O, 1 mL) and formic acid (1.5 mL).The resulting mixture was heated to 60°C overnight. After cooling, H_2O and ethyl acetate were added. The aqueous layer was separated, basified with 30% NaOH and extracted 3 times with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound as an oil (170 mg, 65%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.19 (d, 2H), 6.86 (d, 2H), 4.02 (t, 2H), 3.76 (m, 2H), 3.50 (m, 2H), 2.63 (t, 2H), 2.53 (m, 4H), 2.44 (m, 1H), 2.38 (s, 2H), 2.08 (m, 2H), 2.01 (m, 2H), 1.69 (m, 2H), 1.65 (s, 3H), 1.79 (m, 4H), 0.84 (d, 6H).

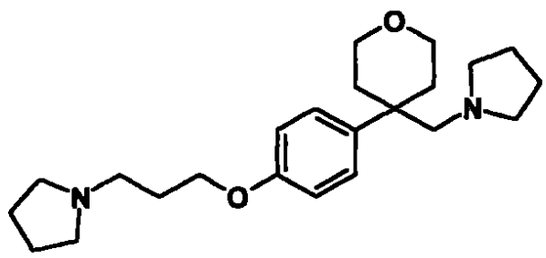
Example 56: cyclopentyl-{4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetra-hydropyran-4-ylmethyl}amine



To a solution of {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (254 mg, 0.798 mmol) in dichloroethane (5 mL) under nitrogen atmosphere were added acetic acid (37 mg, 1.6 mmol), triethylamine (97 mg, 1.6 mmol) and cyclopentanone (10 mg, 1.19 mmol). The mixture was stirred for 30 min at ambient temperature and $NaHB(OAc)_3$ (204 mg, 1.6 mmol) was added at 0°C. After stirring overnight, the reaction mixture was filtered over celite, concentrated *in vacuo* and purified by column chromatography on silica gel eluting with DCM:MeOH:NH_3 (89:10:1) to give the title compound (226 mg, 58%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.20 (d, 2H), 6.88 H), 4.03 (t, 2H), 3.78-3.73 (m, 2H), 3.59-3.53 (m, 2H), 2.84 (q, 1H), 2.73 (t, 2H), 2.65-2.68 (m, 6H), 2.03-2.12 (m, 4H), 1.84-1.94 (m, 6H), 1.65–1.72 (m, 2H), 1.51-1.58 (m, 2H), 1.41-1.48 (m, 2H), 1.07-1.16 (m, 2H).

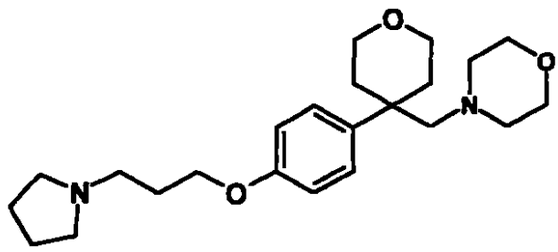
Example 57: 1-{4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl}pyrrolidine



To a stirred solution of {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (150 mg, 0.47 mmol) and 1-bromo-4-chloroethane (54.2 µL, 0.47 mmol) in anhydrous acetonitrile (5 mL) was added potassium carbonate (65 mg, 0.47 mmol). The mixture was heated to 60°C overnight then concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with DCM:MeOH:NH_3 (94:5:1) to give the title compound (40 mg, 23 % yield).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.20 (d, 2H), 6.86 (d, 2H), 4.02 (t, 2H), 3.73 –3.78 (m, 2H), 3.57-3.63 (m, 2H), 2.65 –2.61 (m, 4H), 2.53 (m, 4H), 2.20 (m, 4H), 2.10 – 1.88 (m, 6H), 1.56 (m, 4H).

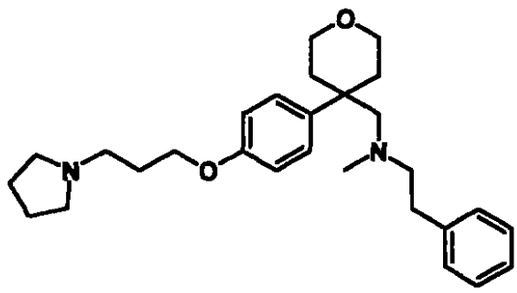
Example 58: 4-{4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl}-morpholine



To a stirred solution of {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (207 mg, 0.65 mmol) and bis(2-bromoethyl)ether (82 µL, 1.3 mmol) in anhydrous acetonitrile (10 mL) was added potassium carbonate (180 mg, 1.3 mmol). The mixture was heated to 60°C overnight then concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with DCM:MeOH (97:3) with 10% NH_3 to give the title compound (90 mg, 23 % yield).

^{1}H NMR (400MHZ, $CDCl_3$) δ 7.22 (d, 2H), 6.83 (d, 2H), 4.04 (m, 2H), 3.73 (m, 2H), 3.51 (m, 6H), 3 (m, 6H), 2.38 (m, 2H), 2.25 (m, 2H), 2.13 – 2.03 (m, 10H), 1.88 (m, 2H).

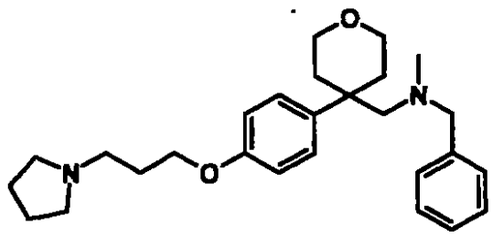
Example 59 : methyl-phenethyl-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetra-hydropyran-4-ylmethyl]amine



Methyl-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl]amine (150 mg, 0.45 mmol) was treated with (2-bromoethyl)benzene (100 mg, 0.54 mmol) and potassium carbonate (187 mg, 1.35 mmol) in a sealed tube under microwave (Smith Personal Synthesiser) (55°C) for 60 min. The reaction mixture was taken in DCM (10 mL) and water (5 mL). The organic layer was separated and washed twice with water and brine. The combined organic extracts were dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by column chromatography on silica gel eluting with DCM:MeOH (90:10) with 10% NH_3 to give the title compound as a colorless oil (41.4 mg, 20%).

^{1}H NMR (400MHz,$CDCl_3$) δ 7.23 (m, 7H), 6.87 (d, 2H), 4.00 (t, 2H), 3.66 (m, 2H), 3.51 (m, 2H), 3.29 (t, 2H), 3.20 (t, 2H), 2.62 (t, 2H), 2.51 (m, 6H), 2.10 (m, 2H), 1.99 (m, 2H), 1.90 (m, 2H), 1.66 (s, 3H), 1.78 (m, 4H).

Example 60 : methyl-benzyl-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetra-hydropyran-4-ylmethyl]amine

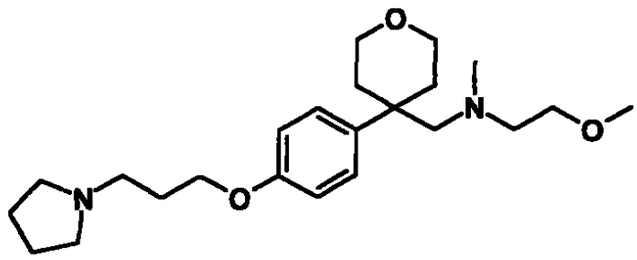


This example was prepared from methyl-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl]amine similarly to the procedure used for example 59.

^{1}H NMR (400MHz, $CDCl_3$) δ7.28-7.19 (m, 7H), 6.87 (d, 2H), 4.00 (t, 2H), 3.69-3.65 (m, 2H), 3.53-3.48 (t,

2H), 3.29 (s, 2H), 2.61 (t, 2H), 2.54-2.50 (m, 6H), 2.10-2.07 (m, 2H), 2.01-1.97 (m, 2H), 1.93-1.88 (m, 2H), 1.86 (s, 3H), 1.78-1.76 (m, 4H).

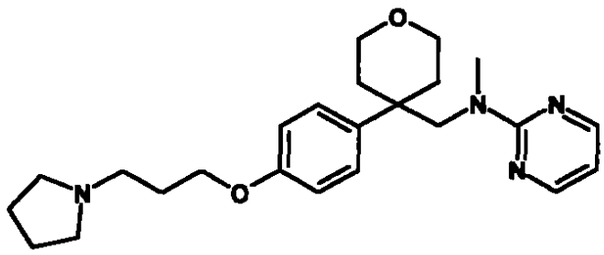
Example 61 : (2-methoxyethyl)-methyl-[4-[4-(3-pyrrolidin-1-ylpropoxy)-phenyl]tetrahydropyran-4-ylmethyl]amine



To a stirred solution of methyl-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetra-hydropyran-4-ylmethyl]amine (150 mg, 0.45 mmol) and 2-bromoethylmethylether (43 µL, 0.45 mmol) in anhydrous acetonitrile (5 mL) was added potassium carbonate (62.4 mg, 0.45 mmol). The mixture was heated to 80°C overnight then to 80°C for a day and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with DCM:MeOH (95:5) with 10% NH_3 to give the title compound as an oil (69 mg, 18% yield).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.20 (d, 2H), 6.86 (d, 2H), 4.02 (t, 2H), 3.78 – 3.48 (m, 4H), 3.29 (t, 2H), 3.27 (s, 3H), 2.67 (t, 2H), 2.59 (m, 4H), 2.48 (s, 2H), 2.39 (t, 2H), 2.11 – 2.00 (m, 4H), 1.98 (s, 3H), 1.92 – 1.85 (m, 2H), 1.84 – 1.80 (m, 4H).

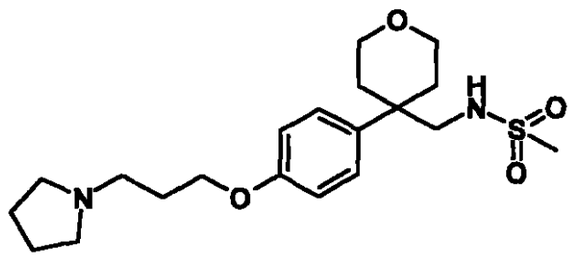
Example 62: methyl-pyrymidin-2-yl-[4-[4-(3-pyrrolidin-1-ylpropoxy)-phenyl]-tetrahydropyran-4-ylmethyl]amine



To a solution of methyl-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl]amine (150 mg, 0.45 mmol) and 2-chloropyrymidine (52 mg, 0.45 mmol) in anhydrous acetonitrile (5 mL) was added potassium carbonate (62 mg, 0.45 mmol). The mixture was heated to 80°C overnight then refluxed for 2 days, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with DCM:MeOH (97:3) with 10% NH_3 to give the title compound (40 mg, 22% yield).

^{1}H NMR (400MHz, $CDCl_3$) δ 8.24 (m, 2H), 7.20 (d, 2H), 6.86 (d, 2H), 6.42 (m, 1H), 4.02 (m, 2H), 3.80 (m, 4H), 3.52 (t, 2H), 2.59 (m, 9H), 2.01 (m, 8H), 1.79 (s, 3H).

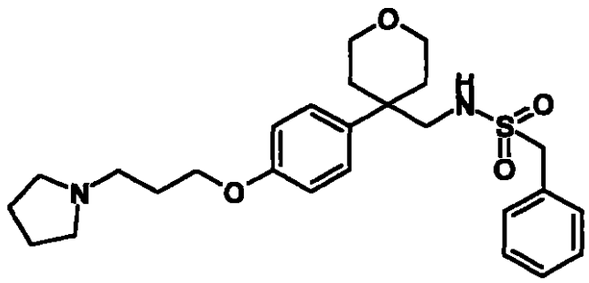
Example 63: N-[4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-methanesulfonamide



To a stirred solution of {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (200 mg, 0.628 mmol) and triethylamine (106 µL, 0.754 mmol) in anhydrous dichloromethane (8 mL) under nitrogen atmosphere was added dropwise a solution of mesyl chloride (58 µL, 0.754 mmol) in anhydrous dichloromethane (2 mL). After stirring overnight, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$. The organic layer was separated and washed with a saturated aqueous solution of $NaHCO_3$ and water then dried over magnesium sulphate, filtered and concentrated under reduced pressure to give the title compound (140 mg, 56 %).

^1H NMR (400MHz, $CDCl_3$) δ 7.19 (d, 2H), 6.94 (d, 2H), 4.04 (t, 2H), 3.79 (m, 2H), 3.57 (m, 2H), 3.24 (d, 2H), 2.75 (s, 3H), 2.63 (t, 2H), 2.54 (m, 4H), 2.12 (m, 2H), 2.01 (m, 2H), 1.88 (m, 2H), 1.80 (m, 4H).

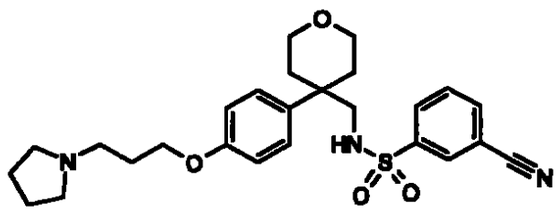
Example 64: C-Phenyl-N-{4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-tetra-hydropyran-4-ylmethyl}-methanesulfonamide



To a stirred solution of {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (200 mg, 0.628 mmol) and triethylamine (106 µL, 0.754 mmol) in anhydrous dichloromethane (8 mL) under nitrogen atmosphere was added dropwise a solution of α-toluenesulfonylchloride (143 mg, 0.754 mmol) in anhydrous dichloromethane (2 mL). After stirring overnight, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$. The organic layer was separated and washed with water, dried over magnesium sulphate, filtered and concentrated under reduced pressure to give the title compound (207 mg, 69 %).

^1H NMR (400MHZ, $CDCl_3$) δ 7.27-7.22 (M, 3H), 7.16-7.14 (M, 2H), 7.07 (D, 2H), 6.83 (D, 2H), 4.05 (S, 2H), 3.95 (T, 2H), 3.68-3.63 (M, 2H), 3.55 (T, 1H), 3.49-3.44 (M, 2H), 3.01(D,2H), 2.57 (T,2H), 2.47 (S,4H), 2.02-1.93 (M, 4H), 1.78-1.72 (M, 6H).

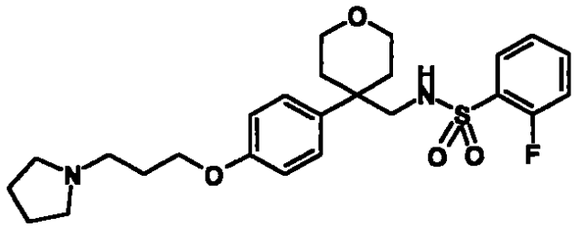
Example 65: 3-Cyano-N-{4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl}-benzenesulfonamide



To a stirred solution of {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (100 mg, 0.314 mmol) and triethylamine (0.1 mL, 0.63 mmol) in anhydrous dichloromethane (3 mL) under nitrogen atmosphere at 0°C was added 3-cyanobenzenesulfonylchloride (100 mg, 0.47 mmol). The reaction mixture was stirred for 2 h allowing it to warm up to room temperature. It was then diluted with dichloromethane and quenched with water. The organic layer was separated and washed with water, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with DCM:MeOH (95:5 to 90:10) to give the title compound.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.93-7.91 (d, 1H), 7.83-7.81 (d, 1H), 7.62-7.58 (m, 1H), 7.11-7.09 (d, 2H), 6.89-6.86 (d, 2H), 4.06-4.03 (m, 3H), 3.77-3.72 (m, 2H), 3.56-3.51 (m, 2H),3.08 (br s,2H), 2.70-2.67 (m, 2H), 3.08 (br s,4H), 2.08-2.01 (m, 4H), 1.85-1.82 (m, 6H).

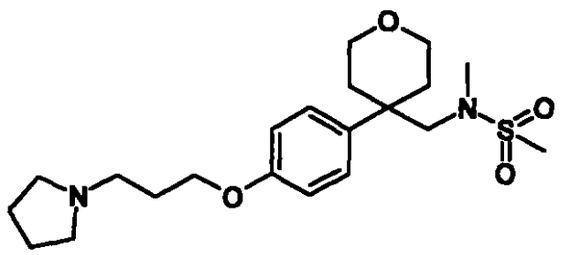
Example 66: 2-Fluoro-N-[4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-benzenesulfonamide



To a stirred solution of {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (100 mg, 0.314 mmol) and triethylamine (0.1 mL, 0.63 mmol) in anhydrous dichloromethane (3 mL) under nitrogen atmosphere at 0°C was added 2-fluorobenzenesulfonylchloride (91 mg, 0.47 mmol). The reaction mixture was stirred for 2 h allowing it to warm up to room temperature. It was then diluted with dichloromethane and quenched with a saturated aqueous solution of $NaHCO_3$. The organic layer was separated and washed with water, dried over sodium sulfate, filtered and concentrated under reduced pressure to give the title compound (120 mg, 80%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.86-7.82 (t, 1H), 7.58-7.52 (m, 1H), 7.28-7.24 (m, 1H), 7.13-7.12 (m, 3H), 6.90-6.88 (m, 2H), 4.19 (m, 1H), 4.05-4.02 (t, 2H), 3.73-3.70 (m, 2H), 3.56-3.51 (t, 2H), 3.10-3.08 (d, 2H), 2.66-2.62 (t, 2H), 2.54 (m, 4H), 2.06-1.99 (m, 4H), 1.85-1.8 (m, 6H).

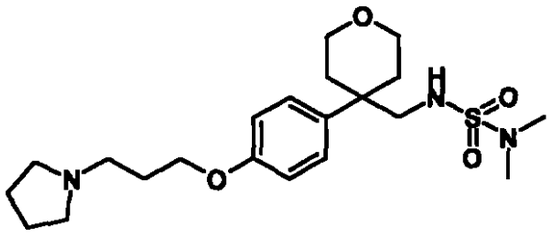
Example 67: N-methyl-N-[4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetra-hydropyran-4-ylmethyl]-methanesulfonamide



To a stirred solution of methyl-{4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl}amine (200 mg, 0.60 mmol) and triethylamine (102 µL, 0.72 mmol) in anhydrous dichloromethane (8 mL) under nitrogen atmosphere was added dropwise a solution of mesyl chloride (56 µL, 0.72 mmol) in anhydrous dichloromethane (2 mL). After stirring overnight, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$. The organic layer was separated, washed with water then dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the title compound (175 mg, 71 %).

^1H NMR (400MHz, $CDCl_3$) δ 7.22 (d, 2H), 6.92-6.90 (d, 2H), 4.03 (t, 2H), 3.83-3.78 (m, 2H), 3.52 (t, 2H), 3.16 (s, 2H), 2.68 (s, 3H), 2.64 (t, 2H), 2.54 (m, 4H), 2.19-2.15 (m, 5H), 2.05-1.91 (m,4H), 1.81-1.78 (m, 4H).

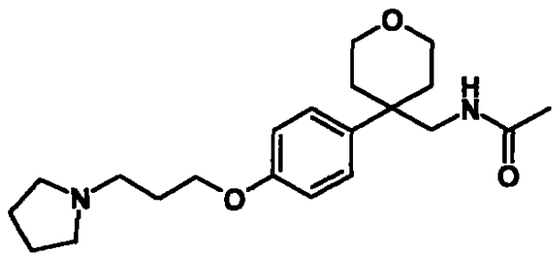
Example 68 : *N'*-[4-(4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]tetrahydro-2*H*-pyran-4-ylmethyl]-*N,N*-dimethylsulfamide



To a stirred solution of {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (200 mg, 0.628 mmol) and triethylamine (106 µL, 0.754 mmol) in anhydrous dichloromethane (8 mL) under nitrogen atmosphere was added dropwise a solution of dimethylsulfamoyl chloride (81 µL, 0.754 mmol) in anhydrous dichloromethane (2 mL). After stirring overnight, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$. The organic layer was separated and washed with water then dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the title compound (207 mg, 77 %).

^1H NMR (400MHZ, $CDCL_3$) δ7.19 (D, 2H), 6.93-6.91 (D, 2H), 4.05 (T, 2H), 3.78-3.76 (M, 2H), 3.58-3.54 (M, 2H), 3.17-3.15 (D, 2H), 2.78-2.70 (M, 12H), 2.15-2.06 (M, 4H), 1.90-1.87 (M, 6H).

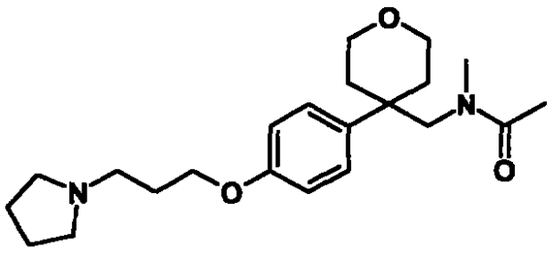
Example 69: N-{4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl}-acetamide



To a stirred solution of {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (200 mg, 0.628 mmol) and triethylamine (108 µL, 0.754 mmol) in anhydrous dichloromethane (8 mL) under nitrogen atmosphere was added dropwise a solution of acetyl chloride (54 µL, 0.754 mmol) in anhydrous dichloromethane (2 mL). After stirring overnight, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$. The organic layer was separated and washed with a saturated aqueous solution of $NaHCO_3$ and water then dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the title compound (102 mg, 45 %).

^1H NMR (400MHz, $CDCl_3$) δ 7.18 (d, 2H), 6.94 (d, 2H), 4.97 (s, 1H), 4.05 (t, 2H), 3.80 (m, 2H), 3.59 (m, 2H), 3.46 (d, 2H), 2.66 (t, 2H), 2.57 (m, 4H), 2.03 (m, 4H), 1.80 (m,8H).

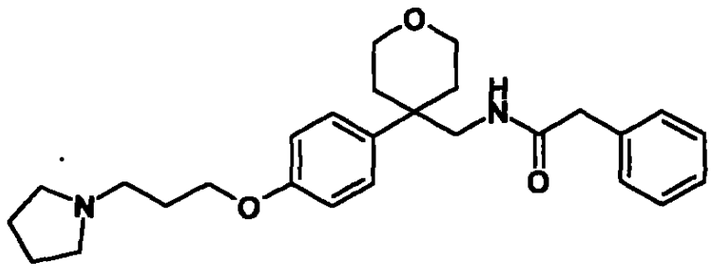
Example 70: N-methyl-N-{4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl}-acetamide



To a stirred solution of methyl-{4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl}amine (200 mg, 0.60 mmol) and triethylamine (102 µL, 0.72 mmol) in anhydrous dichloromethane (8 mL) under nitrogen atmosphere was added dropwise a solution of acetyl chloride (52 µL, 0.72 mmol) in anhydrous dichloromethane (2 mL). After stirring overnight, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$. The organic layer was separated and washed with water then dried over magnesium sulfate, filtered, concentrated under reduced pressure and purified by column chromatography on silica gel eluting with DCM:MeOH (95:5 to 90:10) to give the title compound (66 mg, 36 %).

^1H NMR (400MHz, $CDCl_3$) δ Shows rotomers 7.19-7.13 (2d, 2H), 6.91-6.88 (d, 2H), 4.05-4.02 (m, 2H), 3.85-3.80 (m, 2H), 3.56-3.45 (m, 4H), 2.67-2.65 (m, 2H), 2.60-2.56 (m, 4H), 2.32-1.96 (several multiplets, 12H).

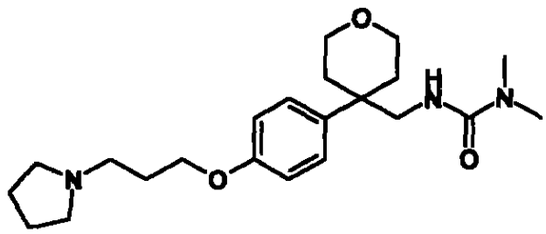
Example 71: 2-Phenyl-N-{4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl}-acetamide



To a stirred solution of {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (200 mg, 0.63 mmol) and triethylamine (93 µL, 0.66 mmol) in anhydrous dichloromethane (8 mL) under nitrogen atmosphere at 0°C was added dropwise a solution of phenylacetyl chloride (93 µL, 0.66 mmol) in anhydrous dichloromethane (2 mL). After stirring for 3 h at 0°C, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$. The organic layer was separated and washed with water then dried over magnesium sulfate, filtered, concentrated under reduced pressure and purified by column chromatography on silica gel eluting with DCM:MeOH (98:2) to give the title compound (34 mg, 12 %).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.32-7.31 (m, 3H), 7.12-7.10 (m, 2H), 6.88-6.87 (d, 2H), 6.76-6.74 (d, 2H), 4.91 (t, 1H), 4.02 (t, 2H), 3.79-3.74 (m, 2H), 3.53-3.51 (m, 2H), 3.47 (s, 2H), 3.37-3.35 (d, 2H), 2.62 (m, 6H), 2.08-2.06 (m, 2H), 1.93-1.85 (m, 6H), 1.76-1.74 (m, 2H).

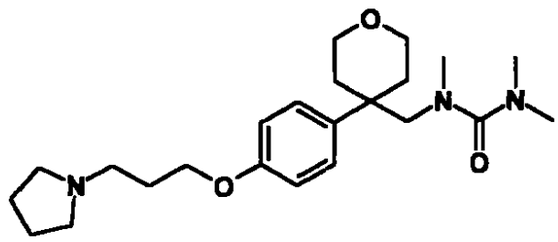
Example 72: 1,1-Dimethyl-3-{4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl}-urea



To a stirred solution of {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (200 mg, 0.63 mmol) and triethylamine (106 µL, 0.754 mmol) in anhydrous dichloromethane (9 mL) under nitrogen atmosphere was added dropwise a solution of dimethylcarbamoylchloride (69 µL, 0.754 mmol) in anhydrous dichloromethane (1 mL). After stirring for 3 h at 0°C, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$. The organic layer was separated and washed with water then dried over magnesium sulfate, filtered, concentrated under reduced pressure and purified by column chromatography on silica gel eluting with DCM:MeOH (95:5 to 90:10) to give the title compound (80 mg, 32 %).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.13 (d, 2H), 6.86 (d, 2H), 3.98 (t, 2H), 3.84 (t, 1H), 3.74 (m, 2H), 3.52 (m, 2H), 3.36 (d, 2H), 2.69 (s, 6H), 2.65 (m, 2H), 2.57 (m, 4H), 2.02-1.95 (m,4H), 1.84-1.78 (m, 6H).

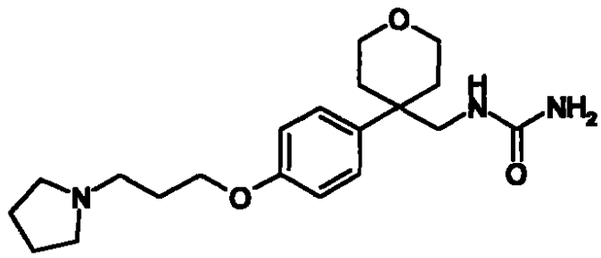
Example 73: 1,1,3-Trimethyl-3-{4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl}-urea



To a stirred solution of methyl-(4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl)amine (200 mg, 0.60 mmol) and triethylamine (102 µL, 0.72 mmol) in anhydrous dichloromethane (6 mL) under nitrogen atmosphere was added dropwise a solution of dimethylcarbamoylchloride (67 µL, 0.72 mmol) in anhydrous dichloromethane (2 mL). After stirring overnight, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$. The organic layer was separated, washed with a saturated aqueous solution of $NaHCO_3$ and water then dried over magnesium sulfate, filtered, concentrated under reduced pressure and purified by column chromatography on silica gel eluting with DCM:MeOH (95:5) followed by DCM:MeOH:NH_3 (90:5:5) to give the title compound (84 mg, 39 %).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.19 (d, 2H), 6.90-6.88 (d, 2H), 4.03 (t, 2H), 3.81-3.78 (m, 2H), 3.56-3.52 (m, 4H), 2.70 (s, 6H), 2.66 (t, 2H), 2.29 (s, 3H), 2.05-2.01 (m, 4H), 1.86-1.81 (m, 6H).

Example 74: (4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl)-urea



To a stirred solution of (4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl) methylamine (200 mg, 0.63 mmol) and acetic acid (108 µL, 1.89 mmol) in water (12 mL) was added portionwise potassium cyanate (153 mg, 1.89 mmol). After stirring overnight, the reaction mixture was quenched with a 0.1N aqueous solution of NaOH. The organic layer was separated and the aqueous layer extracted twice with dichloromethane. The combined organic extracts were dried over magnesium sulfate, filtered, concentrated under reduced pressure and purified by column chromatography on silica gel eluting with DCM:MeOH (95:5) followed by DCM:MeOH (90:10) and DCM:MeOH:NH_3 (90:5:5) to give the title compound (25 mg, 11 %).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.18 (d, 2H), 6.92-6.90 (d, 2H), 4.24 (s, 2H), 4.17 (t, 1H), 4.03 (t, 2H), 3.84-3.79 (m, 2H), 3.61-3.55 (m, 2H), 3.36-3.35 (d, 2H), 2.63 (t, 2H), 2.53 (m, 4H), 2.07-1.97 (m, 4H), 1.88-1.79 (m, 6H).

Intermediate 29: 4-aminomethyl-4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-cyclohexanol

Step 1:

A three-neck reaction vessel was charged with [4-(3-pyrrolidin-1-ylpropoxy)phenyl]acetonitrile (7g, 28.8 mmol), benzyltrimethylammonium hydroxide (40% in methanol, 1.3 mL) in acetonitrile (185 mL). The

solution was heated to reflux and methyl acrylate (25 mL, 286 mmol) was added dropwise. After refluxing for 5 hr, the mixture was concentrated to half, diethyl ether was added and the organics were washed with 1N HCl and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash-chromatography to provide 4-cyano-4-[4-(3-pyrrolidin-1-ylpropoxy)-phenyl]-heptanedioic acid dimethyl ester (8.8 g, 74%).

Step 2:

To a solution of 4-cyano-4-[4-(3-pyrrolidin-1-ylpropoxy)-phenyl]-heptanedioic acid dimethyl ester (8.8 g, 21.1 mmol) in 1,2-dimethoxyethane (176 mL) was charged portions of NaH (60% dispersion, 2.55 g, 63.4 mmol). The reaction mixture was heated to reflux. After 4.5 hr, the ¾ of solvent were evaporated and the mixture cooled to 20°C with an ice bath and quenched with water (100 mL), HCl 1N (100 mL). The aqueous layer was extracted with ether (100 mL). After basification with NaOH the aqueous phases were extracted with dichloromethane. The combined organics were washed with water, dried over Na_2SO_4, filtered and concentrated to provide 5-cyano-2-oxo-5-[4-(3-pyrrolidin-1-ylpropoxy)-phenyl]-cyclohexane-carboxylic acid methyl ester (6.6 g , 81%) as an oil.

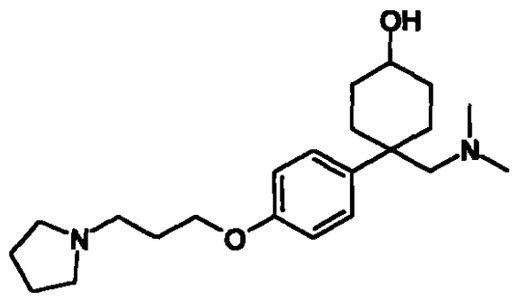
Step 3:

To a solution of 5-cyano-2-oxo-5-[4-(3-pyrrolidin-1-ylpropoxy)-phenyl]-cyclohexanecarboxylic acid methyl ester (6.6 g, 17 mmol) and dimethylsulfoxide (128 mL) was added water (8.0 mL) and sodium chloride (6.4 g, 109 mmol). The reaction mixture was heated to 142-146°C. After 5 hr, the mixture was concentrated and the residue was dissolved in DCM (120 mL), washed with water (100 mL), and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (70 g silica gel, eluant : gradient of DCM/MeOH 95/5 to 90/10) providing 4-oxo-1-[4-(3-pyrrolidin-1-ylpropoxy)-phenyl]-cyclohexanecarbonitrile as a crystallizing oil (2.2 g 45.5 %). After crystallization in ether, 0.2g of analytical sample were obtained.

Step 4:

To a stirred suspension of $LiAlH_4$ (0.69 g, 15 mmol, 10 eq) in diethyl ether (8 mL) was added dropwise at ambient temperature a solution of 4-oxo-1-[4-(3-pyrrolidin-1-ylpropoxy)-phenyl]-cyclohexanecarbonitrile (0.5 g, 1.5 mmol) in diethyl ether (25 mL). The reaction mixture was heated to reflux for 2 h. The reaction mixture was cooled to 0°C and, successively, a solution of water, sodium hydroxide (15% w/v, 0.68 mL) and water again were carefully added dropwise. After being stirred for 15 min at room temperature, the mixture was filtered over diatomaceous earth and concentrated. The residue was purified by flash chromatography (10 g silica gel, DCM/ MeOH (10% NH_3) to provide the title compound (0.27 g, 54%) as an oil.

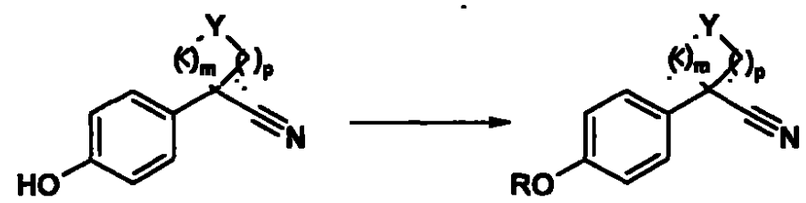
Example 76: 4-dimethylaminomethyl-4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-cyclohexanol



To 4-aminomethyl-4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-cyclohexanol (0.26 g, 0.78 mmol) was added 0.8 mL of formaldehyde (37% w/w solution in H_2O). 1 mL of formic acid was added and the mixture was heated to about 100°C for 20 min. After cooling, water was added and the mixture extracted with ether. Na H was added at the aqueous phase and the mixture extracted 3 times with ether. The organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide 0.23 g of oil. The residue was purified by flash chromatography (25 g silica gel, DCM/ MeOH (10% NH_3) to provide 0.18 g of product. After trituration with 10 mL hexanes (0.13 g, 46.4%) of title compound were obtained.

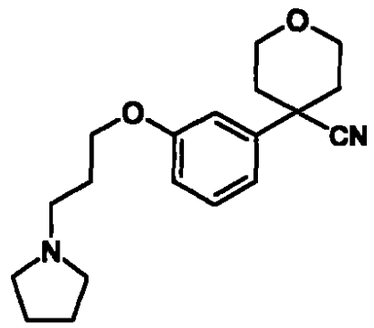
^{1}H NMR (400MHz, $CDCl_3$) δ 7.25 (d, 2H), 6.85(d, 2H), 4. (t, 2H), 3.8 (bs, 1H), 2.82 (t, 2H), 2.58-2.49 (m, 4H), 2.39 (s, 2H), 2.08-1.82 (m, 3H), 1.95 (s,6H), 1.85-1.74 (m, 6H), 1.73-1.64 (m, 4H), 1.62-1.52 (m, 2H).

General procedure E:



Starting phenol (3.69mmol), chloride (5.90mmol), DMF (15ml) and K_2CO_3 (14.83mmol) was heated to 130°C until the reaction is complete (1 to 2 hrs). Cooled to ambient temperature, water (30ml) was added, extracted with EtOAc (3x9ml) and the combined organic extracts were washed with NaOH (2M, 2x25ml). The organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* at 35°C. Purification of the crude material by chromatography on silica, eluant (10%MeOH in DCM) provided the title compounds.

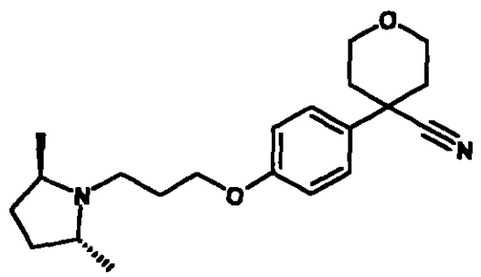
Example 78: 4-[3-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-carbonitrile



4-(3-Hydroxy-phenyl)-tetrahydro-2H-pyran-4-carbonitrile (1.03g, 5.10mmol), 1-(3-chloro-propyl)-pyrrolidine (600mg, 4.08mmol), DMF (6.8ml) and K_2CO_3 (2.82g, 20.4mmol) were reacted together according to general procedure E. The organic phase was washed with 2M NaOH (3 x 50ml), brine (3 x 50ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* at 35°C. The crude mixture was slurried in TBME:heptane (1 :20, 10ml). The solid was filtered, washed with heptane (10ml) and dried on the filter for 2hours to give the title compound (0.4g, 31%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.32 (t, 1H), 7.07-6.99 (m, 2H), 6.87 (dd, 1H), 4.11-4.04 (m, 2H), 4.05 (t, 2H), 3.90 (td, 2H), 2.83 (t, 2H), 2.57-2.49 (m, 4H), 2.18-1.97 (m, 6H), 1.84-1.75 (m, 4H).

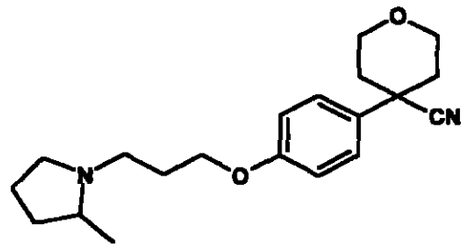
Example 77: 4-[4-[3-(2,5-Dimethylpyrrolidin-1-yl)propoxy]phenyl]-tetra-hydropyran-4-carbonitrile



4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbonitrile (318mg, 1.56mmol), 1-(3-chloro-propyl)-2,5-*trans*-dimethyl-pyrrolidine (250mg, 1.42mmol), DMF (5ml) and K_2CO_3 (785mg, 5.70mmol) were reacted together according to general procedure E. The crude was dissolved in ethyl acetate (20ml), washed with brine (2 x 10ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound (200mg, 56%) as a light brown solid.

^{1}H NMR (400MHz, $CDCl_3$), δ 7.37 (d, 2H), 6.93 (d, 2H), 4.13-3.97 (m, 4H), 3.89 (td, 2H), 3.14-2.98 (m, 2H), 2.76 (m, 1H), 2.55 (m, 1H), 2.16-1.88 (m, 8H), 1.48–1.30 (m, 2H), 0.97 (d, 6H).

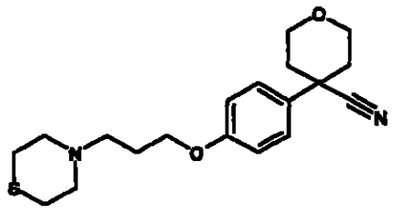
Example 78: 4-[4-[3-(2-Methylpyrrolidin-1-yl)-propoxy]-phenyl]tetra-hydropyran-4-carbonitrile



4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbonitrile (315mg, 1.55m mol), 1-(3-chloro-propyl)-2-methyl-pyrrolidine (400mg, 2.48mmol), DMF (6ml) and K_2CO_3 (833mg, 6.03mmol) were reacted together according to general procedure E. Purification by chromatography on silica, eluant DCM:MeOH:NH_3 (92:6:2) provided the title compound (450mg, 88%) as an orange oil.

^{1}H NMR (400MHz, $CDCl_3$), δ 7.37 (d, 2H), 6.93 (d, 2H), 4.12-3.99 (m, 4H), 3.89 (td, 2H), 2.35-1.62 (m, 14H), 1.42 (m, 1H), 1.09 (d, 3H).

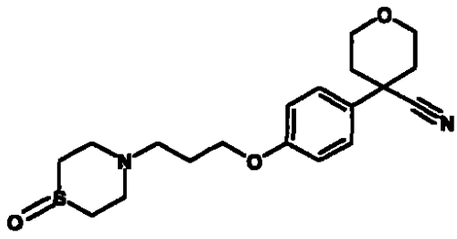
Example 79: 4-[4-(3-Thiomorpholin-4-ylpropoxy)phenyl]tetrahydropyran-4-carbonitrile



4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbonitrile(750mg, 3.69m mol), 4-(3-chloro-propyl)-thiomorpholine (1.08g, 5.91mmol), DMF (15ml) and K_2CO_3 (2.05g, 14.83mmol) were reacted together according to general procedure E. Purification by chromatography on silica, eluant DCM:MeOH:NH_3 (96:3:1) provided the title compound (365mg, 29%) as an off white solid.

^{1}H NMR (400MHz, $CDCl_3$), δ 7.37 (d, 2H), 6.93 (d, 2H), 4.12-4.04 (m, 2H), 4.01 (t, 2H), 3.89 (td, 2H), 2.77-2.64 (m, 8H), 2.54 (t, 2H), 2.16-1.99 (m, 4H), 1.95 (p, 2H).

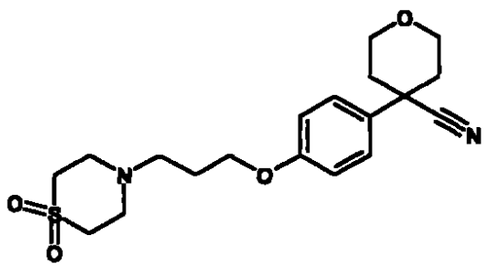
Example 80: 4-[4-[3-(1-Oxo-thiomorpholin-4-yl)-propoxy]-phenyl]-tetra-hydropyran-4-carbonitrile



Sodium perborate tetrahydrate (221mg, 1.43mmol) and glacial acetic acid (5ml) was heated to 50 to 60°C and 4-[4-(3-Thiomorpholin-4-ylpropoxy)phenyl]tetrahydropyran-4-carbonitrile (500mg, 1.43mmol) was added in one portion and the heating was maintained for 3 hours. The reaction mixture was cooled to ambient temperature and filtered. The filtrate was added to ice water (15ml) and extracted with EtOAc (3x5ml), which was discarded. The aqueous phase was basified to pH 8-9 with 2M sodium hydroxide and extracted with DCM (3x25ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* at 35°C. The crude material was subjected to chromatography on silica eluting with DCM:MeOH:NH_3 (97:2:1 to 92:6:2) to provided the title compound (300mg, 58%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$), δ 7.38 (d, 2H), 6.92 (d, 2H), 4.11-4.05 (m, 2H), 4.03 (t, 2H), 3.89 (td, 2H), 3.15-3.03 (m, 2H), 2.94-2.67 (m, 6H), 2.63 (t, 2H), 2.16-1.92 (m, 6H).

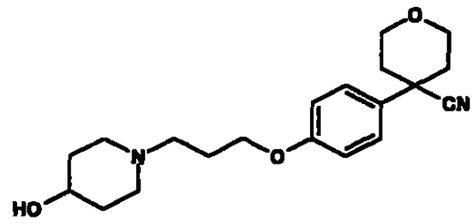
Example 81: 4-[4-[3-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)propoxy]-phenyl]tetrahydro-pyran-4-carbonitrile



To a solution of 4-[4-(3-Thiomorpholin-4-ylpropoxy)phenyl]tetrahydropyran-4-carbonitrile (500mg, 1.44mmol) in TFA (1.65ml) at 0 to 5°C was added drop wise a solution of trifluoro-peracetic acid (4M in TFA, 0.72ml). The reaction was allowed to warm to room temperature and stirred for 3 hours. A further portion of trifluoro-peracetic acid (4M in TFA, 0.097ml) [4M solution prepared by the addition of 27.5% H_2O_2 (0.94ml) to TFA (1.56ml)] was added to the reaction and stirred overnight. The reaction mixture was cooled to 0 to 5°C, diluted with DCM (20ml) and quenched with NaOH (5M solution, 12ml) to attain pH10. The mixture was extracted with DCM (3 x 20ml), the combined DCM extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The isolated yellow oil was purified by column chromatography on basic alumina eluting with DCM(95):MeOH(4):NH_3(1) to give the title compound as an off-white solid (230mg, 42%).

^{1}H NMR (400MHz, $CDCl_3$), δ 7.39 (d, 2H), 6.92 (d, 2H), 4.12-4.06 (m, 2H), 4.03 (t, 2H), 3.89 (td, 2H), 3.11-2.96 (m, 8H), 2.71 (t, 2H), 2.15-1.99 (m, 4H), 1.96 (p, 2H).

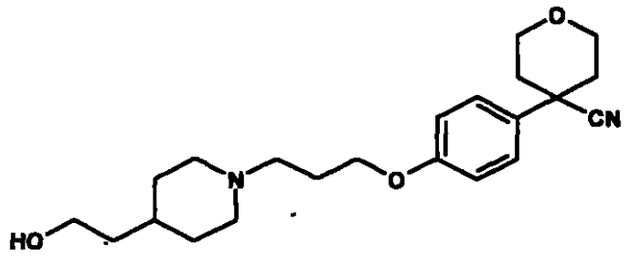
Example 82: 4-[4-[3-(4-Hydroxypiperidin-1-yl)propoxy]phenyl]tetrahydro-pyran-4-carbonitrile



4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbonitrile (533mg, 2.62mmol), 1-(3-chloro-propyl)-piperidin-4-ol (750mg, 4.22mmol), DMF (10ml) and K_2CO_3 (1.44g, 10.42mmol) were reacted together according to general procedure E. Purification by chromatography on silica, eluant DCM:MeOH:NH_3 (92:8:2) provided the title compound (550mg, 61%) as an off white solid.

^{1}H NMR (400MHz, $CDCl_3$), δ 7.38 (d, 2H), 6.93 (d, 2H), 4.13-4.04 (m, 2H), 4.02 (t, 2H), 3.89 (td, 2H), 3.70 (m, 1H), 2.87-2.71 (m, 2H), 2.50 (t, 2H), 2.23-1.84 (m, 10H), 1.68-1.49 (m, 3H).

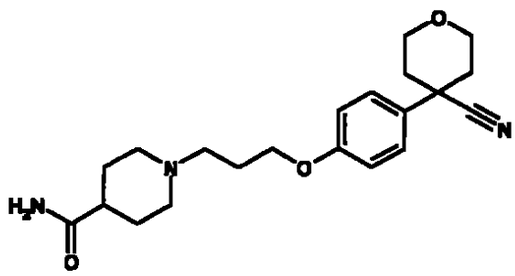
Example 83: 4-[4-[3-[4-(2-Hydroxyethyl)-piperidin-1-yl]propoxy]phenyl]-tetrahydro-pyran-4-carbonitrile



4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbonitrile (185mg, 0.91mmol), 2-[1-(3-chloro-propyl)-piperidin-4-yl]-ethanol (300mg, 1.46mmol), DMF (4ml) and K_2CO_3 (497mg, 3.60mmol) were reacted together according to general procedure E. Purification by chromatography on silica, eluant DCM: MeOH:NH_3 (92:8:2) provided the title compound (220mg, 65%) as a pale pink solid.

^{1}H NMR (400MHz, $CDCl_3$), δ 7.37 (d, 2H), 6.93 (d, 2H), 4.11-4.04 (m, 2H), 4.01 (t, 2H), 3.89 (td, 2H), 3.70 (t, 2H), 2.97-2.87 (m, 2H), 2.48 (t, 2H), 2.15-1.88 (m, 8H), 1.77-1.57 (m, 3H), 1.57-1.38 (m, 3H), 1.35–1.21 (m, 2H).

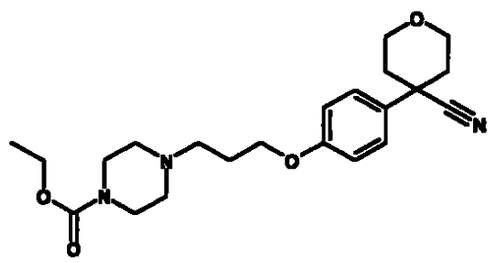
Example 84: 1-[3-[4-(4-Cyano-tetrahydro-pyran-4-yl)-phenoxy]-propyl]-piperidine-4-carboxylic acid amide



-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbonitrile (200mg, 0.98mmol), 1-(3-chloro-propyl)-piperidine-4-carboxylic acid amide (200mg, 0.98mmol), DMF (4ml) and K_2CO_3 (550mg, 3.98mmol) were reacted together according to general procedure E. The reaction mixture was poured onto water (30ml), the resulting precipitate was filtered and redissolved in DCM (20ml). The DCM solution was washed with NaOH solution (2M, 2x5ml) and water (5ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* at 35°C, displacing residual DCM with EtOH to provide the title compound (210mg, 58%) as an off white solid.

^{1}H NMR (400MHz, $CDCl_3$), δ 7.38 (d, 2H), 6.93 (d, 2H), 5.46 (br s, 1H), 5.35 (br s, 1H), 4.12-4.05 (m, 2H), 4.02 (t, 2H), 3.89 (td, 2H), 3.03-2.92 (m, 2H), 2.60 (t, 2H), 2.22-1.84 (m, 11H), 1.81-1.67 (m, 2H).

Example 85: 4-[3-[4-(4-Cyano-tetrahydropyran-4-yl)-phenoxy]-propyl]-piperazine-1-carboxylic acid ethyl ester



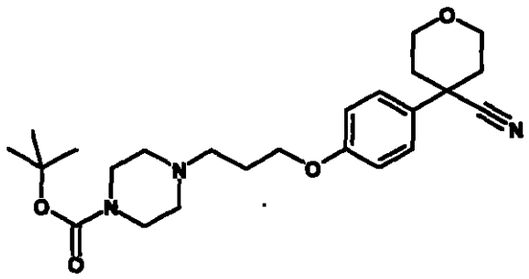
4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbonitrile (500mg, 2.46mmol), 4-(3-chloro-propyl)-piperazine-1-carboxylic acid ethyl ester (570mg, 2.43mmol), DMF (10ml) and K_2CO_3 (1.36g, 9.84mmol) were reacted together according to general procedure E. The organic phase was washed with 2M NaOH (3x 20ml), water (2x 20ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* at 35°C. The crude product was subjected to chromatography on silica eluting with DCM:MeOH:NH_3 (97:2:1) to provide the title compound (280mg, 28%) as an off white solid.

^{1}H NMR (400MHz, $CDCl_3$), δ 7.38 (d, 2H), 6.93 (d, 2H), 4.14 (q, 2H), 4.11-4.05 (m, 2H), 4.03 (t, 2H), 3.89 (td, 2H), 3.55-3.42 (m, 4H), 2.53 (t, 2H), 2.47-2.36 (m, 4H), 2.15-1.92 (m, 6H), 1.26 (t, 3H).

Intermediate 30: 4-(3-Chloro-propyl)-piperazine-1-carboxylic acid tert-butyl ester

4-Piperazine-1-carboxylic acid *tert*-butyl ester (4.0g, 21.5mmol), acetone (80ml, 20vol), 5M NaOH solution (5.16ml, 1.2eq.) and 1-bromo-3-chloropropane (10.15g, 64.5mmol, 3eq.) were reacted together according to general procedure A to give the title compound (2.78g, 66%) as a colourless oil.

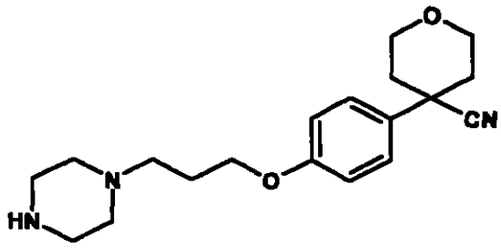
Example 86: 4-[3-[4-(4-Cyano-tetrahydro-pyran-4-yl)-phenoxy]-propyl]-piperazine-1-carboxylic acid tert-butyl ester



4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbonitrile (200mg, 0.99mmol), 4-(3-chloropropyl)-piperazine-1-carboxylic acid *tert*-butyl ester (203mg, 0.76mmol), DMF (4ml) and K_2CO_3 (553g, 4.00mmol) was heated to 70°C and work up according to general procedure E. The organic phase was washed with 2M NaOH (3.x 20ml), water (2x 20ml), dried over $MgSO_4$, filtered and concentrate in vacuo at 35°C to provided the title compound (272mg, 64%) as an off white solid.

^{1}H NMR (400MHz, $CDCl_3$), δ 7.38 (d, 2H), 6.93 (d, 2H), 4.11-4.04 (m, 2H), 4.03 (t, 2H), 3.89 (td, 2H), 3.50-3.37 (m, 4H), 2.53 (t, 2H), 2.45-2.34 (m, 4H), 2.15–2.00 (m, 4H), 1.97 (p, 2H), 1.46 (s, 9H).

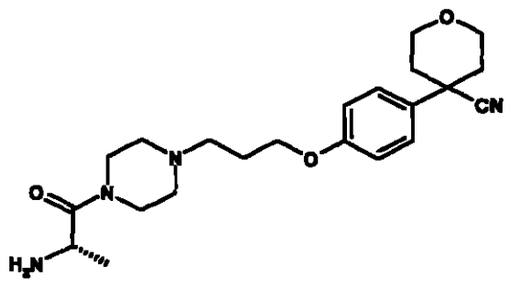
Example 87: 4-[4-(3-Piperazin-1-ylpropoxy)phenyl]tetrahydropyran-4-carbonitrile



4-[3-[4-(4-Cyano-tetrahydro-pyran-4-yl)-phenoxy]-propyl]-piperazine-1-carboxylic acid *tert*-butyl ester (500mg, 1.16mmol), MeOH (5ml), 1,4-dioxane (1ml) and HCl in dioxane (4M, 1.8ml) was stirred at ambient temperature overnight. The reaction mixture was concentrated *in vacuo* at 40°C, and diluted with TBME (5ml). Aqueous NaOH (2M solution) was added to attain a pH of 14 and the mixture separated and extracted with TBME (2x5ml). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide title compound as a yellow oil (275mg, 72%).

^{1}H NMR (400MHz, $CDCl_3$), δ 7.38 (d, 2H), 6.93 (d, 2H), 4.11-4.05 (m, 2H), 4.03 (t, 2H), 3.89 (td, 2H), 2.90 (t, 4H), 2.51 (t, 2H), 2.44 (br s, 4H), 2.15–2.00 (m, 4H), 1.97 (m, 2H), 1.74 (br s, 1H).

Example 88: 4-(4-(3-[4-(2-Aminopropionyl)piperazin-1-yl]propoxy)phenyl)-tetrahydropyran-4-carbonitrile



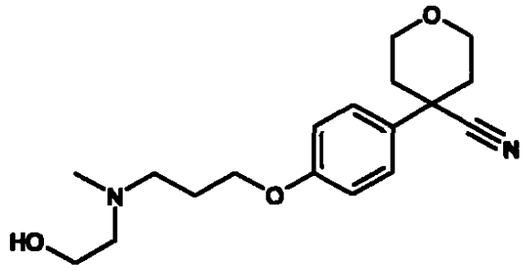
4-[4-(3-Piperazin-1-ylpropoxy)phenyl]tetrahydropyran-4-carbonitrile (285mg, 0.81mmol), DCM (10.6ml), HOBT (120mg, 0.89mmmol), FMoc (L)-aniline (277mg, 0.89mmol) and EDCI.HCl (171mg, 0.89mmol) were stirred at ambient temperature overnight. Water (10ml) was added and stirred for one hour, the mixture was filtered and the organic phase separated and washed with water (10ml), the organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* at 35°C. The residue was dissolved in DCM (9ml) and piperidine (86mg, 10mmol) was added, the mixture was stirred at ambient temperature for one hour. To the reaction mixture, water (5ml) was added and the organic phase separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* at 35°C. The crude material was subjected to chromatography on silica eluting with 2% MeOH in DCM to provide title compound (136mg, 42%).

^{1}H NMR (400MHz, $CDCl_3$), δ 7.38 (d, 2H), 6.93 (d, 2H), 4.11-4.05 (m, 2H), 4.03 (t, 2H), 3.89 (td, 2H), 3.77 (q, 1H), 3.65 (br s, 2H), 3.49 (br s, 2H), 2.55 (t, 2H), 2.45 (br s, 4H), 2.14-2.00 (m, 4H), 1.97 (m, 2H), 1.58 (br s, 2H), 1.25 (d, 3H).

Intermediate 31: 2-[(3-Chloro-propyl)-methyl-amino]-ethanol

2-(Methylamino)-ethanol (1.0g, 13.3mmol), acetone (20ml, 20vol), 5M NaOH solution (3.19ml, 1.2eq.) and 1-bromo-3-chloropropane (6.28g, 39.9mmol, 3eq.) were reacted together according to general procedure A to give the title compound (1.14g, 55%) as a colourless oil.

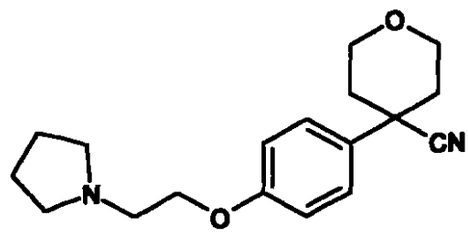
Example 89: 4-[4-[3-[(2-Hydroxyethyl)methylamino]propoxy]-phenyl]tetra-hydropyran-4-carbonitrile



4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbonitrile (800mg, 3.94mmol), 2-[(3-chloro-propyl)-methyl-amino]-ethanol (595mg, 3.94mmol), DMF (8ml) and K_2CO_3 (2.18g, 15.76mmol) were reacted together according to general procedure E. The organic phase was washed with 2M NaOH (3.x 20ml), water (2x 20ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* at 35°C to provided the title compound (550mg, 44%) as a pale yellow oil.

^{1}H NMR (400MHz, $CDCl_3$), δ 7.37 (d, 2H), 6.92 (d, 2H), 4.11-4.04 (m, 2H), 3.88 (dt, 2H), 3.60 (t, 2H), 2.61 (t, 2H), 2.56 (t, 2H), 2.37 (br s, 1H), 2.29 (s, 3H), 2.15–1.91 (m, 6H)

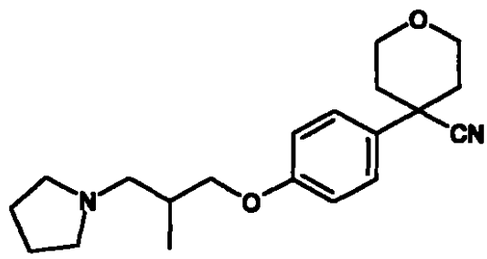
Example 90: 4-[4-(2-Pyrrolidin-1-ylethoxy)phenyl]tetrahydropyran-4-carbonitrile



4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbonitrile (570mg, 2.82mmol), 1-(2-chloro-ethyl)-pyrrolidine (300mg, 2.25mmol), DMF (5.7ml) and K_2CO_3 (1.56g, 1.13mmol) were reacted together according to general procedure E. The organic phase was washed with 2M NaOH (3.x 20ml), water (2x 20ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* at 35°C. The crude material was subjected to chromatography on silica eluting with 5% MeOH in DCM and gradient to 10% MeOH in DCM to provided the title compound (400mg, 47%) as an off white solid.

^{1}H NMR (400MHz, $CDCl_3$), δ 7.38 (d, 2H), 6.95 (d, 2H), 4.13 (t, 2H), 4.10-4.03 (m, 2H), 3.89 (td, 2H), 2.92 (t, 2H), 2.84 (br s, 4H), 2.16–1.99 (m, 4H), 1.88–1.76 (m, 4H).

Example 91: 4-[4-(2-Methyl-3-pyrrolidin-1-ylpropoxy)phenyl]-tetrahydro-pyran-4-carbonitrile



4-(4-Hydroxy-phenyl)-tetrahydro-pyran-4-carbonitrile (790mg, 3.87mmol), 1-(3-chloro-2-methyl-propyl)-pyrrolidine (500mg, 3.10mmol), DMF (5ml) and K_2CO_3 (2.14g, 15.50mmol) were reacted together according to general procedure E. The organic phase was washed with 2M NaOH (3 x 20ml), water (2 x 20ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* at 35°C to provide the title compound (979mg, 96%) as a yellow solid.

^{1}H NMR (400MHz, $CDCl_3$), δ 7.37 (d, 2H), 6.95 (d, 2H), 4.11-4.03 (m, 2H), 4.02 (dd, 1H), 3.89 (td, 2H), 3.77 (dd, 1H), 2.60-2.42 (m, 5H), 2.32 (dd, 1H), 2.22–1.99 (m, 5H), 1.82–1.72 (m, 4H), 1.07 (d, 3H).

Intermediate 32: 1-(3-Chloro-1-methyl-propyl)-pyrrolidine hydrochloride

Step 1:

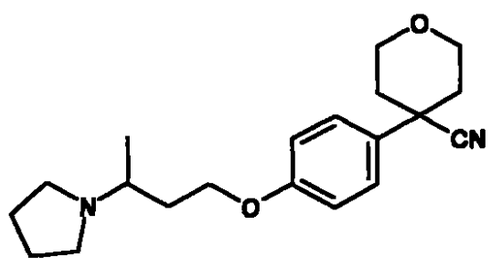
Pyrrolidine (28.15g, 0.4mol), toluene (200ml), catalytic *p*-TsOH (200mg) and ethyl acetoacetate (20g, 0.15mol) were refluxed together with a Dean-Stark apparatus under N_2 for 3hours. The reaction was cooled to room temperature and concentrated *in vacuo*. $NaBH_4$ (3.1g, 82mmol) was dissolved in MeOH (50ml) and cooled to 0-5°C. A portion of the previous crude reaction (5g, 27mmol) in MeOH (25ml) was added to the reaction mixture and stirred for 72hours. The reaction was quenched with an aqueous solution of NaOH (1%w/w, 50ml) and concentrated *in vacuo*. The aqueous was extratcted with TBME (3 x 50ml). The combined organic extracts were dried over $MgSO_4$, filtered, washed with TBME and concentrated *in vacuo* to give a mixture of the title compound, 3-pyrrolidin-1-yl-butanoic acid ethyl ester

and residual TBME (3.5g). The mixture (3.5g) in THF (20ml) was added to a solution of $LiALH_4$ (1M in THF, 33.5ml, 33.5mmol) at 0-5°C under N_2. The reaction was allowed to warm to room temperature and stirred for 3hours. The reaction was quenched with an aqueous solution of NaOH (1%w/w, 50ml) at 0-5°C, filtered and washed with THF (3 x 20ml). The combined organics were dried over $MgSO_4$, filtered, washed with THF and concentrated *in vacuo* to give 3-pyrrolidin-1-yl-butan-1-ol as a yellow oil (2g, 73%).

Step 2:

3-Pyrrolidin-1-yl-butan-1-ol (1.0g, 7mmol) was dissolved in DCM (20ml). The reaction was cooled to 0-5°C and thionyl chloride (1.65g, 14mmol) was added slowly. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was concentrated *in vacuo* and azeotroped with DCM (20ml) to give the title compound (1.4g, 100%) as a brown oil.

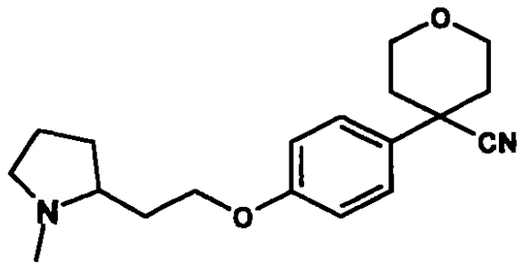
Example 92: 4-[4-(3-Pyrrolidin-1-yl-butoxy)-phenyl]-tetrahydro-pyran-4-carbonitrile



4-(4-Hydroxy-phenyl)-tetrahydro-pyran-4-carbonitrile (1.0g, 4.9mmol), 1-(3-chloro-1-methyl-propyl)-pyrrolidine (780mg, 3.90mmol), DMF (20ml) and K_2CO_3 (2.71g, 19.60mmol) were reacted together according to general procedure E. The organic phase was washed with 2M NaOH (3 x 20ml), water (2 x 20ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* at 35°C and purified by preparative HPLC, eluting with acetonitrile/water/0.1%TFA as a gradient, to provide the title compound (120mg, 9%) as a yellow oil.

^1H NMR (400MHz, $CDCl_3$), δ 7.38 (d, 2H), 6.93 (d, 2H), 4.15-3.98 (m, 4H), 3.89 (td, 2H), 2.75-2.51 (m, 5H), 2.22-1.74 (m, 10H), 1.17 (d, 3H).

Example 93: 4-[4-[2-(1-Methyl-pyrrolidin-2-yl)-ethoxy]-phenyl]-tetrahydro-pyran-4-carbonitrile



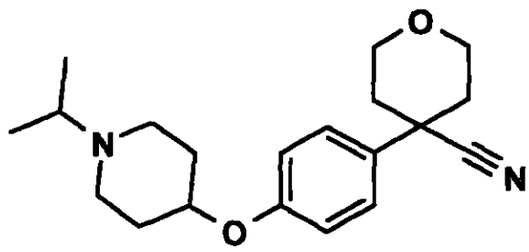
4-(4-Hydroxy-phenyl)-tetrahydro-pyran-4-carbonitrile (1.0g, 4.9mmol), 2-(2-chloro-ethyl)-1-methyl-pyrrolidine (722mg, 3.90mmol), DMF (20ml) and K_2CO_3 (2.71g, 19.60mmol) were reacted together according to general procedure E. The organic phase was washed with 2M NaOH (3 x 20ml), water (2 x

105

20ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* at 35°C and purified by prep TLC, eluting with DCM :MeOH :NH_3 (95 :5 :3), to provide the title compound (180mg, 15%) as a yellow oil.

^1H NMR (400MHz, $CDCl_3$), δ 7.38 (d, 2H), 6.93 (d, 2H), 4.12-4.03 (m, 4H), 3.89 (td, 2H), 3.08 (m, 1H), 2.35 (s, 3H), 2.29–1.94 (m, 8H), 1.85–1.65 (m, 2H), 1.62–1.50 (m, 2H).

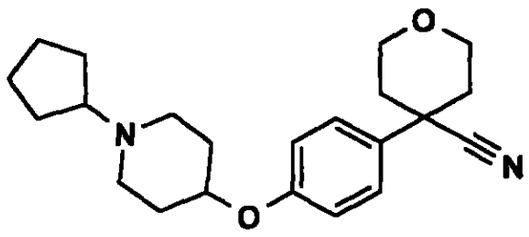
Example 94: 4-[4-(1-Isopropylpiperidin-4-yloxy)phenyl]tetrahydropyran-4-carbonitrile



4-(4-Hydroxy-phenyl)-tetrahydro-pyran-4-carbonitrile (459mg, 2.28mmol) in DMF (2ml) was added to a solution of NaH (100mg, 2.5mmol) in DMF (2ml) at room temperature under N_2. The reaction was stirred for 1 hr and a solution of methanesulfonic acid 1-isopropyl-piperidin-4-yl ester (400mg, 1.81mmol) in DMF (1.3ml) was slowly added. The reaction was heated to 75°C and stirred for 6hrs. The reaction was allowed to cool to room temperature and diluted with TBME (20ml), water (10ml) and 5M NaOH solution (10ml). The organic layer was washed with 2.5M NaOH (2 x 20ml), brine (2 x 20ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude reaction was purified by successive column chromatography, eluting with DCM :MeOH : NH_3 (98 :1 :1) to give the title compound as a pale yellow solid (116mg, 19%).

^1H NMR (400MHz, $CDCl_3$) δ 7.37 (d, 2H), 6.93 (d, 2H), 4.30 (m, 1H), 4.12-4.02 (m, 2H), 3.89 (td, 2H), 2.84-2.68 (m, 3H), 2.45-2.34 (m, 2H), 2.15-1.96 (m, 6H), 1.88-1.75 (m, 2H), 1.06 (d, 6H).

Example 95: 4-[4-(1-Cyclopentylpiperidin-4-yloxy)phenyl]tetrahydropyran-4-carbonitrile



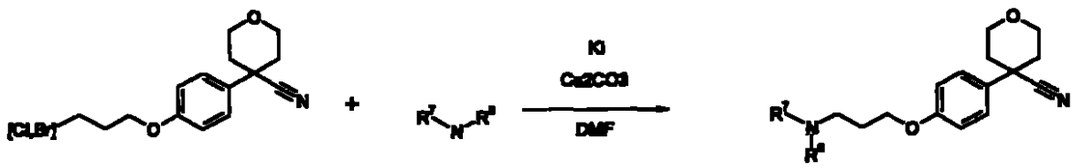
4-(4-Hydroxy-phenyl)-tetrahydro-pyran-4-carbonitrile (459mg, 2.28mmol) in DMF (2ml) was added to a solution of NaH (100mg, 2.5mmol) in DMF (2ml) at room temperature under N_2. The reaction was stirred for 1 hr and a solution of methanesulfonic acid 1-cyclopentyl-piperidin-4-yl ester (447mg, 1.81mmol) in DMF (1.3ml) was slowly added. The reaction was heated to 75°C and stirred for 6hrs. The reaction was allowed to cool to room temperature and diluted with TBME (20ml), water (10ml) and 5M NaOH solution (10ml). The organic layer was washed with 2.5M NaOH (2 x 20ml), brine (2 x 20ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude reaction was purified by successive column chromatography, eluting with DCM :MeOH : NH_3 (98 :1 :1) to give the title compound as a pale yellow solid (81mg, 13%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.37 (d, 2H), 6.93 (d, 2H), 4.36 (m, 1H), 4.11-4.04 (m, 2H), 3.89 (td, 2H), 2.91-2.77 (m, 2H), 2.67-2.25 (m, 2H), 2.15-1.99 (m, 7H), 1.95-1.81 (m, 4H), 1.78-1.64 (m, 2H), 1.62-1.39 (m, 4H).

Intermediates 33 and 34: 4-[4-(3-chloro-propoxy)-phenyl]-tetrahydropyran-4-carbonitrile and 4-[4-(3-bromo-propoxy)-phenyl]-tetrahydropyran-4-carbonitrile

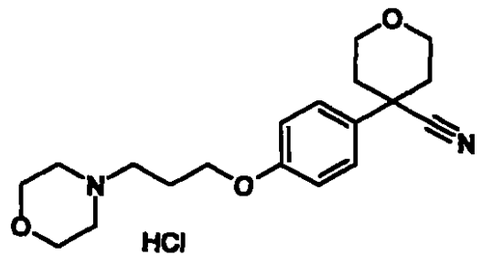
4-(4-hydroxy-phenyl)-tetrahydro-pyran-4-carbonitrile (3.4 g, 16.73 mmol) was taken in DMF (75 ml) and then Cs_2CO_3 (4.84 g, 25.095 mmol) was added followed by dropwise addition of 1-bomo-3-chloropropane (2.45 ml) at 60 °C. The heating was continued at 60 °C overnight. First the reaction mixture was concentrated and quenched by adding water and extracted with ethyl acetate. The compound was purified by column chromatography (0-14 %, ethyl acetate-hexane). Yield: 3.3 g (70 % of a 10:3 mixture of chloro and bromo compound).

General procedure F:



A *mixture of halide (0.7 mmol)*, Cs_2CO_3 *(0.350 g, 1.07 mmol)*, potassium iodide *(0.180 g, 1.07 mmol)* and amines (NR^7R^8) (1.07 mmol) in DMF (7 mL) was heated to 70°C overnight. The mixture was cooled to ambient temperature, water was added, and the resulting mixture was extracted with dichloromethane and the organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the crude material was carried out with flash chromatography (20 g silica gel, DCM/ MeOH gradient).

Example 96: 4-[4-(3-morpholino-4-ylpropoxy)phenyl]tetrahydropyran-4-carbonitrile

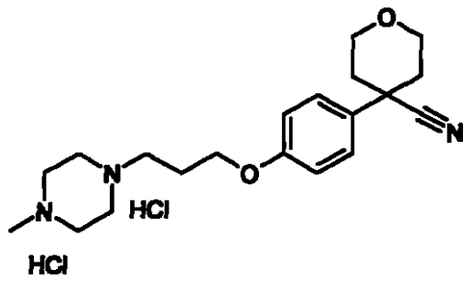


The compound was obtained according the general procedure F, using morpholine as amine. The hydrochloride salt as analytical sample was prepared with ether/HCl 2M in dichloromethane and crystallization in ether.

Yield = 34%

^{1}H NMR (400MHz, DMSO-D6) *δ* 1.95-2.12 (m, 4H); 2.16-2.25 (m, 2H); 3.01-3.12 (m, 2H); 3.19-3.27 (m, 2H); 3.40-3.48 (m, 2H); 3.60-3.69 (t, 2H); 3.80-3.89 (m, 2H); 3.91-4.03 (m, 4H); 4.08-4.13 (m, 2H); 7.20 (d, 2H); 7.46 (d, 2H); 11.33 (bs, 1H)

Example 97: 4-[4-[3-(4-methyl-piperazin-1-yl)-propoxy]phenyl]tetrahydro-pyran-4-carbonitrile

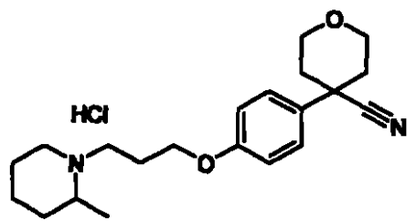


The compound was obtained according the general procedure F, using 1-methylpiperazine as amine. The hydrochloride salt as analytical sample was prepared with ether/HCl 1M in dichloromethane and triturated with pentane.

Yield = 57%

^{1}H NMR (400MHz, DMSO-D_6) δ 11.85 (bs, 1H), 7.46 (d, 2H), 7.02 (d, 2H), 4.13 –4.07 (m, 2H), 4.03 –3.96 (m, 2H), 3.84-3.18 (m, 12H), 2.87-2.78 (m, 3H), 2.24 – 2.13 (m, 2H), 2.11 – 1.96 (m, 4H).

Example 98: 4-[4-[3-(2-methyl-piperidin-1-yl)-propoxy]phenyl]-tetrahydro-pyran-4-carbonitrile

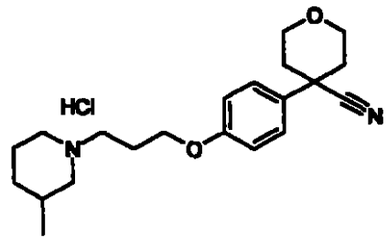


The compound was obtained according the general procedure F, using 2-methylpiperidine as amine. The hydrochloride salt as analytical sample was prepared with ether/HCl 1M in dichloromethane and trituration with pentane.

Yield = 28%

^{1}H NMR (400MHz, DMSO-D6) δ 10.22 (bs, 1H), 7.46 (d, 2H), 7.01(d, 2H), 4.13-4.06 (m, 2H), 4.03-3.96 (dd, 2H), 3.69-3.60 (t, 2H), 3.48-3.38 (m, 1H), 3.25-3.06 (m, 3H), 3.01-2.90 (m, 1H), 2.21-1.95 (m, 7H), 1.88-1.57 (m, 5H), 1.56-1.39 (m, 1H), 1.32 (d, 2H), 1.24 (d, 1H).

Example 99: 4-[4-[3-(3-methyl-piperidin-1-yl)-propoxy]phenyl]-tetrahydro-pyran-4-carbonitrile



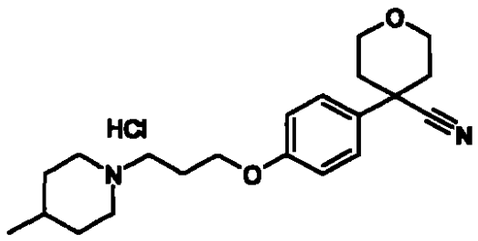
The compound was obtained according the general procedure F, using 3-methylpiperidine as amine. The hydrochloride salt as analytical sample was prepared with ether/HCl 1M in dichloromethane and trituration with pentane.

Yield = 52%

108

^{1}H NMR (400MHz, DMSO-D6) δ 10.32 (bs, 1H), 7.46 (d, 2H), 7.01(d, 2H), 4.11-4.05 (t, 2H), 4.03-3.96 (dd, 2H), 3.69-3.60 (t, 2H), 3.46-3.35 (m, 2H), 3.19-3.11 (m, 2H), 2.82-2.72 (m, 1H), 2.58-2.45 (m, 1H), 2.24-2.16 (m, 2H), 2.12-1.90 (m, 5H), 1.85-1.70 (m, 3H), 1.12-1.02 (m, 1H), 0.89 (d, 3H).

Example 100: 4-[4-[3-(4-methyl-piperidin-1-yl)-propoxy]phenyl]-tetrahydro-pyran-4-carbonitrile

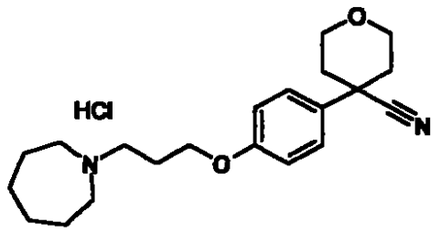


The compound was obtained according the general procedure F, using 4-methylpiperidine as amine. The hydrochloride salt as analytical sample was prepared with ether/HCl 1M in dichloromethane and trituration with pentane.

Yield = 60%

^{1}H NMR: (400MHz, DMSO-D6) δ 10.18 (bs, 1H), 7.46 (d, 2H), 7.01(d, 2H), 4.11-4.05 (t, 2H), 4.03-3.96 (dd, 2H), 3.69-3.60 (t, 2H), 3.49-3.42 (m, 2H), 3.19-3.11 (m, 2H), 2.94-2.83 (m, 2H), 2.22-2.13 (m, 2H), 2.11-1.95 (m, 4H), 1.81-1.73 (m, 2H), 1.65-1.54 (m, 1H), 1.53-1.41 (m, 2H), 0.91 (d, 3H).

Example 101: 4-[4-(3-azepan-1-ylpropoxy)phenyl]tetrahydropyran-4-carbonitrile

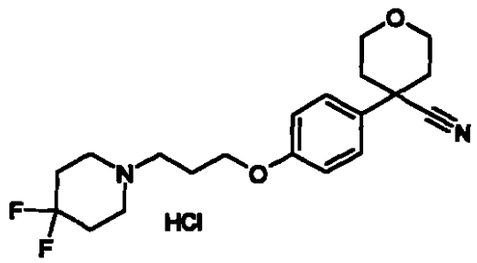


The compound was obtained according the general procedure F, using hexamethyleneimine as amine. The hydrochloride salt as analytical sample was prepared with ether/HCl 1M in dichloromethane and trituration with ether.

Yield = 9%

^{1}H NMR (400MHz, DMSO-D6) δ 10.54 (bs, 1H), 7.41 (d, 2H), 7.01(d, 2H), 4.11-4.05 (t, 2H), 4.03-3.96 (dd, 2H), 3.69-3.60 (dt, 2H), 3.41-3.30 (m, 2H), 3.24-3.17 (m, 2H), 3.16-3.06 (m, 2H), 2.24-2.16 (m, 2H), 2.12-1.95 (m, 4H), 1.92-1.76 (m, 4H), 1.72-1.52 (m, 4H).

Example 102: 4-[4-[3-(4,4-difluoro-piperidin-1-yl)-propoxy]phenyl]-tetra-hydropyran-4-carbonitrile

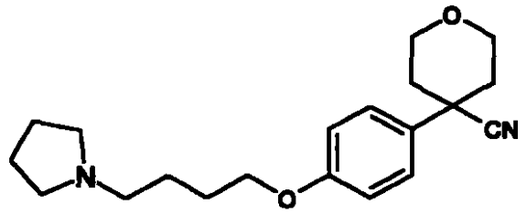


The compound was obtained according the general procedure F, using 4,4-difluoropiperidine hydrochloride as amine (add $(C_2H_5)_3N$ to obtain the free base). The hydrochloride salt as analytical sample was prepared with ether/HCl 1M in dichloromethane and trituration with ether.

Yield = 9%

^{1}H NMR : (400MHz, DMSO-D6) δ 10.28 (bs, 1H), 7.46 (d, 2H), 7.01(d, 2H), 4.12-4.07 (t, 2H), 4.03-3.96 (dd, 2H), 3.69-3.59 (dt, 4H), 3.33-3.25 (m, 2H), 3.21-3.11 (m, 2H), 2.39-2.27 (m, 2H), 2.27-2.17 (m, 2H), 2.12-1.95 (m, 4H).

Example 103: 4-[4-(5-Pyrrolidin-1-ylpentyloxy)phenyl]tetrahydropyran-4-carbonitrile



4-(4-Hydroxy-phenyl)-tetrahydro-pyran-4-carbonitrile (1.5g, 7.39mmol), 1-bromo-4-chlorobutane (1.7ml, 14.77mmol), DMF (20ml) and K_2CO_3 (4.1g, 29.56mmol) were reacted together according to general procedure E. Purification by chromatography on silica, eluant ethyl acetate:heptanes (33:66) provided a mixture of bromo and chloro phenoxy ether (1.3g, 60%) which was used in the next stage. A portion of the mixture (0.5g, 1.70mmol) and pyrrolidine (0.42ml, 5.11mmol) were refluxed in EtOH (5ml, 10vol) overnight. The reaction was concentrated *in vacuo* and partitioned between 2M NaOH (10ml) and ethyl acetate (10ml). The aqueous was extracted with ethyl acetate (3 x 10mL). The combined ethyl acetate layers were washed with brine (3 x 10ml), dried over $MgSO_4$, filtered, washed with ethyl acetate and concentrated *in vacuo*. Purification by chromatography on silica, eluant DCM :MeOH :NH_3 (95:4:1) increasing gradually to DCM :MeOH :NH_3 (93 :6 :1), gave the title compound as a pale yellow solid (350mg, 63%).

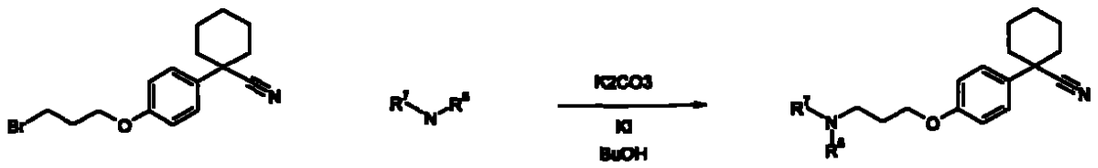
^{1}H NMR (400MHz, DMSO-d_6) δ 7.38 (d, 2H), 6.92 (d, 2H), 4.11-4.03 (m, 2H), 3.99 (t, 2H), 3.89 (td, 2H), 2.58-2.43 (m, 6H), 2.15-1.99 (m, 4H), 1.89-1.64 (m, 8H).

Intermediate 35: 1-[4-(3-bromo-propoxy)-phenyl]-cyclohexanecarbonitrile

1-(4-Hydroxyphenyl)cyclohexanecarbonitrile (2.0 g, 10 mmol) was taken in acetone (150 mL) and then Cs_2CO_3 (8.1 g, 25 mmol) was added followed by dropwise addition of 1,3 dibromopropane (5.1 mL, 50 mmol). The mixture was heated for 3 h at 70°C. After cooling and filtration, the mixture was concentrated and the residue was purified by flash chromatography (50 g silica gel, DCM) to provide the title compound (2.8 g, 87%). Note: presence of allyl derivative as impurity.

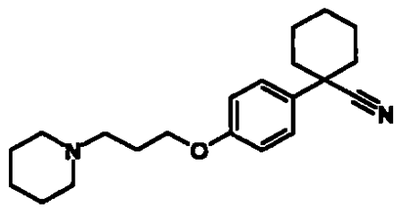
110

General procedure G:



A mixture of 1-[4-(3-bromo-propoxy)-phenyl]-cyclohexanecarbonitrile (0.660 g, 2.0 mmol), amine (NR^7R^8) (0.260g, 3.0 mmol), sodium carbonate (0.320 g, 3 mmol), potassium iodide (20 mg) and 20 mL of butanol was heated for 4 h at 100°C. After cooling, water was added to quench the reaction and the mixture was extracted with DCM. The organics extracts were washed with a saturated aqueous solution of $NaHCO_3$, water and dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (DCM and DCM / MeOH (10% NH_3) to provide (0.440 g, 67%).

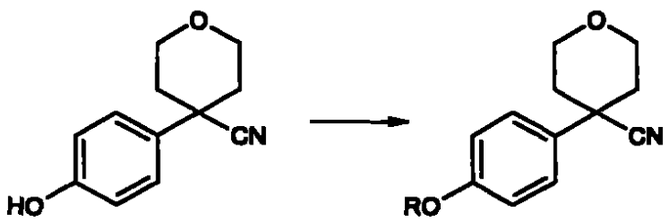
Example 104: 1-[4-(3-piperidin-1-yl-propoxy)-phenyl]-cyclohexane-carbonitrile



A mixture of 1-[4-(3-bromo-propoxy)-phenyl]-cyclohexanecarbonitrile (0.660 g, 2.0 mmol), piperidine (0.260g, 3.0 mmol), sodium carbonate (0.320 g, 3 mmol), potassium iodide (20 mg) and 20 mL of butanol was heated for 4 h at 100°C according to general procedure G. After cooling, water was added to quench the reaction and the mixture was extracted with DCM. The organics extracts were washed with a saturated aqueous solution of $NaHCO_3$, water and dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (DCM and DCM / MeOH (10% NH_3) to provide the title compound (0.440 g, 67%).

^1H NMR (400MHz, $CDCl_3$) δ 7.37 (d, 2H), 6.90(d, 2H), 4.00 (t, 2H), 2.49-2.36 (m, 6H), 2.17-2.09 (m, 2H), 1.97 (qt, 2H), 1.88-1.67 (m, 7H), 1.62-1.55 (m, 4H), 1.47-1.40 (m, 2H), 1.32-1.20 (m, 1H).

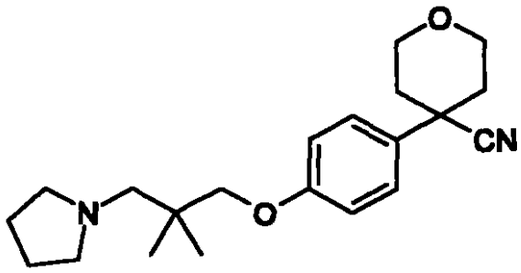
General procedure H:



4-(4-Hydroxy-phenyl)-tetrahydro-pyran-4-carbonitrile (1eq.), alcohol (R-OH) (0.8eq.) and PPh_3 (1eq.) were mixed together in THF (10vol) and cooled to 0°C under N_2. DIAD (1eq.) in THF (10vol) was added slowly to the reaction and allowed to warm to room temperature overnight. The reaction was quenched with 2M HCl solution (10vol) and extracted with ethyl acetate (3 x 10vol). The aqueous was basified to pH 14 with NaOH (~30vol) and extracted with ethyl acetate (3 x 10vol). The organics were dried over $MgSO_4$, filtered

and concentrated *in vacuo* at 35°C. Purification of the crude material by chromatography on silica, eluant (10%MeOH in DCM) provided the title compounds.

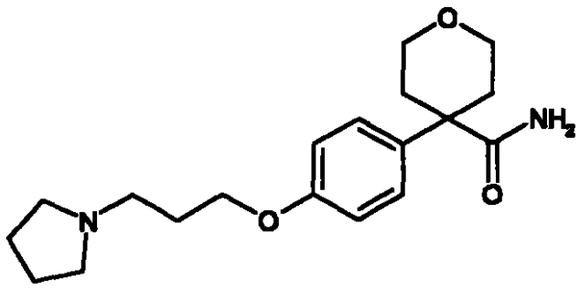
Example 105: 4-[4-(2,2-Dimethyl-3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-pyran-4-carbonitrile



4-(4-Hydroxy-phenyl)-tetrahydro-pyran-4-carbonitrile (1.28g, 6.4mmol), 2,2-dimethyl-3-pyrrolidin-1-yl-propan-1-ol (0.8g, 5.1mmol), PPh_3 (1.67g, 6.4mmol), THF (16ml) and DIAD (1.25ml, 6.4mmol) were reacted together according to general procedure H. The crude material was subjected to chromatography on silica eluting with DCM :MeOH (98 :2). The resulting solid was slurried in TBME:heptanes (1:2, 1ml) to provide the title compound (120mg, 5%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$), δ 7.37 (d, 2H), 6.94 (d, 2H), 4.12-4.03 (m, 2H), 3.89 (td, 2H), 3.71 (s, 2H), 2.57 (br s, 4H), 2.47 (s, 2H), 2.15–1.99 (m, 4H), 1.70 (brs, 4H), 1.00 (s, 6H).

Example 106: 4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxylic acid amide

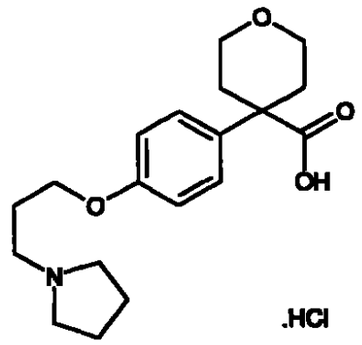


4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-carbonitrile (400 mg, 1.27 mmol) was treated with polyphosphoric acid at 80°C overnight. After allowing the mixture to cool to room temperature, ethyl acetate and water were added. The organic layer was separated. The aqueous layer was basified to pH 10 with concentrated NaOH and extracted with DCM. The combined organic extracts were dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by column chromatography on silica gel eluting to give the title compound (88 mg, 26%).

^{1}H NMR (400MHz, $CDCl_3$) δ7.29 (d, 2H), 6.91(d, 2H), 5.64-5.30 (d, 2H), 4.02 (t, 2H), 3.76 (t, 4H), 2.62 (t, 2H), 2.52 (m, 4H), 2.37-2.30 (m, 2H), 2.08-1.96 (m, 4H), 1.81-1.75 (m, 4H).

Example 107: 4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carboxylic acid

112



.HCl

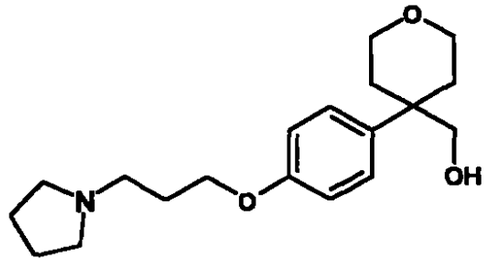
A solution of 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbonitrile (20g, 0.0636mol) in concentrated hydrochloric acid (200ml, 10vol) was heated and stirred at reflux for 16h after which time LC/LCMS analysis showed the reaction had stalled at 85-90% conversion. The solution was evaporated to dryness *in vacuo*, azeotroped with methanol (200ml, 20vol) and toluene (2x 200ml, 2x 20vol) to yield title compound as a beige solid which was used directly.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, 2H), 6.98 (d, 2H), 4.12 (t, 2H), 3.94-3.84 (m, 2H), 3.74-3.66 (m, 2H), 3.60 (dt, 2H), 3.42 (t, 2H), 2.50-2.44 (m, 2H), 2.26-2.00 (m, 8H), 2.96-2.84 (m, 2H);HRMS (ESI$^+$) 334.2013 $(M+H)^+$.

Intermediate 36: Methyl 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carboxylate

A suspension of 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carboxylic acid (23.5g, 0.0636mol) in methanol (235ml, 10vol) was stirred and cooled to 0 to -5°C under nitrogen. Thionyl chloride (9.3ml, 0.1272mol, 0.40vol) was charged dropwise over 20minutes, maintaining the temperature -5 to +5°C. The resulting slurry was then heated and stirred at reflux under nitrogen for 16h after which time LC analysis showed 1.4% by area of acid remaining. The solution was evaporated to dryness *in vacuo* at 40°C to give a brown sludge. The sludge was dissolved in ethyl acetate (118ml, 5vol) and water (235ml, 10vol) and the layers separated. The aqueous layer was washed with ethyl acetate (118ml, 5vol) and basified to pH 11 with saturated aqueous potassium carbonate (118ml, 5vol). The product was extracted into dichloromethane (3x 118ml, 3x 5vol) and the combined extracts dried over magnesium sulfate (23g, 1wt) and concentrated *in vacuo* at 40°C to yield title compound (21.7g, 98% from the nitrile) as a cream solid.

Example 108: {4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methanol



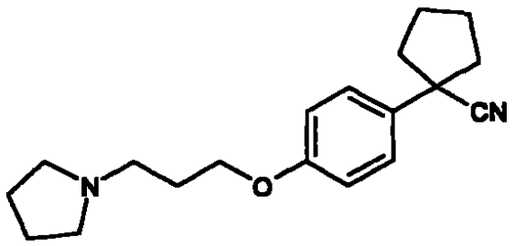
Anhydrous tetrahydrofuran (141ml, 10vol) was charged rapidly onto stirred and cooled (0-5°C) lithium aluminium hydride (6.2g, 0.1634mol, 0.44wt) under nitrogen (Note: very exothermic). The resulting slurry

113

was cooled to 0-5°C and then a solution of methyl 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carboxylate (14.1g, 0.04058mol) in tetrahydrofuran (99ml, 7vol) was added dropwise over 30 minutes maintaining 0-5°C. On complete addition the reaction was allowed to warm to room temperature over 30 minutes and stirred at 18-25°C for 30 minutes, LC analysis showed the reaction to be complete. The mixture was cooled to 0 to 5°C, a 1:1 mixture of tetrahydrofuran and water (18.6ml, 1.32vol) was added very slowly (Note: very exothermic, gas evolution, temperature maintained below 16°C, toward the end of the quench the reaction mixture sets and then becomes freer with continued stirring.). The mixture was further quenched with 20% w/v sodium hydroxide solution (6.2ml, 0.44vol) and water (18.6ml, 1.32vol) and the resulting white suspension stirred vigorously for 30 minutes at 18-25°C. The slats were removed by filtration and rinsed with tetrahydrofuran (3x 150ml). The combined filtrates were evaporated to dryness at 40°C to yield title compound (12.1g, 94%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.25 (d, 2H), 6.90 (d, 2H), 4.05 (t, 2H), 3.80 (dt, 2H), 3.55 (td, 2H), 2.80 (t, 2H), 2.62-2.41 (m, 4H), 2.10 (dt, 2H), 2.00 (p, 2H), 2.00-1.85 (m, 2H), 1.95-1.72 (m, 4H).

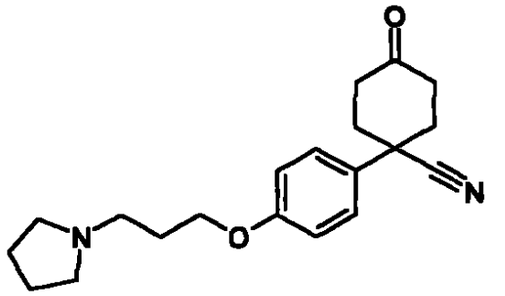
Example 109: 1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclo-pentane-carbonitrile



To a suspension of NaH (60%, 0.574 g, 14.35 mmol) in DMF (8 mL) at 0°C was added dropwise [4-(3-pyrrolidin-1-ylpropoxy)phenyl]acetonitrile (1 g, 4.10 mmol) in DMF (3 mL). The reaction mixture was stirred at 0°C for 5 min then at room temperature for 30 min. After cooling to 0°C, 1,4-dibromobutane (0.960 mL, 8.2 mmol) in DMF (2 mL) was added dropwise. The reaction mixture was allowed to warm up to room temperature then heated to 50°C overnight. It was poured into ice-cold water and extracted with DCM. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was purified by column chromatography, eluting with a gradient of DCM:MeOH:NH_3 (from 99:0:1 to 90:10:1) to give the title compound (0.443 g, 38%).

^{1}H NMR (400MHz, DMSO-d_6) δ7.29 (d, 2H), 6.79 (d, 2H), 4.02 (m, 2H), 3.18 (m, 2H), 2.47-2.28 (m, 4H), 2.19-1.75 (m, 11H), 1.19 (m, 3H).

Example 110: 4-oxo-1-[4-(3-pyrrolidin-1-ylpropoxy)-phenyl]-cyclohexane-carbonitrile



114

Step 1:

A three neck reaction vessel was charged with [4-(3-pyrrolidin-1-ylpropoxy)phenyl]acetonitrile (7g, 28.6 mmol), benzyltrimethylammonium hydroxide (40% in methanol, 1.3 mL) in acetonitrile (185 mL). The solution was heated to reflux and methyl acrylate (25 mL, 286 mmol) was added dropwise. After refluxing for 5 hr, the mixture was concentrated to half, diethyl ether was added and the organics were washed with HCl 1N and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash-chromatography to provide 4-cyano-4-[4-(3-pyrrolidin-1-ylpropoxy)-phenyl]-heptanedioic acid dimethyl ester (8.8 g, 74%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.28 (d, 2H); 6.95 (d, 2H); 4.08-4.0 (m, 2H); 3.6 (s, 6H); 2.68-2.60 (m, 2H); 2.58-2.45 (m, 6H); 2.40-2.20 (m, 4H); 2.20-2.12 (m, 2H); 2.08-2.0 (m, 2H); 1.80-1.75 (m, 4H)

Step 2:

To a solution of 4-cyano-4-[4-(3-pyrrolidin-1-ylpropoxy)-phenyl]-heptanedioic acid dimethyl ester (8.8 g, 21.1 mmol) in 1,2-dimethoxyethane (176 mL) was charged portions of NaH (60% dispersion, 2.55 g, 63.4 mmol). The reaction mixture was heated to reflux. After 4.5 hr, the ¾ of solvent were evaporated and the mixture cooled to 20°C with an ice bath and quenched with water (100 mL), HCl 1N (100 mL). The aqueous layer was extracted with ether (100 mL). After basification with NaOH the aqueous phases were extracted with dichloromethane. The combined organics were washed with water, dried over Na_2SO_4, filtered and concentrated to provide 5-cyano-2-oxo-5-[4-(3-pyrrolidin-1-ylpropoxy)-phenyl]-cyclohexane-carboxylic acid methyl ester (6.6 g, 81%) as an oil.

^{1}H NMR (400MHz, $CDCl_3$) δ 12.2 (bs, 1H); 7.33 (d, 2H); 6.95 (d, 2H); 4.08-4.00 (m, 2H); 3.75 (s, 3H); 2.95 (d, 1H); 2.80-2.70 (m, 1H); 2.65-2.60 (m, 2H); 2.50-2.42 (m, 6H); 2.30-2.15 (m, 2H); 2.05-1.95 (m, 2H); 1.90-1.85 (m, 4H).

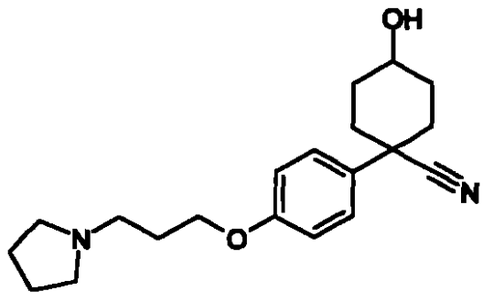
Step 3:

To a solution of 5-cyano-2-oxo-5-[4-(3-pyrrolidin-1-ylpropoxy)-phenyl]-cyclohexanecarboxylic acid methyl ester (6.6 g, 17 mmol) and dimethylsulfoxide (128 mL) was added water (8.0 mL) and sodium chloride (6.4 g, 109 mmol). The reaction mixture was heated to 142-146°C. After 5 hr, the mixture was concentrated and the residue was dissolved in DCM (120 mL), washed with water (100 mL), and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (70 g silica gel, eluent: gradient of DCM/MeOH 95/5 to 90/10) providing 4-oxo-1-[4-(3-pyrrolidin-1-ylpropoxy)-phenyl]-cyclohexanecarbonitrile as a crystallizing oil (2.2 g, 45.5%). After crystallization in ether, 0.2g of analytical sample were obtained.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.32 (d, 2H), 6.88 (d, 2H), 4.1 (t, 2H), 2.95-2.8 (m, 2H), 2.65-2.38 (m, 10H), 2.3-2.15 (m, 2H), 2.0-1.9 (m, 2H), 1.8-1.7 (m, 4H).

Example 111: 4-hydroxy-1-[4-(3-pyrrolidin-1-ylpropoxy)-phenyl]cyclo-hexanecarbonitrile

115



To a stirred suspension of $LiAlH_4$ (0.070 g, 1.85 mmol, 5 eq) in diethyl ether (1.9 mL) was added dropwise at 0°C a solution of 4-oxo-1-[4-(3-pyrrolidin-1-ylpropoxy)-phenyl]-cyclohexanecarbonitrile (0.12 g, 0.37 mmol) in diethyl ether (5.5 mL). The reaction mixture was stirred at ambient temperature for 4 h .The reaction mixture was cooled to 0°C and, successively, a solution of water, sodium hydroxide (15% w/v, 0.08 mL) and water again were carefully dropped. After being stirred for 15 min at room temperature, the mixture was filtered over diatomaceous earth and concentrated. The residue was purified by flash chromatography (10 g silica gel, DCM/ MeOH (10% NH_3) to provide 0.050 g of title compound.

^{1}H NMR (400MHz,DMSO-D6) δ 10.6 (bs, 1H), 7.42 (d, 2H); 7(d, 2H), 4.1-3.95 (m, 2H), 3.8-3.2 (m, 5H), 3.03-2.87 (m, 2H), 2.15-1.8 (m, 10H), 1.85-1.5 (m, 2H).

Intermediate 37: (*R*)-2-Methylpyrrolidine

Pure enantiomers of 2-methyl pyrrolidine can be obtained by resolution with +/- tartaric acid as described in *Acta. Pharm. Suecica* 15, 255-263; 1978.

Intermediate 38: 3-[(2*R*)-2-Methylpyrrolidin-1-yl]propan-1-ol

3-Bromopropan-1-ol (5.28 mL, 58.4 mmol) was added to a solution of (*R*)-2-methylpyrrolidine (7.1 g, 58.4 mmol) in water (200 mL). KOH (7.53 g, 134 mmol) was then added and the mixture stirred at ambient temperature for 48 hours. The reaction mixture was then extracted with dichloromethane (5 x 80 mL) and ethyl acetate (5 x 80 mL). The combined organic extracts were dried using $MgSO_4$, filtered and concentrated *in vacuo*. The compound was purified by column chromatography on Biotage® silica gel, eluting with dichloromethane:methanol:ammonia, (90:10:1) to give the title compound as a pale brown oil (5.44, 65 %).

LCMS (APCI$^+$) 144 $(M+H)^+$.

Intermediate 39: *tert*-Butyl (3*S*)-3-methoxypyrrolidine-1-carboxylate

Sodium hydride (60 % dispersion in mineral oil, 940 mg, 0.024 mmol) was added in two portions at 0 °C to a solution of *tert*-butyl (3*S*)-3-hydroxypyrrolidine-1-carboxylate (4.00 g, 0.02 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 1 h before being cooled once more to 0 °C. Methyl iodide (2.00 mL, 0.032 mmol) was added slowly and the reaction mixture warmed to room temperature overnight. The mixture was poured slowly onto 200 mL of ice and stirred until the ice was fully thawed. The product was extracted using dichloromethane (2 x 250 mL), dried (Na_2SO4) and concentrated in vacuo. The compound was purified by column chromatography on Biotage® silica gel, eluting with dichloromethane to give the product as a colourless oil (2.88 g, 67 %).

116

Intermediate 40: (3S)-3-Methoxypyrrolidine

A solution of trifluoroacetic acid (2.5 ml) in dichloromethane (5 mL) was added slowly at 0 °C to a solution of *tert*-Butyl (3*S*)-3-methoxypyrrolidine-1-carboxylate (2.88 g, mmol) and the reaction allowed to warm to room temperature and stirred for 2.5 h. The reaction mixture was quenched with saturated sodium carbonate solution (100mL) and extracted with dichloromethane (2 x 200mL). The organics were combined, dried over magnesium sulphate and concentrated *in vacuo*. The residue was taken up in dichloromethane (30 mL) and cooled to 0 °C in an ice bath. Hydrogen chloride gas was bubbled through the suspension for 1 hour and the reaction mixture allowed to stir at room temperature for 48 hours. The reaction mixture was basified with saturated sodium hydrogencarbonate solution (100 mL) and extracted with dichloromethane (2 x 200mL) and ethyl acetate (3 x 150mL). The aqueous was concentrated *in vacuo* and then extracted with warm methanol to yield the title product, 2.00g.

Intermediate 41: (3*R*)-1-Benzyl-3-methoxypyrrolidine

(3*R*)-1-Benzyl-3-methoxypyrrolidine was prepared as described in the following patent WO 91/08206 and taken on to the next step as the crude mixture.

Intermediate 42: (3*R*)-3-Methoxypyrrolidine

A solution of (3*R*)-1-Benzyl-3-methoxypyrrolidine (2.35 g, 12.3 mmol) in methanol (50 mL) containing concentrated HCl (1 mL) was hydrogenated at ambient temperature at 50 psi in the presence of a catalytic amount of 10 % $Pd(OH)_2$ on carbon (250 mg, 10% w/w). The reaction mixture was filtered over celite and rinsed with dichloromethane (60 mL) and methanol (60 mL) to remove the catalyst. The organic layer was basified with NaOH (2.0M, 10 mL) and extracted with diethylether (3 x 30 mL). The aqeous layer was further acidified to pH3 using concentrated HCl, concentrated in vacuo and azeotroped with toluene to give the product as a yellow solid which was further used without purification.

Intermediate 43: 2,2-Dimethylpyrrolidine

Step 1: 1-Benzyl-2,2-dimethylpyrrolidine was prepared according to the procedure described in the following reference. S. M. Denton and A. Wood, *Synlett*, 1999, 55.

Step 2: A solution of 1-Benzyl-2,2-dimethylpyrrolidine (1.02g, 5.40 mmol) in ethanol (60 mL) and concentrated HCl (0.5 mL) was hydrogenated over 20 % $Pd(OH)_2$ (100 mg, 10 % w/w) at 60 psi at ambient temperature for 4 hours. The reaction mixture was filtered over arbocel to remove the catalyst and a further 2 mL of concentrated HCl was added to the crude product. The reaction mixture was then concentrated in vacuo and azeotropically dried using toluene to give the product as a brown solid, which appeared to be slightly hygroscopic (732 mg, 100 %).

Intermediate 44: (2*R*,5*S*)-2,5-Dimethylpyrrolidine

The free base of *cis*-2,5-dimethylpyrrolidine was prepared as described by C. G. Overberger, L. C. Palmer, B. S. Marks and N. R. Byrd, *J. Am. Chem. Soc.*, 1955, 77, 4100. This was then acidified using HCl (2.0 M solution in diethylether) which, upon filtration and subsequent recrystallisation from acetonitrile

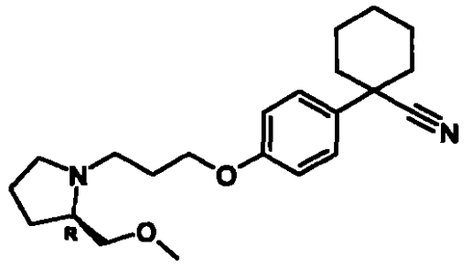
117

and *i*-propylalcohol gave the title compound as a white crystalline solid (5.29 g, 22 %) in a ratio of approximately 10:1 ratio of cis:trans.

Intermediates 45 and 46: 1-[4-(3-bromo-propoxy)phenyl]cyclohexane-carbonitrile and 1-[4-(3-chloro-propoxy)-phenyl]-cyclohexane-carbonitrile

K_2CO_3 (3.02 g, 21.9 mmol) was added to a solution of 1-(4-hydroxyphenyl)cyclohexanecarbonitrile (4.0 g, 19.9 mmol) in DMF (50 mL). 1-bromo-3-chloropropane (1.97 ml, 19.9 mmol) was then added dropwise and the reaction heated at 60°C overnight. The reaction mixture was concentrated, quenched by adding water (50 mL), extracted with dichloromethane (2 x 50 mL) and the organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The compound was purified by column chromatography on Biotage® silica gel, eluting with diethylether:dichloromethane, 50:50 to 0:100. Yield: 5.32 g (98 % of a 3:1 mixture of chloro and bromo compound).

Example 112: 1-(4-[3-[(2*R*)-2-(methoxymethyl)pyrrolidin-1-yl]propoxy)-phenyl]cyclohexanecarbonitrile



A (1:3) mixture of 1-[4-(3-bromo-propoxy)-phenyl]-cyclohexanecarbonitrile and 1-[4-(3-chloro-propoxy)-phenyl]-cyclohexanecarbonitrile (2.00g, 7.20 mmol), Cs_2CO_3 (2.58 g, 7.20 mmol), potassium iodide (0.20 g, 1.20 mmole) and (R)-(-)-2-(methoxymethyl)pyrrolidine (1.07 mL, 8.60 mmol) in NMP (20 mL) was heated to 75 °C overnight. The reaction mixture was cooled to ambient temperature, concentrated in *vacuo*, and quenched by adding water (30 mL). The crude product was extracted with ethyl acetate (30 x mL) and the organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The compound was purified by column chromatography on Biotage® silica gel, eluting with dichloromethane:methanol:ammonia, 100:0:0 to 90:10:1 to give the title compound as a brown oil (1.39 g, 54%).

^{1}H NMR (400MHz, $CDCl_3$) δ7.38 (d, 2H), 6.70 (d, 2H), 4.02 (t, 2H), 3.46-3.36 (m, 1H), 3.36-3.26 (m, 3H), 3.24-3.16 (m, 1H), 3.12-3.04 (m, 1H), 2.72-2.58 (m, 1H), 2.52-2.44 (m, 1H), 2.30-2.20 (m, 1H), 2.18-2.06 (m, 2H), 1.98 (pentet, 2H), 1.92-1.60 (m, 12H), 1.36-1.16 (m, 1H); HRMS (ESI^+) 357.2537 $(M+H)^+$.

Example 113: 1-(4-[3-[(3*S*)-3-methoxypyrrolidin-1-yl]propoxy)phenyl]cyclo-hexanecarbonitrile

This page is not part of

the document!

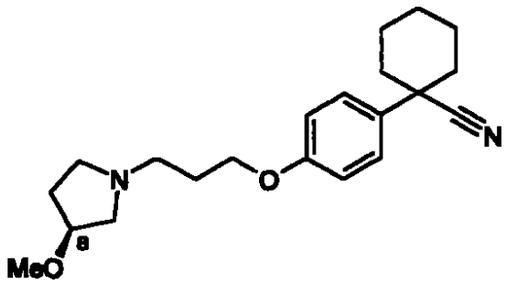
IB2005001114 / 2005-108384

2/2

Date: Nov 17, 2005

Recipient: IB

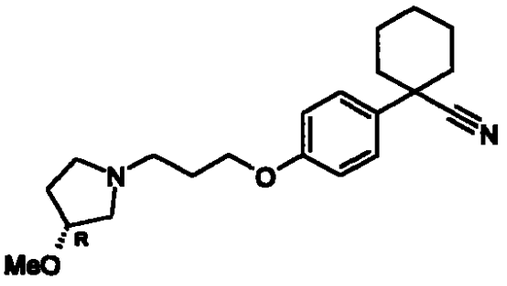
Address: Bureau international de l'OMPI 34, chemin des Colombettes Geneve 20 1211 CH



A (1:3) mixture of 1-[4-(3-bromo-propoxy)-phenyl]-cyclohexanecarbonitrile and 1-[4-(3-chloro-propoxy)-phenyl]-cyclohexanecarbonitrile (200 mg, 0.72 mmol), *N,N*-diisopropylethylamine (251 µL, 1.44 mmol) and (*S*)-3-methoxy-pyrrolidine (198 mg, 1.96 mmol) in NMP (0.5 mL) was heated at 160 °C in the microwave (Smith Personal Synthesiser) for 400 seconds. The reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (2 x 10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The compound was purified by column chromatography on Biotage® silica gel, eluting with dichloromethane:methanol:ammonia, 97:3:0.3 to 95:5:0.5. to give the product as a clear oil (102 mg, 41%).

^{1}H NMR (400MHz, $CDCl_3$) δ7.36 (d, 2H), 6.90 (d, 2H), 4.02 (t, 2H), 3.96-3.88 (m, 1H), 3.28 (s, 3H), 2.86-2.52 (m, 6H), 2.18-1.96 (m, 5H), 1.88-1.66 (m, 8H), 1.38-1.16 (m, 1H); LCMS (APCI$^+$) 343 $(M+H)^+$.

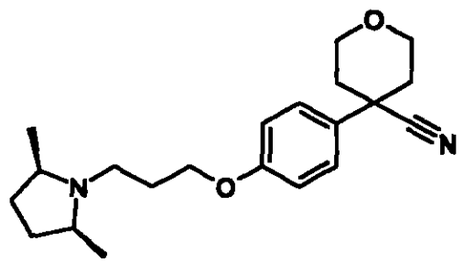
Example 114: 1-(4-(3-[(3*R*)-3-methoxypyrrolidin-1-yl]propoxy)phenyl)-cyclohexanecarbonitrile



A (1:3) mixture of 1-[4-(3-bromo-propoxy)-phenyl]-cyclohexanecarbonitrile and 1-[4-(3-chloro-propoxy)-phenyl]-cyclohexanecarbonitrile (200 mg, 0.72 mmol), *N,N*-diisopropylethylamine (251 µL, 1.44 mmol) and (*R*)-3-methoxy-pyrrolidine (198 mg, 1.44 mmol) in NMP (0.5 mL) was heated at 160 °C in the microwave (Smith Personal Synthesiser) for 600 seconds. The reaction mixture was quenched with water (30 mL) and extracted with ethylacetate (2 x 30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The compound was purified by column chromatography on Biotage® silica gel, eluting with dichloromethane:methanol:ammonia, 98:2:0.2 to 95:5:0.5 to give a brown oil (37 mg, 11 %).

^{1}H NMR (400MHz, $CDCl_3$) δ7.38 (d, 2H), 6.90 (d, 2H), 4.02 (t, 2H), 3.94-3.88 (m, 1H), 3.28 (s, 3H), 2.74-2.66 (m, 2H), 2.64-2.56 (m, 2H), 2.46 (quintet, 2H), 2.17-1.94 (m, 5H) 1.88-1.66 (m, 8H) 1.32-1.18 (m, 1H); HRMS (ESI$^+$) 343.2380 $(M+H)^+$.

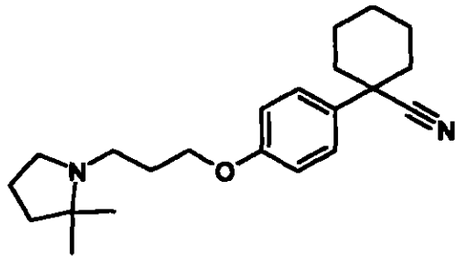
Example 115: 4-(4-[3-[(2*R*,5*S*)-2,5-dimethylpyrrolidin-1-yl]propoxy]-phenyl)-tetrahydro-2*H*-pyran-4-carbonitrile



A (1:3) mixture of 1-[4-(3-bromo-propoxy)-phenyl]-cyclohexanecarbonitrile and 1-[4-(3-chloro-propoxy)-phenyl]-cyclohexanecarbonitrile (150 mg, 0.54 mmol), *N,N*-diisopropylethylamine (187 µL, 1.07 mmol) and (2*R*,5*S*)-2,5-dimethylpyrrolidine (145 mg, 1.07 mmol) in NMP (0.5 mL) was heated at 160°C in the microwave (Smith Personal Synthesiser) for 400 seconds then 170 °C for 600 seconds. The reaction mixture was quenched with $NaHCO_3$ (15 mL) and extracted with ethyl acetate (2 x 15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The compound was purified by column chromatography on Biotage® silica gel, eluting with dichloromethane:methanol:ammonia, 97:3:0.3 to 90:10:1. Yield = 28 %

^{1}H NMR (400MHz, $CDCl_3$) δ7.36 (d, 2H), 6.82 (d, 2H), 4.10-4.04 (*m*, 2H), 4.00 (t, 2H), 3.88 (dt, 2H), 2.72 (t, 2H), 2.64-2.52 (m, 2H), 2.14-1.98 (*m*, 4H), 1.94 (*pentet*, 2H), 1.86-1.78 (*m*, 2H), 1.42-1.28 (*m*, 2H), 1.10 (d, 6H); HRMS (ESI^+) 343.2380 $(M+H)^+$.

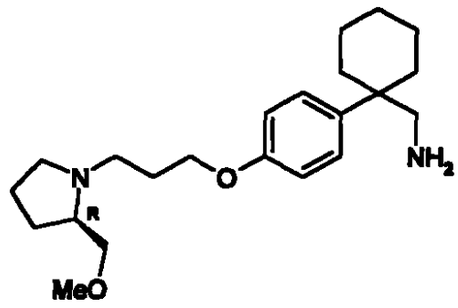
Example 116: 1-[4-[3-(2,2-dimethylpyrrolidin-1-yl)propoxy]phenyl]cyclo-hexanecarbonitrile



A (1:3) mixture of 1-[4-(3-bromo-propoxy)-phenyl]-cyclohexanecarbonitrile and 1-[4-(3-chloro-propoxy)-phenyl]-cyclohexanecarbonitrile (150 mg, 0.54 mmol), *N,N*-diisopropylethylamine (188 µL, 1.08 mmol) and 2,2-dimethyl-pyrrolidine (131 mg, 1.08 mmol) in NMP (0.5 mL) was heated at 180°C in the microwave (Smith Personal Synthesiser) for 600 seconds. The reaction mixture was quenched with water (15 mL) and extracted with ethyl acetate (2 x 15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The compound was purified by column chromatography on Biotage® silica gel, eluting with dichloromethane:methanol:ammonia, 98:2:0.2 to 95:5:0.5 to give the title compound as a brown oil (31 mg, 17 %).

^{1}H NMR (400MHz, $CDCl_3$) δ7.38 (d, 2H), 6.90 (d, 2H), 4.04 (t, 2H), 2.78 (t, 2H), 2.54 (t, 2H), 2.16-2.12 (m, 2H), 1.94 (pentet, 2H), 1.90-1.64 (m, 11H), 1.20-1.34 (m, 1H), 0.98 (s, 6H); HRMS (ESI^+) 341.2588 $(M+H)^+$.

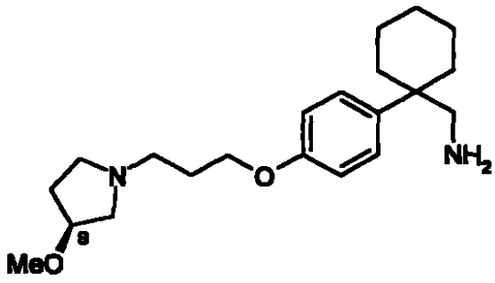
Example 117: 1-[1-(4-[3-[(2*R*)-2-(methoxymethyl)pyrrolidin-1-yl]propoxy)-phenyl]cyclohexyl]methanamine



To a stirred suspension of $LiAlH_4$ (1.0M in diethyl ether, 13.7 ml, 13.7 mmol) at 0°C under an atmosphere of nitrogen was added 1-(4-{3-[(2*R*)-2-(methoxymethyl)pyrrolidin-1-yl]propoxy}phenyl)cyclohexanecarbonitrile (0.980 g, 2.7 mmol) in Et_2O (15 mL) over 15 minutes maintaining the temperature at 5 to 10°C. The reaction mixture was allowed to warm up to ambient temperature for 20 minutes then refluxed for 30 minutes until complete. The reaction mixture was cooled to 0°C, water (0.5 mL) was added followed by NaOH (2.0M, 1.5 mL) and water (0.5 mL). Ethyl acetate (5 mL) was added and the mixture filtered through a short pad of celite, eluting with ethyl acetate (2 x 15 mL). The organic washings were dried over Na_2SO_4 and concentrated *in vacuo*. The compound was purified by column chromatography on Biotage® silica gel, eluting with dichloromethane:methanol:ammonia, 98:2:0.2 to 95:5:0.5 to give the title compound as a clear oil (309 mg, 32 %).

^1H NMR (400MHz, $CDCl_3$) δ 7.22 (d, 2H), 6.88 (d, 2H), 4.04-3.96 (m, 2H), 3.32 (m, 3H), 3.26-3.20 (m, 1H), 3.14-3.04 (m, 1H), 2.74-2.62 (m, 1H), 2.60 (s, 2H), 2.56-2.46 (m, 1H), 2.28 (quartet, 1H), 2.12-1.96 (m, 4H), 1.96-1.90 (m, 1H), 1.82-1.70 (m, 2H), 1.68-1.46 (m, 8H), 1.36-1.30 (m, 3H); HRMS (ESI^+) 361.2850 $(M+H)^+$.

Example 118: {[1-(4-{3-[(3*S*)-3-methoxypyrrolidin-1-yl]propoxy}-phenyl)-cyclohexyl]methyl}amine

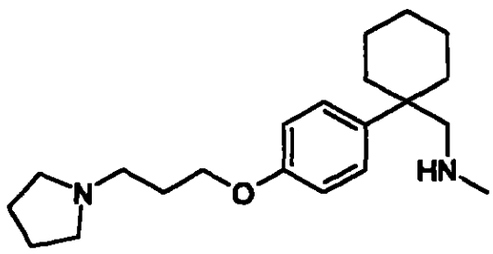


To a stirred suspension of $LiAlH_4$ (1.0M in diethyl ether, 1.46 ml, 1.46 mmol) at 0°C under an atmosphere of nitrogen was added a solution of 1-(4-{3-[(3*S*)-3-methoxypyrrolidin-1-yl]propoxy}phenyl)cyclohexanecarbonitrile (0.10 g, 0.29 mmol) in Et_2O (2 mL) over 15 minutes maintaining the temperature at 5 to 10°C. The reaction mixture was allowed to warm up to ambient temperature for 20 minutes then refluxed for 30 minutes until complete. The reaction mixture was cooled to 0°C, water (0.5 ml) was added dropwise followed by sodium hydroxide (2.0M, 1.5 ml) and water (0.5 ml). Ethyl acetate (5 mL) was added and the mixture filtered through a short pad of celite, eluting with ethyl acetate (2 x 15 mL). The organic washings were dried over Na_2SO_4 and concentrated *in vacuo*. The compound

was purified by column chromatography on Biotage® silica gel, eluting with dichloromethane:methanol:ammonia, 97:3:0.3 to 90:10:1 to give the title compound as a clear oil (75 mg, 75 %).

^{1}H NMR (400MHz, $CDCl_3$) δ7.20 (d, 2H), 6.86 (d, 2H), 4.02 (t, 2H), 3.94-3.88 (m, 1H), 3.28 (s, 3H), 2.78-2.68 (m, 2H), 2.58-2.66 (m, 3H), 2.45-2.52 (m, 1H), 2.12-2.04 (m, 3H), 1.98 (pentet, 2H), 1.84-1.74 (m, 1H), 1.56-1.44 (m, 5H), 1.38-1.30 (m, 3H), 1.16-1.25 (m, 2H); HRMS (ESI$^+$) 347.2693 $(M+H)^+$.

Example 119: *N*-methyl-1-[1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclo-hexyl]methanamine



To a stirred solution of ({1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclo-hexyl}methyl)amine (0.60 g, 1.90 mmol) and *N,N*-diisopropylethylamine (330µL, 1.90 mmol) in dry dichloromethane (6 mL) at 0 °C was added dropwise a solution of di-*tert*-butyldicarbonate (455 mg, 2.09 mmol) in dry dichloromethane (4 mL). The reaction was allowed to warm to ambient temperature and stirred for a further 2 hours. The reaction mixture was concentrated *in vacuo*, partitioned between $NaHCO_3$ (20 mL) and dichloromethane (20 mL) and extracted with a further 20 mL of dichloromethane. The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure to provide the crude product. The compound was purified by column chromatography on silica gel, eluting with DCM/MeOH/NH_3 (95:5:0.5) to give *tert*-butyl ({1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl}methyl)-carbamate as a clear oil (642 mg, 81 %).

^{1}H NMR complicated by the presence of rotamers.

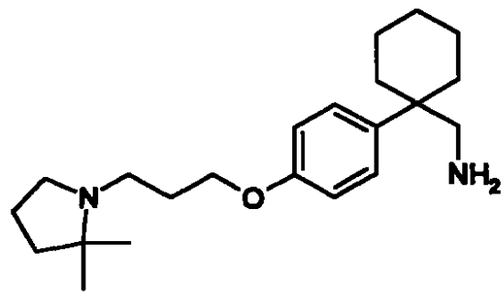
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, 2H), 6.80 (d, 2H), 4.12 (brs, 1H), 4.02 (t, 2H), 3.24-3.06 (m, 2H), 2.66 (t, 2H) 2.56-2.46 (m, 4H), 2.08-1.94 (m, 4H), 1.84-1.72 (m, 4H), 1.62-1.54 (m, 4H), 1.48-1.28 (m, 13H) LCMS (ESI$^+$) 417 $(M+H)^+$ 439 $(M+Na)^+$.

Step 2:

A solution of *tert*-butyl ({1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl}methyl)-carbamate (600 mg, 1.44 mmol) in Et_2O (5 mL) was added dropwise to a stirred solution of $LiAlH_4$ (1.0M solution in Et_2O, 4.32 mL, 4.32 mmol) at 0°C. THF (5 mL) was added and the reaction mixture heated at reflux overnight. Reaction mixture was cooled to 0°C quenched with water (0.5 mL), aqueous NaOH (2.0M, 0.5 mL) and water (0.5 mL). Dichloromethane and ethyl acetate were added and the mixture filtered over a short pad of celite, and concentrated *in vacuo*. The compound was purified by column chromatography on Biotage® silica gel, eluting with dichloromethane:methanol:ammonia, 96:4:0.4 to 90:10:1 to give the title compound as a clear oil (230 mg, 48 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, 2H), 6.68 (d, 2H), 4.02 (t, 2H), 2.64 (t, 2H) 2.54 (s, 2H), 2.50-2.58 (m, 4H), 2.26 (s, 3H), 2.14-2.08 (m, 2H), 1.96 (pentet, 2H), 1.84-1.76 (m, 4H), 1.68-1.56 (m, 2H), 1.52-1.32 (m, 6H); HRMS (ESI$^+$) 331.2744 $(M+H)^+$.

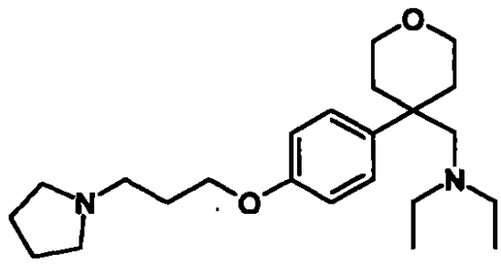
Example 120: [(1-{4-[3-(2,2-dimethylpyrrolidin-1-yl)propoxy]phenyl}-cyclo-hexyl)methyl]amine



To a stirred suspension of $LiAlH_4$ (1.0M in diethyl ether, 0.4 ml, 0.40 mmol) at 0°C under an atmosphere of nitrogen was added 1-{4-[3-(2,2-dimethylpyrrolidin-1-yl)propoxy]phenyl}cyclohexanecarbonitrile (27 mg, 0.079 mmol) in Et_2O (15 mL) over 15 minutes maintaining the temperature at 5 to 10°C. The reaction mixture was allowed to warm up to ambient temperature for 20 minutes then refluxed for 30 minutes until complete. The reaction mixture was cooled to 0°C, water (0.5 mL) was added followed by NaOH (2.0M, 1.5 mL) and water (0.5 mL). Ethyl acetate (5 mL) was added and the mixture filtered through a short pad of celite, eluting with ethyl acetate (2 x 15 mL) and concentrated *in vacuo*. The compound was purified by column chromatography on Biotage® silica gel, eluting with dichloromethane:methanol:ammonia, 97:3:0.3 to give the title compound as a clear oil (10 mg, 37 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, 2H), 6.84 (d, 2H), 4.02 (t, 2H), 2.88-2.78 (m, 2H), 2.66 (s, 2H), 2.58-2.50 (m, 2H), 2.18-2.06 (m, 2H), 2.00-2.90 (m, 2H), 1.84-1.72 (m, 2H), 1.70-1.64 (m, 2H), 1.58-1.46 (m, 4H), 1.40-1.32 (m, 4H), 1.02 (s, 6H). HRMS (ESI$^+$) 345.2901 $(M+H)^+$.

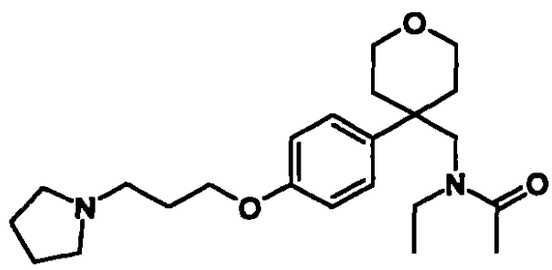
Example 121: *N*-ethyl-*N*-{(4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl)methyl}ethanamine



A solution of *N*-ethyl-*N*-{(4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl)methyl}acetamide (119mg, 0.307 mmol) in tetrahydrofuran (1 mL) was added dropwise at 0°C to a solution of $LiAlH_4$ (1.0M in diethylether, 0.614 mL, 0.614 mmol) under an atmosphere of nitrogen. The reaction mixture was allowed to warm to ambient temperature overnight. The reaction mixture was cooled to 0°C, water (0.5 mL) was then added dropwise followed by sodium hydroxide (2.0M, 0.5 mL) and water (0.5 mL) again. The resulting solid was filtered over a small pad of celite, washed with DCM (100 mL) and concentrated *in vacuo*. The compound was purified by column chromatography on Biotage® silica gel, eluting with dichloromethane:methanol:ammonia, 94.5:5.5:0.55 to 91:9:0.9 to give the title compound as a pale yellow oil (61 mg, 53%).

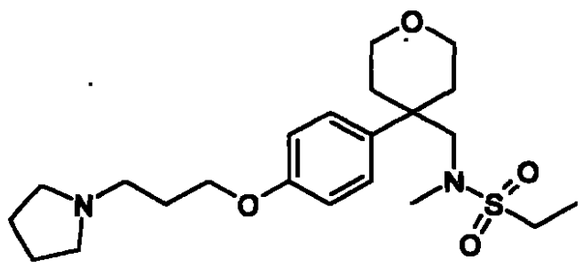
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, 2H), 6.86 (d, 2H), 4.02 (t, 2H), 3.70-3.78 (m, 2H), 3.48 (dt, 2H), 2.84 (t, 2H), 2.58-2.46 (m, 4H), 2.38 (s, 2H), 2.20 (quartet, 4H), 2.13-1.96 (m, 4H), 1.92-1.86 (m, 2H), 1.82-1.78 (m, 4H), 0.82 (t, 6H); HRMS (ESI$^+$) 375.3006 $(M+H)^+$.

Example 122: *N*-ethyl-*N*-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}methyl)acetamide



Acetyl chloride (14 µL, 0.20 mmol) was added dropwise to a solution of *N*-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}methyl)ethanamine (70 mg, 0.20 mmol) and triethylamine (28 µL, 0.20 mmol) in THF (0.50 mL) at 0°C and the reaction stirred for 2 hours. The reaction was quenched using $NaHCO_3$ (10 mL), extracted with dichloromethane (3 x 10 mL) and the organic extracts dried over Na_2SO_4, filtered and concentrated *in vacuo*. The compound was purified by column chromatography on silica, eluting with DCM/MeOH/NH_3 (95:5:0.5) to provide the title compound as a clear oil (33 mg, 42 %).
^{1}H NMR complicated by the presence of rotamers.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.12 (m, 2H), 6.92-6.86 (m, 2H), 4.06-4.00 (m, 2H), 3.88-3.76 (m, 2H), 2.56-2.48 (m, 2H), 3.42 (s, 2H), 2.66 (t, 2H), 2.58-2.52 (m, 4H), 2.48 (quartet, 2H), 2.08 (s, 3H), 2.06-1.92 (m, 6H), 1.84-1.76 (m, 4H), 0.98 (t, 0.6 H) 0.86 (t, 2.4H). HRMS (ESI$^+$) 389.2799 $(M+H)^+$.

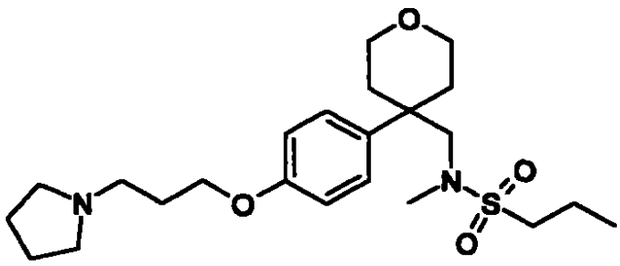
Example 123: *N*-methyl-*N*-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]-tetrahydro-2*H*-pyran-4-yl}methyl)ethanesulfonamide



Ethanesulfonyl chloride (43 µL, 0.456 mmol) was added dropwise to a solution of triethylamine (58 µL, 0.418 mmol) and *N*-methyl-1-[1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl]methanamine (125 mg, 0.38 mmol) in dichloromethane (1 mL) at 0°C and the reaction stirred for 30 minutes. The reaction was quenched with $NaHCO_3$ (20 mL), extracted using dichloromethane (3 x 10 mL), dried using Na_2SO_4 and concentrated *in vacuo*. The compound was purified by column chromatography on Biotage® silica gel, eluting with dichloromethane:methanol:ammonia, 98:2:0.2 to 96:4:0.4 to give the title compound as a pale brown oil (152 mg, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, 2H), 6.90 (d, 2H), 4.04 (t, 2H), 3.84-3.76 (m, 2H), 2.56-2.50 (m, 2H), 3.26 (s, 2H), 2.88 (quartet, 2H), 2.68 (t, 2H), 2.60-2.52 (m, 4H), 2.22 (s, 3H), 2.30-2.12 (m, 2H), 2.02 (pentet, 2H), 1.98-1.90 (m, 2H), 1.86-1.76 (m, 4H) 1.34 (t, 3H); HRMS (ESI$^+$) 425.2469 $(M+H)^+$.

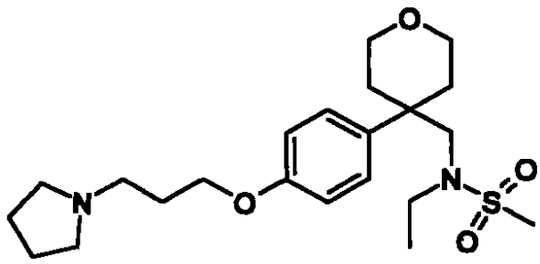
Example 124: *N*-methyl-*N*-{[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]-tetrahydro-2*H*-pyran-4-yl]methyl}propane-1-sulfonamide



n-Propylsulfonyl chloride (33 μL, 0.289 mmol) was added dropwise to a solution of triethylamine (37 μL, 0.265 mmol) and *N*-methyl-1-[1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl]methanamine (80 mg, 0.24 mmol) in dichloromethane (1 mL) at 0°C and the reaction stirred for 1 hour. The reaction was quenched with $NaHCO_3$ (20 mL), extracted using dichloromethane (3 x 15 mL), dried using Na_2SO_4 and concentrated *in vacuo*. The compound was purified by column chromatography on Biotage® silica gel, eluting with dichloromethane:methanol:ammonia, 98:2:0.2 to 92:8:0.8 to give the title compound as a pale brown oil (82 mg, 59%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, 2H), 6.90 (d, 2H), 4.02 (t, 2H), 3.82-3.74 (m, 2H), 3.50 (dt, 2H), 3.20 (s, 2H), 2.74 (dt, 2H), 2.64 (t, 2H), 2.56-2.48 (m, 4H), 2.20 (s, 3H), 2.18-2.12 (m, 2H), 2.02 (pentet, 2H), 1.98-1.84 (m, 2H), 1.82-1.68 (m, 6H) 1.00 (t, 3H); HRMS (ESI$^+$) 439.2625 $(M+H)^+$.

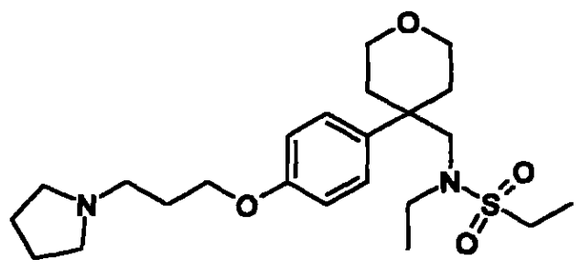
Example 125: *N*-ethyl-*N*-{[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl]methyl}methanesulfonamide



Methanesulfonyl chloride (19 μL, 0.24 mmol) was added dropwise to a solution of triethylamine (31 μL, 0.22 mmol) and *N*-{[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl]methyl}ethanamine (70 mg, 0.20 mmol) in dichloromethane (0.6 mL) at 0°C then was allowed to warm to ambient temperature and stirred overnight. The reaction was quenched with $NaHCO_3$ (10 mL), extracted using dichloromethane (3 x 15 mL), dried using Na_2SO_4 and concentrated *in vacuo*. The compound was purified by column chromatography on Biotage® silica gel, eluting with dichloromethane:methanol:ammonia, 98.5:3.5:0.35 to 95:5:0.5 to give the title compound as a pale brown oil (60 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, 2H), 6.90 (d, 2H), 4.02 (t, 2H), 3.84-3.72 (m, 2H), 3.50 (dt, 2H), 3.28 (s, 2H), 2.72-2.60 (m, 7H), 2.58-2.52 (m, 4H), 2.16 (m, 2H), 2.04 (pentet, 2H), 1.96-1.90 (m, 2H), 1.84-1.76 (m, 4H), 0.90 (t, 3H); HRMS (ESI$^+$) 425.2469 $(M+H)^+$.

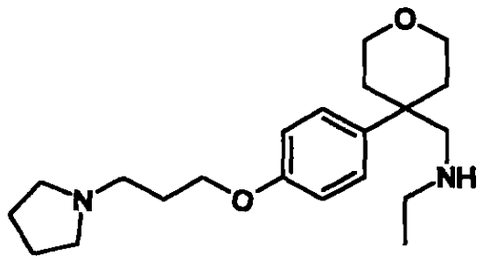
Example 126: *N*-ethyl-*N*-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}methyl)ethanesulfonamide



Ethanesulfonyl chloride (26 µL, 0.28 mmol) was added dropwise to a solution of triethylamine (35 µL, 0.25 mmol) and *N*-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}methyl)ethanamine (76 mg, 0.23 mmol) in dichloromethane (0.5 mL) at 0°C allowed to warm to ambient temperature and stirred overnight. The reaction was quenched with $NaHCO_3$ (10 mL), extracted using dichloromethane (3 x 10 mL), dried using Na_2SO_4 and concentrated *in vacuo*. The compound was purified by column chromatography on Biotage® silica gel, eluting with dichloromethane:methanol:ammonia, 98.5:3.5:0.35 to 95:5:0.5 to give the title compound as a pale brown oil (55 mg, 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, 2H), 6.90 (d, 2H), 4.02 (t, 2H), 3.84-3.72 (m, 2H), 3.48 (t, 2H), 3.32 (s, 2H), 2.78 (quartet, 2H), 2.72-2.60 (m, 4H), 2.60-2.48 (m, 4H), 2.20-2.08 (m, 2H), 2.04 (pentet, 2H), 1.98-1.90 (m, 2H), 1.86-1.76 (m, 4H), 1.30 (t, 3H), 0.88 (t, 3H). HRMS (ESI$^+$) 439.2625 $(M+H)^+$.

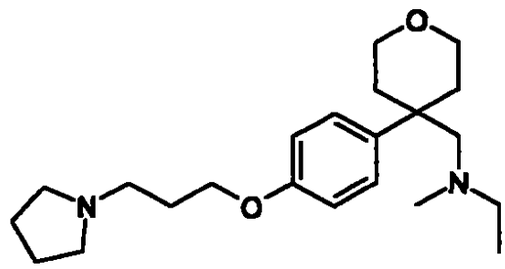
Example 127: *N*-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}methyl)ethanamine



$LiAlH_4$ (1.0M in diethylether, 4.72 mL, 4.72 mmol) was added dropwise at 0°C to a solution of (*N*-[4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-acetamide (848 mg, 2.36 mmol) in tetrahydrofuran (2 mL) under an atmosphere of nitrogen. The reaction mixture was allowed to warm to ambient temperature for 2 hours then heated to 50°C for 10 hours. The reaction mixture was cooled to 0°C, water (3 mL) was added dropwise followed by sodium hydroxide (2.0M, 6 mL) and water (3 mL). The resulting solid was filtered over a small pad of celite, washed with Et_2O/DCM (1:1 6 x 50 mL) and concentrated *in vacuo* to give the title compound as a pale yellow solid (635 mg, 78 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, 2H), 6.88 (d, 2H), 4.02 (t, 2H), 3.80-3.68 (m, 2H), 3.55 (dt, 2H), 2.68 (s, 2H), 2.60 (t, 2H), 2.58-2.42 (m, 6H), 2.18-2.08 (m, 2H), 2.00 (pentet, 2H) 1.94-1.86 (m, 2H), 1.84-1.76 (m, 4H), 1.92 (t, 3H). HRMS (ESI$^+$) 347.2693 $(M+H)^+$.

Example 128: *N*-methyl-*N*-[(4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetra-hydro-2*H*-pyran-4-yl)methyl]ethanamine



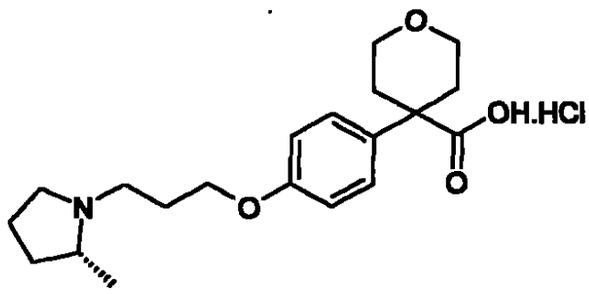
A solution of $LiAlH_4$ (1.0M in diethylether, 1.20 mL, 0.60 mmol) was added dropwise at 0°C to a solution of *N*-methyl-*N*-[4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-acetamide (220 mg, 0.60 mmol) in tetrahydrofuran (1 mL) under an atmosphere of nitrogen. The reaction mixture was allowed to warm to ambient temperature overnight. The reaction mixture was cooled to 0°C, water (1 mL) was added dropwise followed by sodium hydroxide (2.0M, 3 mL) and water (1 mL). The resulting solid was filtered over a small pad of celite, washed with DCM (150 mL) and concentrated *in vacuo*. The compound was purified by column chromatography on Biotage® silica gel, eluting with dichloromethane:methanol:ammonia, 97.5:2.5:0.25 to 95.5:4.5:0.45 to give the title compound as a pale yellow oil (114 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, 2H), 6.86 (d, 2H), 4.04 (t, 2H), 3.78-3.70 (m, 2H), 3.52 (dt, 2H), 2.66 (t, 2H), 2.52-2.66 (m, 4H), 2.36 (s, 2H), 2.16 (quartet, 2H), 2.00-2.12 (m, 4H), 1.92-1.86 (m, 5H), 1.82-1.76 (m, 4H), 0.86 (t, 3H); HRMS (ESI$^+$) 361.2850 $(M+H)^+$.

Intermediate 47: 4-(4-[3-[(2*S*)-2-methylpyrrolidinyl]propoxy]phenyl)-tetrahydro-2*H*-pyran-4-carbonitrile

A solution of 4-(4-hydroxy-phenyl)-tetrahydro-pyran-4-carbonitrile (203 mg, 1.0 mmol) and tri-*n*-butylphosphine (299 µL, 1.20 mmol) in toluene (6 mL) were added to a solution of 3-[(2*R*)-2-methylpyrrolidin-1-yl]propan-1-ol (172 mg, 1.20 mmol) in toluene (6 mL) and tetrahydrofuran (2 mL) at ambient temperature. 1'1-azobis(*N*,*N*-dimethylformamide) (206 mg, 1.20 mmol) was added and the reaction heated to 85°C overnight. The reaction mixture was concentrated *in vacuo* followed by addition on dichloromethane (30 mL). The organic solution was then washed with NaOH (2.0M, 2 x 20 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The compound was purified by column chromatography on Biotage® silica gel, eluting with dichloromethane:methanol:ammonia, 98:2:0.2 to 96:4:0.4 to give the title compound as a pale yellow oil (70mg, 21%). HRMS (ESI$^+$) 329.2224 $(M+H)^+$.

Example 129: 4-(4-[3-[(2*R*)-2-methylpyrrolidin-1-yl]propoxy]phenyl)-tetra-hydro-2*H*-pyran-4-carboxylic acid



A solution of 4-(4-{3-[(2*S*)-2-methylpyrrolidinyl]propoxy}phenyl)tetrahydro-2*H*-pyran-4-carbonitrile (70 mg, 0.21 mmol) in concentrated hydrochloric acid (1 mL) was heated at reflux for 3 days. A further 2mL of concentrated hydrochloric acid was added and the reaction heated at reflux for a further 2 days. The solution was evaporated to dryness *in vacuo*, triturated using acetone and azeotroped with toluene to give a pale brown solid (51 mg, 73 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, 2H), 6.94 (d, 2H), 4.12 (t, 2H), 3.92-3.84 (m, 2H), 3.76-3.46 (m, 6H), 2.54-2.44 (m, 2H), 2.20-2.02 (m, 1H), (m, 8H), (m, 3H); HRMS (ESI$^+$) 348.2170 $(M+H)^+$.

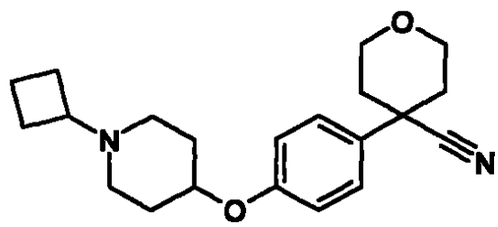
Intermediate 48: *tert*-butyl 4-[4-(4-cyanotetrahydro-2*H*-pyran-4-yl)phenoxy]-1-piperidinecarboxylate

tert-Butyl 4-[(methylsulfonyl)oxy]-1-piperidinecarboxylate (1.35g, 4.93mmol), 4-(4-hydroxyphenyl)tetrahydro-2*H*-pyran-4-carbonitrile (1.00g, 4.93mmol) and potassium carbonate (1.36g, 9.85mmol) were stirred in 10ml DMF at 56°C for 28 hours. The reaction mixture was partitioned between ethyl acetate (50ml) and water (50ml). The ethyl acetate was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified by column chromatography on silica gel eluting with 2% diethylamine in ethylacetate. This only gave a poor separation, so the impure material was triturated with diisopropylether (20ml) to give a white powder (1.5g). This solid was dissolved in diethylether (100ml) and washed with 2M NaOH (50ml) then with water (50ml). The diethylether was dried over Na_2SO_4 and evaporated to give *tert*-butyl 4-[4-(4-cyanotetrahydro-2*H*-pyran-4-yl)phenoxy]-1-piperidinecarboxylate as white crystals (740mg, 39%).

Intermediate 49: 4-[4-(4-piperidinyloxy)phenyl]tetrahydro-2*H*-pyran-4-carbonitrile

tert-Butyl 4-[4-(4-cyanotetrahydro-2*H*-pyran-4-yl)phenoxy]-1-piperidinecarboxylate (720mg) was dissolved in dichloromethane (50ml) at 0°C. TFA (10ml) was added and the mixture stirred whilst warming to room temperature over 2 hours. The reaction mixture was then concentrated *in vacuo*, and partitioned between dichloromethane (80ml) and 0.5M NaOH (50ml). The dichloromethane solution was dried over Na_2SO_4 and evaporated to give 4-[4-(4-piperidinyloxy)phenyl]tetrahydro-2*H*-pyran-4-carbonitrile as a colurless oil which crystallized on standing (500mg, 94%).

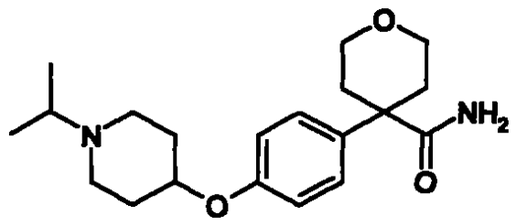
Example 130: 4-[4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl]tetrahydro-2*H*-pyran-4-carbonitrile



4-[4-(4-Piperidinyloxy)phenyl]tetrahydro-2*H*-pyran-4-carbonitrile (130mg, 0.45mmol) and cyclobutanone (140µl, 1.9mmol) were stirred in THF (2ml) and acetic acid (26µl, 0.45mmol) at ambient temperature for 15 mins. Sodium triacetoxyborohydride (340mg, 1.6mmol) was added and the mixture stirred for 18 hrs. The reaction was quenched by adding 10% aqueous Na_2CO_3 (5ml) and then partitioned between ethyl acetate (50ml) and water (30ml). The organics were dried over Na_2SO_4 and evaporated to give a solid which was purified by column chromatography on silica gel eluting with dichloromethane:methanol:ammonia, 98:2:0.2 to 94:6:0.6 to give the product which was then crystallized from diisopropylether (5ml) to give 4-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}tetrahydro-2*H*-pyran-4-carbonitrile as a white powder (50mg, 33%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.36 (d, 2H), 6.93 (d, 2H), 4.33 (m, 1H), 4.08 (m, 2H), 3.89 (m, 2H), 2.75 (pentet, 1H), 2.62 (m, 2H), 2.20-1.58 (m, 16H)

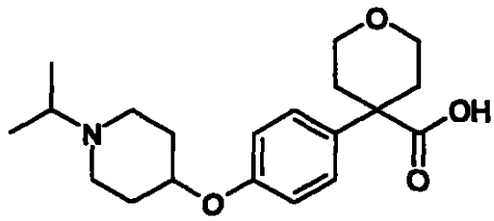
Example 131: 4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-carboxamide



4-[4-(1-isopropylpiperidin-4-yloxy)phenyl]tetrahydropyran-4-carbonitrile (50 mg, 0.152 mmol) was combined with boron trifluoride-acetic acid complex (500 µL, 3.8 mmol) and stirred at ambient temperature for 18 hours, followed by 65°C for 3 hours. The reaction mixture was allowed to cool and then basified with saturated $NaHCO_3$ solution (15 mL). The product was extracted with dichloromethane (2 x 35 mL). The combined organic extracts were dried using Na_2SO_4 filtered and concentrated *in vacuo*. The compound was purified by column chromatography on silica gel (15 g), eluting with dichloromethane:methanol:ammonia, (96:4:0.4) to dichloromethane:methanol:ammonia, (90:10:1) to give the title compound as a white solid (22 mg, 42%).

^{1}H NMR (400 MHz, CD_3OD) δ 7.3 (d, 2H), 6.9 (d, 2H), 4.4 (m, 1H), 3.8 (m, 2H), 3.65 (m, 2H), 2.78-2.85 (m, 3H), 2.5 (m, 2H), 2.4 (d, 2H), 1.95-2.08 (m, 4H), 1.8 (m, 2H), 1.1 (d, 6H)

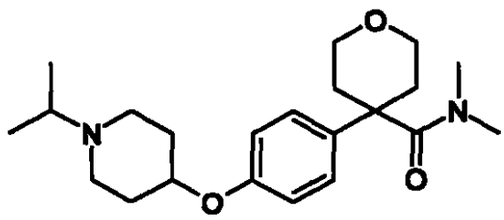
Example 132: 4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-carboxylic acid



4-[4-(1-isopropylpiperidin-4-yloxy)phenyl]tetrahydropyran-4-carbonitrile (1g, 3 mmol) and concentrated hydrochloric acid (10 mL) were combined and heated at reflux for 44 hours. Reaction mixture was concentrated *in vacuo* the resulting grey solid was triturated with acetone (20 mL) to give a cream coloured solid. The compound was purified using an SCX isolelute column flushed with methanol (60 mL) and then flushed with 2M NH_3 in methanol (150 mL). The title compound was isolated as a cream coloured solid (550mg, 52%).

^{1}H NMR (400 MHz, CD_3OD) δ 7.4 (d, 2H), 6.9 (d, 2H), 4.4 (m, 1H), 3.85 (m, 2H), 3.65 (m, 2H), 3.4 (m, 1H), 3.2 (m, 2h), 3.03 (m, 2H), 2.5 (m, 2H), 2.0- 1.8 (m, 6H), 1.3 (d, 6H)

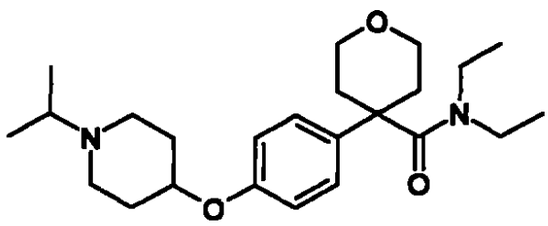
Example 133: 4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl]-*N,N*-dimethyltetrahydro-2*H*-pyran-4-carboxamide



4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-carboxylic acid (150 mg, 3.9 mmol), O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (222 mg, 5.8 mmol), dimethylamine hydrochloride (96mg, 1.1 mmol), pyridine (126uL, 1.56 mmol) were combined and dissolved in dimethylformamide (2 mL). The reaction mixture was stirred at ambient temperature for 18 hours. Further O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (222 mg, 5.8 mmol) and dimethylamine in ethanol (33%) (500 µL) was added and the reaction mixture was stirred at ambient temperature for 18 hours. The reaction mixture was diluted with water (20 mL) and was then extracted with ethyl acetate (2 x 40 mL). The combined organic extracts were dried using Na_2SO_4, filtered and concentrated *in vacuo*. The compound was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:ammonia (97:3:0.3) to dichloromethane:methanol:ammonia (90:10:1) to give a compound as a clear colourless oil. This was dissolved in ethyl acetate (70 mL) and washed with saturated $NaHCO_3$ solution (2 x 10 mL). The organic extract was dried using Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound as a clear crystaline solid (72mg, 50%).

^{1}H NMR (400 MHz, CD_3OD) δ 7.2 (d, 2H), 6.85 (d, 2H), 4.4 (m, 1H), 3.85 (m, 2H), 3.7 (m, 2H), 2.9-2.5 (m, 11H), 2.28 (m, 2H), 2.0 (m, 4H), 1.8 (m, 2H), 1.1 (d, 6H)

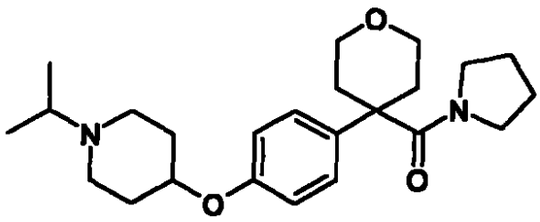
Example 134: 4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl]-*N,N*-diethyltetra-hydro-2*H*-pyran-4-carboxamide



4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-carboxylic acid (66mg, 0.2 mol), diethylamine (27 µL, 0.26 mmol), O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (108mg, 0.29 mmol), pyridine (53 uL, 0.66 mmol) were combined and dissolved in dimethylformamide (1.5 mL). The reaction mixture was stirred at 60°C for 5 hours. Further diethylamine was added (500 µL). The reaction mixture was stirred at ambient temperature for 60 hours. The reaction mixture was diluted with water (25 mL), and extracted with ethyl acetate (2 x 35 mL). The combined organics were dried using Na_2SO_4, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 15g of silica gel, eluting with dichloromethane:methanol:ammonia (96:4:0.4) to dichloromethane:methanol:ammonia (90:10:1) to give the title compound as a clear yellow oil (10mg, 11%).

^{1}H NMR (400 MHz, CD_3OD) δ 7.2 (d, 2H), 6.95 (d, 2H), 4.4 (m, 1H), 3.85-3.7 (m, 4H), 3.3 (m, 2H), 3.05-2.9 (m, 5H), 2.8 (m, 2H), 2.25 (d, 2H), 2.0 (m, 4H), 1.8 (m, 2H), 1.1 (m, 9H), 0.83(m, 3H)

Example 135: 4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-ylcarbonyl]pyrrolidine



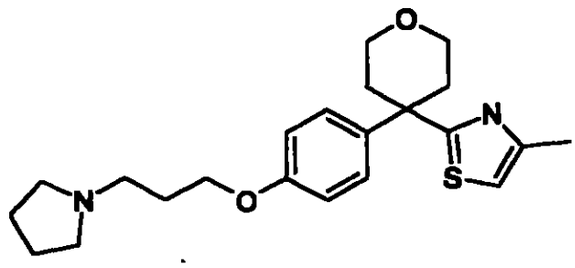
4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-carboxylic acid (93mg, 0.27 mmol) was supended in dimethylformamide (3mL), O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (203mg, 0.53 mmol), and triethylamine (112µL, 0.8 mmol) were added. The reaction mixture was stirred at ambient temperature for 1 hour. Pyrrolidine (300µL) was added and the reaction mixture was stirred at ambient temperature for 2.5 hours. The reaction mixture was concentrated *in vacuo*, then partitioned between saturated $NaHCO_3$ solution (50 mL) and dichloromethane (2 x 75 mL). The combined organics were dried using Na_2SO_4, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 20g of silica gel, eluting with dichloromethane:methanol:ammonia (96:4:0.4) to dichloromethane:methanol:ammonia (94:6:0.6) to give the title compound as a clear oil (34mg, 32%).

^{1}H NMR (400 MHz, CD_3OD) δ 7.2 (d, 2H), 6.9 (d, 2H), 4.4 (m, 1H), 3.85-3.7 (m, 4H), 3.45 (m, 2H), 2.95 (m, 2H), 2.8-2.7 (m, 3H), 2.5 (m, 2H), 2.3 (m, 2H), 2.0 (m, 4H), 1.8-1.7 (m, 4H), 1.6 (m, 2H), 1.1 (d, 6H).

Intermediate 80: 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbothioamide

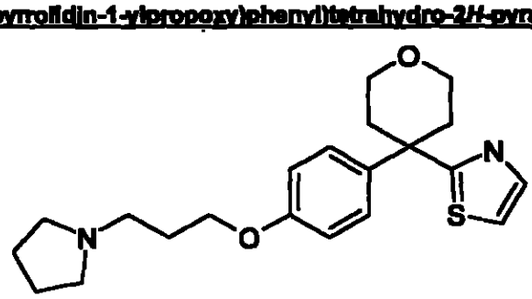
4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-carbonitrile (2g, 6.4 mmol), diethyl dithiophosphate (15 mL, 8.9 mmol), and water (1.5 mL) were combined and stirred at ambient temperature for 5 hours, 55 °C for 2 hours then 70°C for 2 hours. The reaction mixture was diluted with dichloromethane (100mL) and basified to pH 8 with a saturated solution of $NaHCO_3$ in water, and solid $NaHCO_3$. The layers were separated, and further dichloromethane (100 mL) was used to extract the product. The combined organics were dried using Na_2SO_4, filtered and concentrated *in vacuo* to leave a yellow oil. The compound was purified with column chromatography on 50g of silica, eluting with dichloromethane:methanol:ammonia (96:4:0.4) to dichloromethane:methanol:ammonia (90:10:1) to give a clear oil. The clear oil was dissolved in ethyl acetate (150 mL) and washed with 10% Na_2CO_3 solution. The organic layer was dried using Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound as a white solid (0.61g, 28%).

Example 136: 4-methyl-2-[4-(4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl]-1,3-thiazole



4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbothioamide (100mg, 0.29 mmol), chloroacetone (46 µL, 0.57 mmol) and ethanol (5 mL) were combined and heated at reflux for 18 hours. The reaction mixture was concentrated *in vacuo* to give a cream coloured solid. This was dissolved in dichloromethane (100 mL) and washed with saturated $NaHCO_3$ solution (50 mL). The organic extract was dried using Na_2SO_4, filtered and concentrated *in vacuo*. The compound was purified by column chromatography using 15g of silica gel, eluting with dichloromethane:methanol:ammonia (97:3:0.3) to dichloromethane:methanol:ammonia (94:6:0.6) to give the title compound as a white solid (68mg, 61%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3 (d, 2H), 6.9 (d, 2H), 6.75 (s, 1H), 4.0 (t, 2H), 3.83 (m, 2H), 3.7 (m, 2H), 2.75-2.58 (m, 8H), 2.4 (s, 3H), 2.35 (m, 2H), 2.03 (m, 2H), 1.8 (m, 4H)

Example 137: 2-[4-(4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl]-1,3-thiazole



4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbothioamide (150 mg, 0.43 mmol), bromoacetaldehyde diethylacetal (67 µL, 0.43 mmol), concentrated hydrochloric acid (5 drops) and

ethanol were combined and heated at reflux for 5 hours. The reaction mixture was concentrated *in vacuo* and partitioned between 10% Na_2CO_3 (20mL) and dichloromethane (2 x 35 mL). The combined organics were dried using Na_2SO_4, filtered and concentrated *in vacuo*. The compound was purified using column chromatography using 15g of silica gel, eluting with dichloromethane:methanol:ammonia (95:5:0.5) to give a cream coloured solid. This was triturated with 3mL of diethyl ether to give the title compound as a cream coloured solid (25mg, 16%).

^{1}H NMR (400 MHz, CD_3OD) δ 7.7 (s, 1H), 7.45 (s, 1H), 7.3 (d, 2H), 6.9 (d, 2H), 4.0 (t, 2H), 3.8 (m, 2H), 3.7 (m, 2H), 2.85-2.75 (m, 6H), 2.6 (m, 2H), 2.4 (m, 2H), 2.03 (m , 2H), 1.9 (m, 4H)

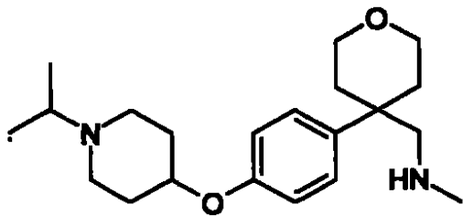
Intermediate 51: (4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-yl)methylamine

To a stirred solution 4-[4-(1-isopropylpiperidin-4-yloxy)phenyl]tetrahydropyran-4-carbonitrile (2.5 g, 7.62 mmol) in dry diethyl ether (15 ml) at 0°C was added dropwise a solution of $LiAlH_4$ (1.0M solution in Et_2O, 22.87 ml, 22.9 mmol). Reaction stirred at 0°C for 30 mins, then warmed up to ambient temperature overnight under a nitrogen atmosphere until complete. The reaction was cooled to 0°C, water (0.9 ml) was added dropwise followed by sodium hydroxide (2.0M, 0.9 ml) and water (2.7 ml). Dichloromethane (25 ml) and methanol (1 ml) were added and the mixture filtered through a short pad of arbocel, eluting with 2% methanol in dichloromethane (200 ml). The organic washings were dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as an orange oil (2.59 g, 100%).

Intermediate 52: *tert*-butyl [4-(4-[(1-isopropylpiperidin-4-yl)oxy]phenyl)tetrahydro-2*H*-pyran-4-yl]methylcarbamate

To a stirred solution of (4-(4-[(1-isopropylpiperidin-4-yl)oxy]phenyl)tetrahydro-2*H*-pyran-4-yl)methylamine (600 mg, 1.81 mmol) and triethylamine (576 µl, 5.42 mmol) in dichloromethane (2.5 ml) at 0°C, was added dropwise a solution of di-*tert*-butyldicarbonate (540 µl, 2.35 mmol) in dichloromethane (2.5 ml). Solution stirred at 0°C for 2 hours then allowed to warm up to ambient temperature and stirred until reaction complete. Reaction mixture diluted with dichloromethane (10 ml), washed with water (3 x 10 ml) then brine (2 x 10 ml). Organic washings dried over Na_2SO_4 and concentrated *in vacuo*. The compound was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:ammonia, 100:0:0 to 96:4:0:0.4 to give the title compound as a foam (532 mg, 68%).

Example 138: *N*-[(4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-yl)methyl]-*N*-methylamine

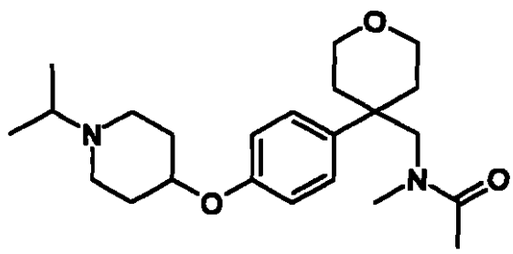


To a stirred solution of *tert*-butyl [4-(4-[(1-isopropylpiperidin-4-yl)oxy]phenyl)tetrahydro-2*H*-pyran-4-yl]methylcarbamate (532 mg, 1.23 mmol) in THF (3.5 ml) at 0°C was added dropwise a solution of $LiAlH_4$ (1.0M solution in Et_2O, 3.69 ml, 3.69 mmol). Reaction stirred for 60 hours at ambient temperature before

a further dropwise addition of $LiAlH_4$ (1.0M solution in Et_2O, 0.6 ml, 0.6 mmol). Heated at 40°C until reaction complete. The reaction was then cooled to 0°C, water (0.2 ml) was added dropwise followed by sodium hydroxide (2.0M, 0.2 ml) and water (0.6 ml). 1% methanol in dichloromethane (10ml) was added and the mixture filtered through a short pad of arbocel, eluting with 1% methanol in dichloromethane (25 ml). The organic washings were dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a solid (399 mg, 94%).

^1H NMR (400MHz, $CDCl_3$) δ 7.20 (d, 2H), 7.88 (d, 2H), 4.22-4.34 (m, 1H), 3.70-3.80 (m, 2H), 3.80-4.01 (d, 2H), 2.70-2.88 (m, 3H), 2.64 (s, 2H), 2.32-2.44 (m, 2H) 2.24 (s, 3H), 2.10-2.18 (M, 2H), 1.99-2.08 (m, 2H), 1.79-1.96 (m, 4H), 1.03 (d, 6H).

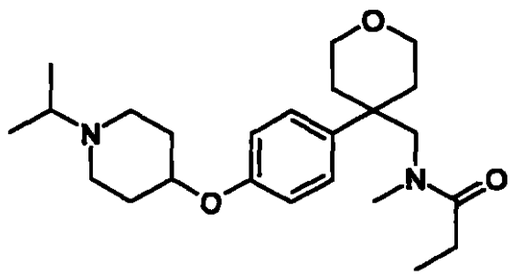
Example 139: *N*-[(4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-yl)methyl]-*N*-methylacetamide



To a stirred solution of *N*-[(4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-yl)methyl]-*N*-methylamine (120 mg, 0.347 mmol) and triethylamine (121 µl, 0.867 mmol) in dichloromethane (1ml) at 0°C was added dropwise acetic anhydride (36 µl, 0.382 mmol). The reaction mixture was warmed to ambient temperature until reaction complete. Water (1 ml) and dichloromethane (15 ml) added to the reaction, the extracted with saturated $NaHCO_3$ (2 x 10 ml). Organic washings were dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as an oil (113 mg, 83%).

^1H NMR (400MHz, $CDCl_3$) δ 7.10-7.22 (2 doublets due to rotamers, 2H), 6.80 (d, 2H), 4.24-4.38 (m, 1H), 3.79-3.80 (m, 2H), 3.42-3.60 (m, 2H), 2.70-2.90 (m, 3H), 2.39-2.48 (m, 2H), 3.20-3.35 (singlet and doublet due to rotamers, 3H), 1.75-2.10 (m, 11H), 1.10 (d, 6H).

Example 140: *N*-[(4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-yl)methyl]-*N*-methylpropanamide

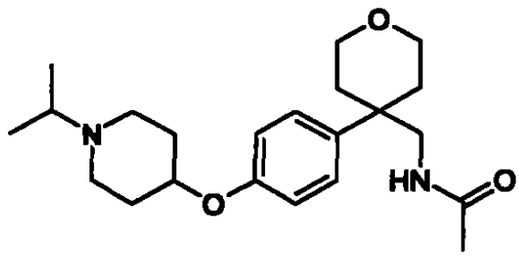


To a stirred solution of *N*-[(4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-yl)methyl]-*N*-methylamine (120 mg, 0.347 mmol) and triethylamine (121 µl, 0.867 mmol) in dichloromethane (1 ml) at 0°C was added dropwise propionic anhydride (44 µl, 0.382 mmol). Reaction allowed to warm up to

ambient temperature until reaction complete. Water (0.5 ml) and dichloromethane (15 ml) added to the reaction. The organic phase was separated and extracted with saturated $NaHCO_3$ (3 x 10 ml). Organic washings were dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as an oil (153 mg, 82%).

^1H NMR (400MHz, CD_3OD) δ 7.20-7.32 (2 doublets due to rotamers, 2H), 7.95 (d, 2H), 3.95-4.05 (m, 1H), 3.76-3.85 (m, 2H), 3.40-3.60 (multiple peaks due to rotamers, 4H), 2.70-2.88 (multiple peaks due to rotamers, 4H), 2.42-2.58 (*m*, 2H), 2.40 (s, 2H), 2.20-2.38 (*m*, 2H), 1.52-2.58 (several multiplets, 8H), 1.10 (d, 6H), 0.70-1.06 (two triplets due to rotamers, 3H).

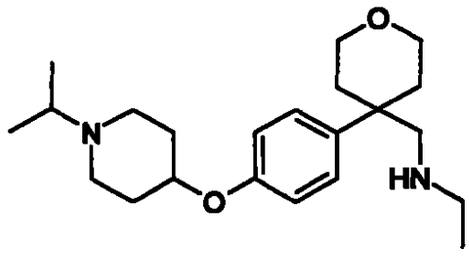
Example 141: *N*-[[4-(4-[(1-isopropylpiperidin-4-yl)oxy]phenyl)tetrahydro-2*H*-pyran-4-yl]methyl]-acetamide



To a stirred solution of (4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-yl)methylamine (250 mg, 0.753 mmol) and triethylamine (200 µl. 1.88mmol) in dichloromethane (2ml) was added dropwise acetic anhydride (78 µl, 0.828 mmol). Reaction left at ambient temperature until reaction complete. Dichloromethane (10 ml) added to the reaction, the organic phase extracted with saturated $NaHCO_3$ (3 x 10 ml). Organic washings were dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as an oil (203 mg, 72%).

^1H NMR (400MHz, $CDCl_3$) δ 7.19 (d, 2H), 6.94 (d, 2H), 4.95-5.02 (broad, 1H), 4.24-4.38 (m, 1H), 3.79-3.88 (m, 2H), 3.52-3.64 (m, 2H), 3.45 (d, 2H), 2.70-2.88 (m, 3H), 2.36-2.45 (m, 2H), 1.98-2.10 (m, 4H), 1.78-1.90 (m, 7H), 1.05 (d, 6H).

Example 142: *N*-[[4-(4-[(1-isopropylpiperidin-4-yl)oxy]phenyl)tetrahydro-2*H*-pyran-4-yl]methyl]-*N*-ethylamine

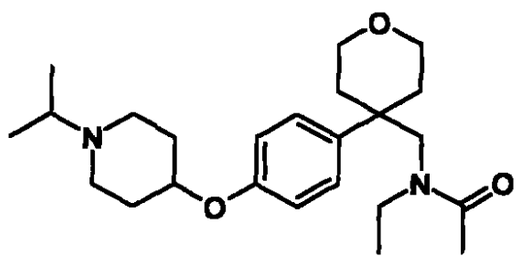


To a stirred solution of *N*-[[4-(4-[(1-isopropylpiperidin-4-yl)oxy]phenyl)tetrahydro-2*H*-pyran-4-yl]methyl]-acetamide (192 mg, 0.513 mmol) in THF (1.5 ml) at 0°C was added dropwise a solution of $LiAlH_4$ (1.0M solution in Et_2O, 1.54 ml, 1.54 mmol). Reaction heated at 40°C for 24 hours, then increased to 50°C. A further dropwise addition of $LiAlH_4$ (1.0M solution in Et_2O, 2 ml, 2 mmol) and further heating at 50°C for 24

hours was required for reaction to reach completion. The reaction was then cooled to 0°C, water (0.15 ml) was added dropwise followed by sodium hydroxide (2.0M, 0.15 ml) and water (0.45 ml). 1% methanol in dichloromethane (15 ml) was added and the mixture filtered through a short pad of Arbocel®, eluting with 1% methanol in dichloromethane (25 ml). The organic washings were dried over Na_2SO_4 and concentrated *in vacuo* (185 mg crude, 82%). The compound was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:ammonia, 98:2:0.2, to give the title compound as a white solid (9.9 mg, 4.4%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.20 (d, 2H), 7.88 (d, 2H), 4.24-4.58 (m, 1H), 3.71-3.82 (m, 2H), 3.62-3.63 (m, 2H), 2.72-2.88 (m, 3H), 2.70 (s, 2H), 2.46-2.52 (quartet, 2H), 2.34-2.42 (m, 2H), 1.78-2.18 (several multiplets, 8H), 1.08 (d, 6H), 0.96 (t, 3H).

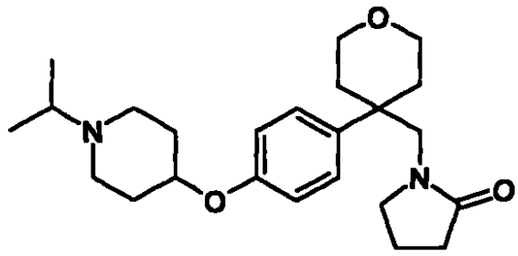
Example 143: *N*-[(4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-yl)methyl]-*N*-ethylacetamide



To a stirred solution of *N*-[(4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-yl)methyl]-*N*-ethylamine (102 mg, 0.283 mmol) and triethylamine (99 µl, 0.708 mmol) in dichloromethane (1 ml) was added dropwise acetic anhydride (29 µl, 0.312 mmol). Reaction left at ambient temperature for 4 hours until reaction complete. Water (1 ml) and dichloromethane (10 ml) added to the reaction, the extracted with saturated $NaHCO_3$ (2 x 10 ml). Organic washings were dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as an oil (107mg, 94%).

^{1}H NMR (400MHz, CD_3OD) δ 7.20-7.31 (multiplet due to rotamers, 2H), 6.92-7.00 (multiplet due to rotamers, 2H), 4.36-4.46 (m, 1H), 3.70-3.88 (m, 2H), 3.20-3.55 (several peaks due to rotamers, 4H), 2.78-2.90 (m, 3H), 2.60, (q, 2H), 2.25-2.52 (multiple peaks due to rotamers, 2H), 1.70-2.10 (multiple peaks, 11H), 1.10 (d, 6H), 0.80-1.00 (two triplets due to rotamers, 3H).

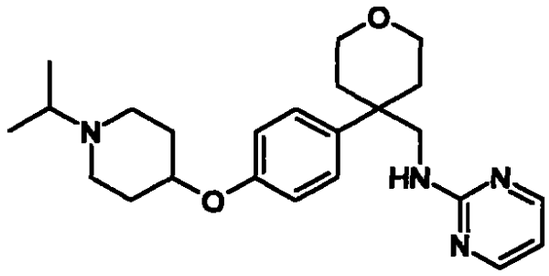
Example 144: 1-[(4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-yl)methyl]pyrrolidin-2-one



To a solution of (4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-yl)methylamine (100 mg, 0.301 mmol) in toluene (2 ml) was added ethyl-4-bromobutyrate (43 µl, 0.301 mmol), *N,N*-diisopropylethylamine (157 µl, 0.904 mmol) and potassium iodide (5 mg, 0.030 mmol). Reaction mixture heated at 80°C for 48 hours, then increased to reflux. Potassium carbonate (83 mg, 0.602 mmol) was added and reaction left at reflux for a further 24 hours until reaction complete. Reaction mixture was partitioned between ethyl acetate (20 ml) and saturated $NaHCO_3$ (10 ml). Organic washings were dried over Na_2SO_4 and concentrated *in vacuo* to give a brown oil (101 mg crude, 84%). The compound was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:ammonia, 100:0:0 to 98:2:0.2, to give the title compound as an oil (7 mg, 6%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.20 (d, 2H), 7.90 (d, 2H), 4.22-4.36 (m, 1H), 4.80-4.90 (m, 2H), 3.52-3.67 (m, 2H), 3.40 (s, 2H), 2.72-3.88 (several multiplets, 3H), 2.50 (t, 2H), 2.34-2.44 (m, 2H), 2.21-2.30 (t, 2H), 1.60-2.10 (several multiplets, 10H), 1.08 (d, 6H).

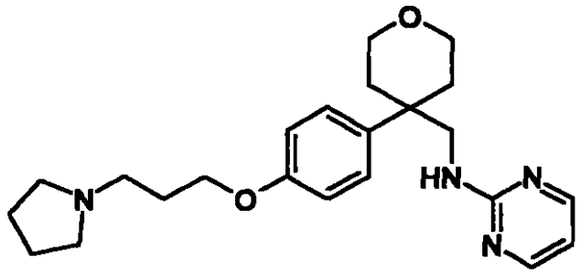
Example 145: *N*-[(4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-yl)methyl]pyrimidin-2-amine



A mixture of (4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-yl)methylamine (150 mg, 0.422 mmol), 2-chloropyrimidine (52 mg, 0.422 mmol) and *N,N*-diisopropylethylamine (161 µl, 0.904 mmol) in *N*-methyl pyrrolidinone (0.5 ml) was heated at 150°C in the microwave (Smith Personal Synthesiser) for 900 seconds. The reaction mixture was partitioned between ethyl acetate (10 ml) and saturated $NaHCO_3$ (10 ml). The organic washings were dried over Na_2SO_4 and concentrated *in vacuo* to give an orange oil. The compound was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:ammonia, 100:0:0 to 96:4:0.4, to give the title compound as a solid (87 mg, 47%).

^{1}H NMR (400MHz, $CDCl_3$) δ 8.20 (d, 2H), 7.21 (d, 2H), 6.90 (d, 2H), 6.48 (t, 2H), 4.71 (m, 1H), 4.20-4.35 (broad, 1H), 3.80-3.90 (m, 2H), 3.55-3.70 (multiple peaks, 4H), 2.70-2.90 (m, 3H), 2.32-2.49 (m, 2H), 1.78-2.19 (several multiplets, 8H), 1.10 (d, 6H).

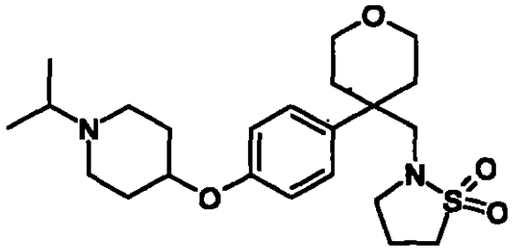
Example 146: *N*-[(4-{4-(3-Pyrrolidin-1-ylpropoxy)phenyl}tetrahydro-2*H*-pyran-4-yl)methyl]pyrimidin-2-amine



A mixture of {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (100 mg, 0.314 mmol), 2-chloropyrimidine (50 mg, 0.346 mmol) and *N,N*-diisopropylethylamine (112 µl, 0.629 mmol) in *N*-methyl pyrrolidinone (0.5 ml) was heated at 180°C in the microwave (Smith Personal Synthesiser) for 600 seconds. The reaction mixture was partitioned between ethyl acetate (10 ml) and saturated $NaHCO_3$ (10 ml). The organic washings were dried over Na_2SO_4 and concentrated *in vacuo* to give an oil. The compound was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:ammonia, 100:0:0 to 88:12:1.2. Compound still impure so purified further on the Fraction Lynx automated LC system to give the title compound as a solid (22 mg, 17%)

^{1}H NMR (400MHz, $CDCl_3$) δ 8.30 (brs, 2H), 7.34 (d, 2H), 6.92 (d, 2H), 6.70 (t, 1H), 4.10 (t, 2H), 3.78-3.84 (m, 2H), 3.62-3.72 (multiple peaks, 4H), 3.44-3.55 (m, 2H), 3.40 (m, 2H), 3.04-3.18 (m, 2H), 1.85-2.25 (multiple peaks, 10H).

Example 147: 2-[[4-(4-[(1-isopropylpiperidin-4-yl)oxy]phenyl)tetrahydro-2*H*-pyran-4-yl]methyl]isothiazolidine 1,1-dioxide



A solution of {4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-yl)methylamine (100mg, 0.30 *mmol*), 3-chloropropanesulphonyl chloride (51µl, 0.40 *mmol*) and *N,N*-diisopropylethylamine (52µl, 0.30 mmol) in dichloromethane (2ml) was stirred at room temperature for 18hrs. The reaction mixture was concentrated *in vacuo* and then partitioned between dichloromethane (10ml) and sodium bicarbonate solution (10ml). The aqueous layer was extracted with a further 10ml dichloromethane and the combined organics dried over sodium sulphate and concentrated *in vacuo* to give an oil. This was dissolved in tetrahydrofuran (2ml). Potassium *tert*-butoxide (65mg, 0.60 mmol) was added to the solution and the reaction mixture stirred at 40°C for 18hrs. This was then concentrated *in vacuo* and partitioned between diethyl ether (10ml) and water (10ml). The aqueous layer was extracted with a further 10ml diethyl ether and the combined organics dried over sodium sulphate and concentrated *in vacuo* to give a pale yellow oil. The compound was purified by column chromatography on Biotage® silica gel, eluting with dichloromethane:methanol:ammonia, 96:4:0.4 to give the title compound as a pale yellow oil (19mg, 15%).

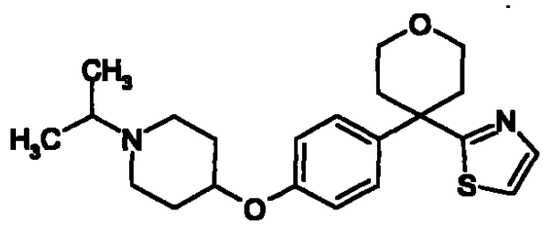
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, 2H), 6.90 (d, 2H), 4.26 (m, 2H), 3.80 (m, 2H), 3.58 (m, 2H), 3.15 (s, 2H), 2.99 (t, 2H), 2.80 (m, 2H), 2.75(m, 2H), 2.40 (t, 2H), 2.38 (m, 2H), 2.16 (m, 2H), 2.02 (m, 4H), 1.90 (m, 2H) 1.81 (m, 2H), 1.03 (d, 6H); HRMS (ESI$^+$) 437.2457 $(M+H)^+$.

Intermediate 53: 4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-carbothioamide

The title compound (320mg, 74%) was prepared from 4-[4-(1-isopropylpiperidin-4-yloxy)phenyl]tetrahydropyran-4-carbonitrile and diethyl dithiophosphate similarly to the procedure used for intermediate 50.

LRMS APCI$^+$ m/z 363 $[MH]^+$.

Example 148: 1-isopropyl-4-[4-[4-(1,3-thiazol-2-yl)tetrahydro-2*H*-pyran-4-yl]phenoxy]piperidine



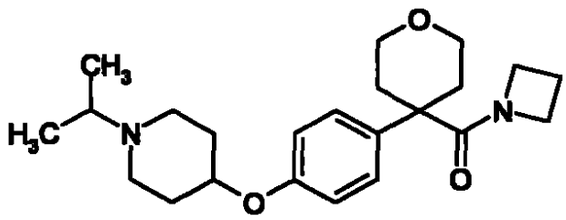
The title compound (320mg, 74%) was prepared from 4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-carbothioamide and bromoacetaldehyde diethylacetal similarly to the procedure used for example 137.

^{1}H NMR (400 MHz, CD_3OD) δ 1.10 (d, 6H), 1.75-1.80 (m, 2H), 1.98-2.02 (m, 2H), 2.37-2.44 (m, 2H), 2.47-2.51 (m, 2H), 2.61-2.65 (m, 2H), 2.75-2.84 (m, 3H), 3.66-3.70 (m, 2H), 3.78-3.83 (m, 2H), 4.37 (m, 1H), 6.89 (d, 2H), 7.28 (d, 2H), 7.46 (d, 1H), 7.70 (d, 1H).

HRMS ESI$^+$ m/z 387.2090 $[MH]^+$.

Microanalysis: Found: C, 67.42; H, 7.83; N, 7.08%. $C_{22}H_{30}N_2O_2S$. $0.2H_2O$ requires C, 67.73; H, 7.85; N, 7.18%.

Example 149: 4-[4-[4-(azetidin-1-ylcarbonyl)tetrahydro-2*H*-pyran-4-yl]phenoxy]-1-isopropylpiperidine



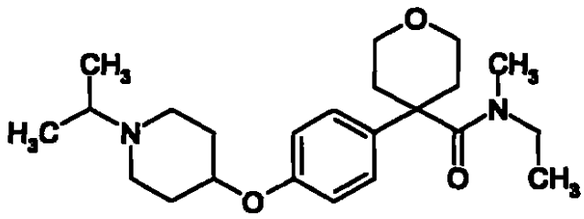
4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-carboxylic acid (200mg, 0.58mmol), azetidine hydrochloride (81mg, 0.87mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (121mg, 0.63mmol), 1-hydroxybenzotriazole hydrate (97mg, 0.63mmol) and triethylamine (210μL, 1.51mmol) were stirred in dichloromethane (8mL) at room temperature for 18 hours. The reaction was diluted with dichloromethane (60mL) and washed with aqueous sodium bicarbonate. The aqueous were extracted again with dichloromethane. The organics were combined, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on

silica gel eluting with dichloromethane:methanol:ammonia (96:4:0.5, by volume) to provide the title compound (97mg, 43%) as a white solid.

^{1}H NMR (400 MHz, CD_3OD) δ 1.11 (d, 6H), 1.77-1.82 (m, 2H), 1.88-1.95 (m, 2H), 2.01-2.08 (m, 4H), 2.26-2.29 (m, 2H), 2.47-2.52 (m, 2H), 2.76-2.86 (m, 3H), 3.66-3.74 (m, 4H), 3.79-3.82 (m, 2H), 3.92-3.96 (m, 2H), 4.40 (m, 1H), 6.95 (d, 2H), 7.22 (d, 2H).

HRMS ESI$^+$ m/z 387.2634 $[MH]^+$.

Example 160: *N*-ethyl-4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl]-*N*-methyltetrahydro-2*H*-pyran-4-carboxamide

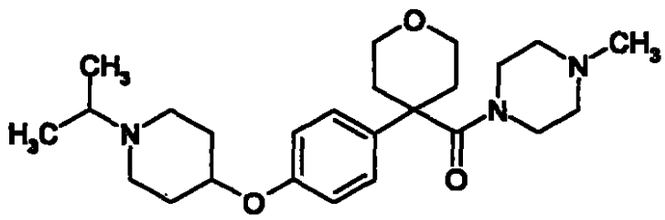


O-(1*H*-Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (286mg, 0.75mmol) was added to a solution of 4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-carboxylic acid (200mg, 0.58mmol) in *N*,*N*-dimethylformamide (6mL). Then triethylamine (243μL, 1.74mmol) was added. The mixture was stirred at room temperature for 15 minutes. Ethylmethylamine (500μL, 5.8mmol) was added and the reaction mixture stirred at room temperature for 18 hours. The reaction was concentrated *in vacuo*. The residue was partitioned between aqueous sodium bicarbonate solution (30mL) and ethyl acetate (2x75mL). The organics were combined, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (96:4:0.5, by volume) to provide the title compound (80mg, 35%).

^{1}H NMR (400 MHz, CD_3OD) δ 1.06-1.25 (m, 9H), 1.90-2.02 (m, 4H), 2.08-2.12 (m, 2H), 2.25-2.28 (m, 2H), 2.58 (m, 2H), 2.87 (m, 3H), 2.96 (m, 2H), 3.09-3.12 (m, 3H), 3.71-3.76 (m, 2H), 3.82-3.86 (m, 2H), 4.53 (m, 1H), 6.98 (d, 2H), 7.20 (d, 2H).

HRMS ESI$^+$ m/z 389.2791 $[MH]^+$.

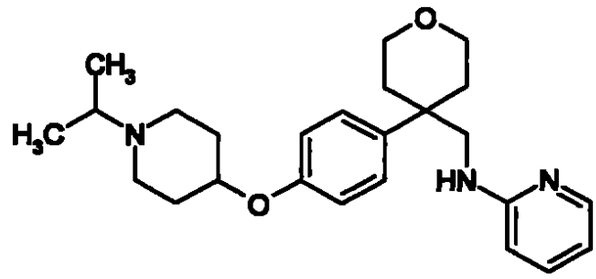
Example 161: 1-[(4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-yl)carbonyl]-4-methylpiperazine



The title compound (60mg, 48%) was prepared from 4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-carboxylic acid and *N*-methyl piperazine similarly to the procedure used for example 160.

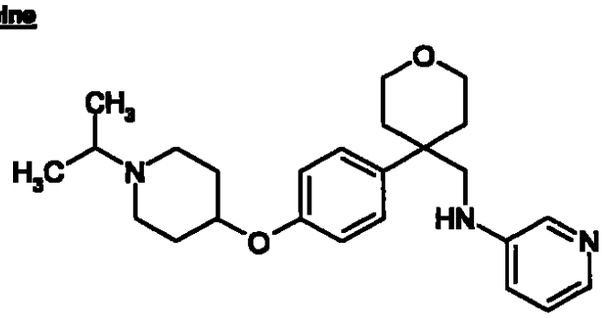
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, 6H), 1.79-1.81 (m, 2H), 2.00-2.03 (m, 7H), 2.15 (s, 3H), 2.18-2.22 (m, 2H), 2.37-2.42 (m, 2H), 2.77-2.79 (m, 3H), 2.99 (m, 1H), 3.27-3.56 (m, 4H), 3.78 (t, 2H), 3.87-3.89 (m, 2H), 4.28 (m, 1H), 6.88 (d, 2H), 7.14 (d, 2H).
HRMS ESI$^+$ m/z 430.3062 $[MH]^+$.

Example 162: *N*-[(4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-yl)methyl]pyridin-2-amine



(4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-yl)methylamine (300mg, 0.9mmol), 2-bromopyridine (50μL, 0.75mmol), tris(dibenzylideneacetone)dipalladium(0) (15mg, 0.018mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (19mg, 0.036mmol) and sodium *tert*-butoxide (100mg, 1mmol) were heated at 70°C in toluene (6ml) for 24 hours under nitrogen. The reaction was partitioned between aqueous sodium bicarbonate (30ml) and dichloromethane (2x75ml). The organics were combined, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (96:4:0.4, to 94:6:0.6 by volume) to provide the title compound (81mg, 22%) as a white solid after trituration in diethyl ether.
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (d, 6H), 1.86-1.95 (m, 4H), 2.07-2.16 (m, 4H), 2.46-2.51 (m, 2H), 2.82-2.86 (m, 3H), 3.49 (d, 2H), 3.56-3.61 (m, 2H), 3.80-3.85 (m, 2H), 4.03 (m, 1H), 4.33 (m, 1H), 6.22 (d, 1H), 6.51 (t, 1H), 6.91 (d, 2H), 7.24 (d, 2H), 7.32 (t, 1H), 8.01 (d, 1H).
HRMS ESI$^+$ m/z 410.2793 $[MH]^+$.

Example 163: *N*-[(4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-yl)methyl]pyridin-3-amine



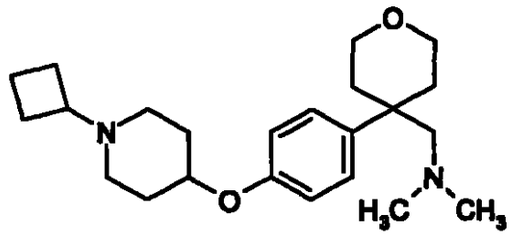
The title compound (20mg, 5%) was prepared from (4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-yl)methylamine and 3-iodopyridine similarly to the procedure used for example 162.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (d, 6H), 1.88-1.95 (m, 4H), 2.10-2.21 (m, 4H), 2.51 (m, 2H), 2.83-2.88 (m, 3H), 3.22-3.27 (m, 3H), 3.55-3.59 (m, 2H), 3.77-3.82 (m, 2H), 4.35 (m, 1H), 6.73 (d, 1H), 6.93 (d, 2H), 7.00 (t, 1H), 7.24 (d, 2H), 7.87-7.90 (m, 2H).
HRMS ESI$^+$ m/z 410.2791 $[MH]^+$.

Intermediate 54: 1-cyclobutylpiperidin-4-ol

4-Hydroxypiperidine (2.41g, 23.8mmol), cyclobutanone (5g, 71.4mmol) and acetic acid (1.36ml, 23.8mmol) were stirred in tetrahydrofuran (35ml) at 0°C for 1.5 hours. Sodium triacetoxyborohydride (10.1g, 47.7mmol) was then added at 0°C and the reaction mixture stirred at 0°C for 1 hour. The mixture was warmed to room temperature and stirred for 1 hour, then heated to 40°C for 18 hours. The reaction was concentrated *in vacuo*. The residue was taken up in water (30ml). The aqueous layer was basified to pH 9 with ammonia and extracted with diethyl ether (3x50ml). The organics were combined, dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (100:0:0 to 93:7:0.7 by volume) to provide the title compound (2.47g, 67%) as an oil.
LRMS APCI$^+$ m/z 156 $[MH]^+$.

Example 154: 1-(4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-yl)-*N*,*N*-dimethylmethanamine



4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (0.75g, 3.19mmol), 1-cyclobutylpiperidin-4-ol (0.45g, 2.90mmol), PPh_3 (0.84g, 3.18mmol), THF (10ml) and DIAD (0.66ml, 3.19mmol) were reacted together similarly to general procedure C. The crude material was subjected to chromatography on silica gel eluting with dichloromethane:methanol:ammonia (98:2:0.2) to provide the title compound (114mg, 11%) as an off-white solid.
^{1}H NMR (400MHz, CD_3OD) δ 1.71-1.77 (m, 4H), 1.85-1.90 (m, 4H), 1.94 (s, 6H), 1.99-2.06 (m, 4H), 2.12-2.16 (m, 2H), 2.20-2.28 (m, 2H), 2.45 (s, 2H), 2.58-2.70 (m, 2H), 2.79 (m, 1H), 3.48-3.53 (m, 2H), 3.72-3.75 (m, 2H), 4.39 (m, 1H), 6.91 (d, 2H), 7.26 (d, 2H).
HRMS ESI$^+$ m/z 373.2846 $[MH]^+$.

Intermediate 55: ethyl [4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]acetate

DIAD (9.8ml, 47.3mmol) was added dropwise over 10 minutes to a solution of ethyl-4-hydroxy phenylacetate (7.7g, 42.7mmol), 1-cyclobutylpiperidin-4-ol (6.58g, 42.5mmol) and PPh_3 (12.3g, 47mmol) in THF (150ml) at 0°C. The reaction mixture was then stirred at room temperature for 18 hours. The reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate (150ml). The organic layer was washed with water (150ml) and 2N aqueous hydrochloric acid (50ml) twice. The acid layers were

basified with sodium carbonate and extracted with dichloromethane (2x80ml). These organics were combined, dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate:pentane:diethylamine (70:30:2 by volume) to provide the title compound (2.0g, 15%) as a colourless oil.

LRMS APCI$^+$ m/z 318 $[MH]^+$.

Intermediate 66: ethyl 4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-carboxylate

NaH (60% dispersion in oil, 800mg, 20mmol) was added at 0°C to a solution of ethyl (4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]acetate (2g, 6.3mmol) in THF (25ml) and *N*-methylpyrrolidinone (2ml) under nitrogen. The reaction was stirred at 0°C for 15 minutes. Bis(2-bromoethyl)ether (1.2ml, 9.54mmol) and potassium iodide (500mg, 3mmol) were added and the mixture stirred at 0°C for 45 minutes. The reaction was then warmed to room temperature and stirred for 18 hours. The reaction was cooled to 0°C, quenched with ice and solid carbon dioxide. The mixture was diluted with water and extracted with ethyl acetate (100ml and 20ml). The combined organic extracts were dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate:diethylamine (99:1 by volume) to provide the title compound (870mg, 36%) as a pale yellow oil.

LRMS APCI$^+$ m/z 388 $[MH]^+$.

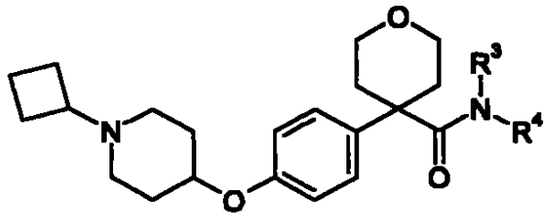
Intermediate 67: 4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-carboxylic acid

Sodium hydroxide (200mg, 5mmol) was added to a solution of ethyl 4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-carboxylate (870mg, 2.25mmol) in dioxane (10ml) and water (2ml). The reaction mixture was heated to reflux for 18 hours under nitrogen. The reaction was not complete. More sodium hydroxide (190mg, 4.75mmol) in water (4ml) was added and the reaction heated at reflux for 18 hours. 2N Hydrochloric acid (5ml, 9.75mmol) was added and the mixture concentrated *in vacuo* to a white powder (2.0g) containing the title compound and sodium chloride.

LRMS APCI$^+$ m/z 360 $[MH]^+$.

Examples 155-160

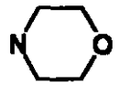
The compounds of the following tabulated Examples of the general formula



were prepared using 4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-carboxylic acid and the appropriate amines similarly to the procedure used for example 149.

Ex No	NR^3R^4	Analytical Data
156	NMe_2	4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]-*N*,*N*-dimethyltetrahydro-2*H*-

144
145

		pyran-4-carboxamide ^{1}H NMR (400MHz, CD_3OD) δ 1.70-1.79 (m, 4H), 1.89-2.02 (m, 6H), 2.07-2.10 (m, 2H), 2.25 (d, 4H), 2.63-2.67 (m, 9H), 3.73 (t, 2H), 3.82-3.85 (m, 2H), 4.41 (m, 1H), 6.94 (d, 2H), 7.16 (d, 2H). HRMS ESI$^+$ m/z 387.2637 $[MH]^+$. 25% yield
156	NHMe	4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]-N-methyltetrahydro-2H-pyran-4-carboxamide ^{1}H NMR (400MHz, CD_3OD) δ 1.70-1.76 (m, 4H), 1.88-2.08 (m, 8H), 2.22-2.25 (m, 2H), 2.38-2.42 (m, 2H), 2.59-2.63 (m, 2H), 2.66 (s, 3H), 2.80 (m, 1H), 3.61 (t, 2H), 3.75-3.80 (m, 2H), 4.39 (m, 1H), 6.90 (d, 2H), 7.27 (d, 2H). HRMS ESI$^+$ m/z 373.2480 $[MH]^+$. 10% yield
157		4-[(4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]tetrahydro-2H-pyran-4-yl)carbonyl]morpholine ^{1}H NMR (400MHz, CD_3OD) δ 1.70-1.76 (m, 4H), 1.85-2.09 (m, 8H), 2.20-2.24 (m, 4H), 2.63-2.67 (m, 2H), 2.81 (m, 1H), 3.25-3.31 (m, 6H), 3.33-3.39 (m, 2H), 3.73 (t, 2H), 3.82-3.87 (m, 2H), 4.41 (m, 1H), 6.96 (d, 2H), 7.20 (d, 2H). HRMS ESI$^+$ m/z 429.2740 $[MH]^+$. 20% yield
158	NH_2	4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]tetrahydro-2H-pyran-4-carboxamide ^{1}H NMR (400MHz, CD_3OD) δ 1.76-1.82 (m, 2H), 1.94-2.00 (m, 4H), 2.06-2.10 (m, 4H), 2.20-2.22 (m, 2H), 2.42 (d, 2H), 2.65-2.79 (m, 2H), 2.89-2.99 (m, 2H), 3.26 (m, 1H), 3.66 (t, 2H), 3.78-3.82 (m, 2H), 4.55 (m, 1H), 6.95 (d, 2H), 7.34 (d, 2H). HRMS ESI$^+$ m/z 359.2322 $[MH]^+$. 13% yield
159	NHiPr	4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]-N-isopropyltetrahydro-2H-pyran-4-carboxamide ^{1}H NMR (400MHz, CD_3OD) δ 1.04 (d, 6H), 1.70-1.77 (m, 4H), 1.88-2.00 (m, 6H), 2.05-2.08 (m, 2H), 2.20-2.26 (m, 2H), 2.42 (d, 2H), 2.60-2.68 (m, 2H), 2.81 (m, 1H), 3.62 (t, 2H), 3.77-3.82 (m, 2H), 3.99 (m, 1H), 4.39 (m, 1H), 6.90 (d, 2H), 7.28 (d, 2H). HRMS ESI$^+$ m/z 401.2789 $[MH]^+$. 13% yield

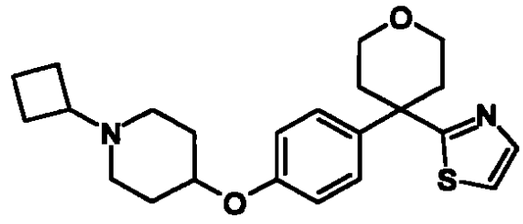
160	NHEt	4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]-N-ethyltetrahydro-2H-pyran-4-carboxamide ^{1}H NMR (400MHz, CD_3OD) δ 1.01 (t, 3H), 1.69-1.75 (m, 4H), 1.88-2.01 (m, 6H), 2.04-2.07 (m, 2H), 2.16-2.28 (m, 2H), 2.41 (d, 2H), 2.56-2.68 (m, 2H), 2.79 (m, 1H), 3.15 (q, 2H), 3.62 (t, 2H), 3.76-3.80 (m, 2H), 4.38 (m, 1H), 6.89 (d, 2H), 7.28 (d, 2H). HRMS ESI$^+$ m/z 387.2636 $[MH]^+$. 22% yield

Intermediate 58: 4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-carbothioamide

The title compound (223mg, 50%) was prepared from 4-[4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl]tetrahydro-2*H*-pyran-4-carbonitrile and diethyl dithiophosphate similarly to the procedure used for intermediate 50.

LRMS APCI$^+$ m/z 375 $[MH]^+$.

Example 161: 1-cyclobutyl-4-[4-[4-(1,3-thiazol-2-yl)tetrahydro-2*H*-pyran-4-yl]phenoxy]piperidine

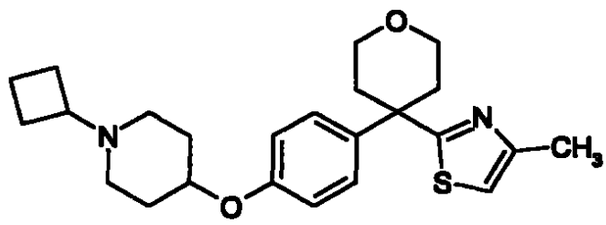


The title compound (92mg, 39%) was prepared from 4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-carbothioamide and bromoacetaldehyde diethylacetal similarly to the procedure used for example 137.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66-1.72 (m, 2H), 1.77-1.89 (m, 5H), 1.95-2.04 (m, 4H), 2.11 (m, 1H), 2.36-2.43 (m, 2H), 2.58-2.72 (m, 5H), 3.71 (t, 2H), 3.84-3.88 (m, 2H), 4.27 (m, 1H), 6.84 (d, 2H), 7.23-7.26 (m, 3H), 7.70 (s, 1H).

LRMS APCI$^+$ m/z 399 $[MH]^+$.

Example 162: 1-cyclobutyl-4-[4-[4-(4-methyl-1,3-thiazol-2-yl)tetrahydro-2*H*-pyran-4-yl]phenoxy]piperidine



The title compound (155mg, 83%) was prepared from 4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-carbothioamide and chloroacetone similarly to the procedure used for example 136.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64-1.71 (m, 2H), 1.78-1.81 (m, 2H), 1.88-2.04 (m, 6H), 2.10-2.20 (m, 2H), 2.31-2.38 (m, 2H), 2.42 (s, 3H), 2.61-2.64 (m, 4H), 2.74 (m, 1H), 3.71 (t, 2H), 3.81-3.85 (m, 2H), 4.28 (m, 1H), 6.75 (s, 1H), 6.83 (d, 2H), 7.23 (d, 2H).

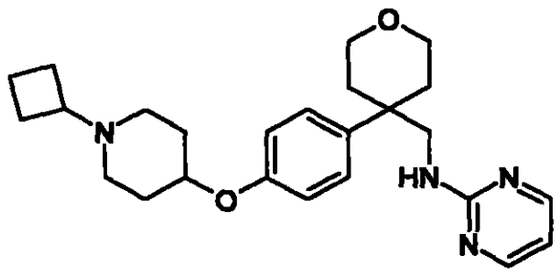
HRMS ESI$^+$ *m/z* 413.2257 $[MH]^+$.

Intermediate 69: 1-(4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-yl)methanamine

The title compound (1.05g, 100%) was prepared from 4-[4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl]tetrahydro-2*H*-pyran-4-carbonitrile and lithium aluminium hydride similarly to the procedure used for intermediate 51.

LRMS APCI$^+$ m/z 345 $[MH]^+$.

Example 163: *N*-[(4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-yl)methyl]pyrimidin-2-amine

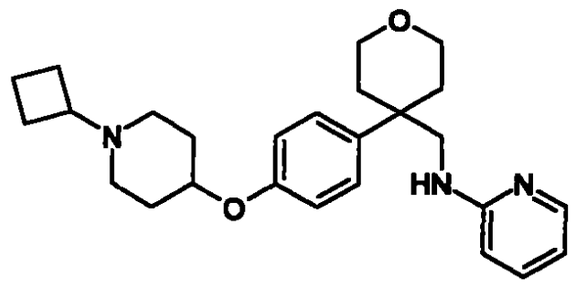


The title compound (31mg, 25%) was prepared from 1-(4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-yl)methanamine and 2-chloropyrimidine similarly to the procedure used for example 145.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66-1.73 (m, 2H), 1.83-1.95 (m, 6H), 1.98-2.15 (m, 8H), 2.60-2.66 (m, 2H), 2.75 (m, 1H), 3.57-3.62 (m, 2H), 3.66 (d, 2H), 3.81-3.85 (m, 2H), 4.31 (m, 1H), 4.68 (t, 1H), 6.47 (t, 1H), 6.90 (d, 2H), 7.23 (d, 2H), 8.20 (d, 2H).

LRMS APCI$^+$ m/z 423 $[MH]^+$.

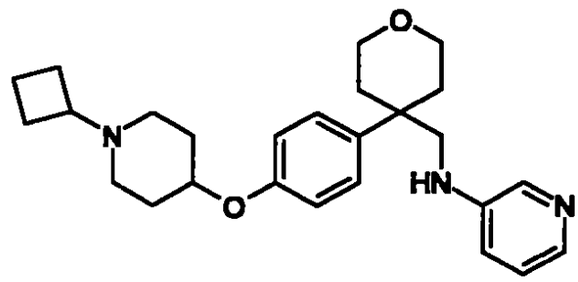
Example 164: *N*-[(4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-yl)methyl]pyridin-2-amine



The title compound (25mg, 31%) was prepared from 1-(4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-yl)methanamine and 2-bromopyridine similarly to the procedure used for example 152.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68-1.72 (m, 2H), 1.84-1.94 (m, 6H), 2.00-2.16 (m, 8H), 2.63-2.67 (m, 2H), 2.74 (m, 1H), 3.49 (d, 2H), 3.56-3.62 (m, 2H), 3.80-3.85 (m, 2H), 4.02 (m, 1H), 4.31 (m, 1H), 6.22 (d, 1H), 6.51 (t, 1H), 6.91 (d, 2H), 7.24 (d, 2H), 7.32 (t, 1H), 8.01 (d, 1H).
HRMS ESI$^+$ m/z 422.2782 $[MH]^+$.

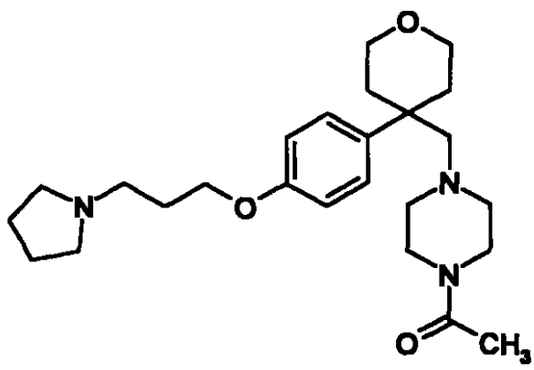
Example 165: *N*-[(4-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-yl)methyl]pyridin-3-amine



The title compound (28mg, 18%) was prepared from 1-(4-[4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-yl)methanamine and 3-iodopyridine similarly to the procedure used for example 153.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68-1.94 (m, 8H), 2.01-2.06 (m, 4H), 2.17-2.20 (m, 4H), 2.60-2.68 (m, 2H), 2.76 (m, 1H), 3.22-3.27 (m, 3H), 3.57 (t, 2H), 3.77-3.81 (m, 2H), 4.32 (m, 1H), 6.73 (d, 1H), 6.82 (d, 2H), 6.99 (m, 1H), 7.23 (d, 2H), 7.88 (m, 2H).
HRMS ESI$^+$ m/z 422.2789 $[MH]^+$.

Example 166: 1-acetyl-4-{[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl]methyl}piperazine

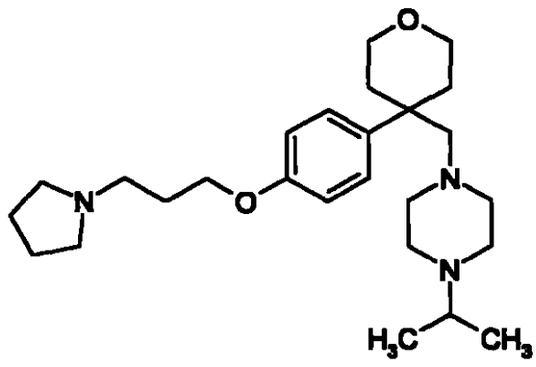


To a stirred solution of 1-{4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl}piperazine (160mg, 0.41mmol) and *N,N*-diisopropylethylamine (180µl, 1.03mmol) in dichloromethane (2ml) at 0°C was added dropwise acetic anhydride (47µl, 0.49mmol). The reaction was allowed to warm up to room temperature and stirred for 18 hours. The reaction mixture was concentrated under reduced pressure and the residue partitioned between dichloromethane (20ml) and aqueous sodium carbonate solution (20ml). The layers were separated and the aqueous layer was extracted again with dichloromethane (20ml). The organics were combined, dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (96:4:0.4 to 90:10:1 by volume) to provide the title compound (34mg, 19%) as a clear oil.

^{1}H NMR (400MHz, $CDCl_3$) δ 1.78-1.81 (m, 4H), 1.83-1.89 (m, 2H), 1.99 (s, 3H), 2.01-2.03 (m, 2H), 2.06-2.11 (m, 3H), 2.15-2.18 (m, 3H), 2.40 (s, 2H), 2.51-2.53 (m, 4H), 2.83 (t, 2H), 3.22 (t, 2H), 3.42-3.44 (m, 2H), 3.62 (t, 2H), 3.73-3.76 (m, 2H), 4.02 (t, 2H), 6.86 (d, 2H), 7.21 (d, 2H).

HRMS ESI$^+$ m/z 430.3052 $[MH]^+$.

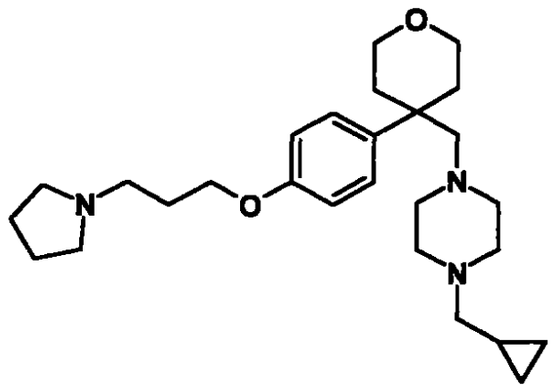
Example 167: 1-isopropyl-4-{[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl]methyl}piperazine



The title compound (78mg, 44%) was prepared from 1-{4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl}piperazine and acetone similarly to the procedure used for example 54.

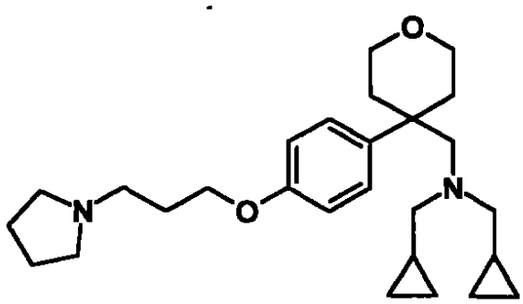
^{1}H NMR (400MHz, $CDCl_3$) δ 0.98 (d, 6H), 1.77-1.80 (m, 4H), 1.86-1.93 (m, 2H), 1.98-2.02 (m, 2H), 2.06-2.09 (m, 2H), 2.20-2.22 (m, 4H), 2.34-2.38 (m, 6H), 2.50-2.54 (m, 5H), 2.62 (t, 2H), 3.52 (t, 2H), 3.71-3.75 (m, 2H), 4.02 (t, 2H), 6.85 (d, 2H), 7.21 (d, 2H).
HRMS ESI$^+$ m/z 430.3417 $[MH]^+$.

Example 168: 1-(cyclopropylmethyl)-4-{[4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-2*H*-pyran-4-yl]methyl}-piperazine



The title compound (28mg, 14%) was prepared from 1-{4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-ylmethyl}piperazine and cyclopropane carboxaldehyde similarly to the procedure used for example 54.
^{1}H NMR (400MHz, $CDCl_3$) δ 0.02 (q, 2H), 0.43 (q, 2H), 0.76 (m, 1H), 1.74-1.76 (m, 4H), 1.83-1.89 (m, 2H), 1.95-1.99 (m, 2H), 2.03-2.06 (m, 3H), 2.13 (d, 2H), 2.19-2.21 (m, 4H), 2.28-2.40 (m, 5H), 2.47-2.51 (m, 4H), 2.59 (t, 2H), 3.49 (t, 2H), 3.68-3.72 (m, 2H), 3.98 (t, 2H), 6.82 (d, 2H), 7.17 (d, 2H).
HRMS ESI$^+$ m/z 442.3412 $[MH]^+$.

Example 169: 1-cyclopropyl-*N*-(cyclopropylmethyl)-*N*-{[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]-tetrahydro-2*H*-pyran-4-yl]methyl}methanamine



The title compound (169mg, 51%) was prepared from {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine free base and cyclopropane carboxaldehyde similarly to the procedure used for example 54. 3 equivalents of cyclopropane carboxaldehyde were required for the synthesis of this Example.

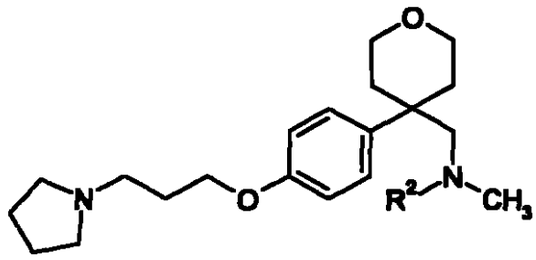
150
1st

^{1}H NMR (400MHz, $CDCl_3$) δ -0.04 (q, 4H), 0.39 (q, 4H), 0.71-0.76 (m, 2H), 1.80-1.86 (m, 4H), 1.94-2.12 (m, 6H), 2.16 (d, 4H), 2.55-2.72 (m, 6H), 3.51 (t, 2H), 3.75-3.79 (m, 2H), 4.04 (t, 2H), 6.88 (d, 2H), 7.21 (d, 2H).

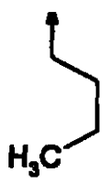
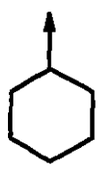
HRMS ESI$^+$ *m/z* 427.3306 $[MH]^+$.

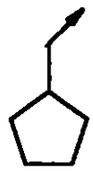
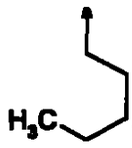
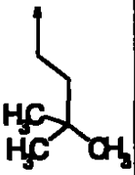
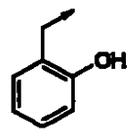
Examples 170-178

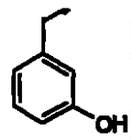
The compounds of the following tabulated Examples of the general formula



were prepared using methyl-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]-tetrahydropyran-4-ylmethyl]amine and the appropriate aldehydes or ketones similarly to the procedure used for example 54.

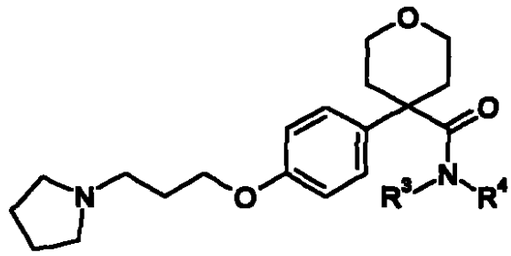
Ex No	R^2	Analytical Data
170		N-methyl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)cyclopentanamine ^{1}H NMR (400MHz, $CDCl_3$) δ 1.21-1.28 (m, 2H), 1.39-1.43 (m, 2H), 1.53-1.60 (m, 4H), 1.83-1.94 (m, 9H), 2.07-2.12 (m, 4H), 2.41 (s, 2H), 2.61-2.72 (m, 7H), 3.49 (t, 2H), 3.73-3.79 (m, 2H), 4.02 (t, 2H), 6.89 (d, 2H), 7.20 (d, 2H). HRMS ESI$^+$ m/z 401.3162 $[MH]^+$. 53% yield
171		N-methyl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)butan-1-amine ^{1}H NMR (400MHz, $CDCl_3$) δ 0.83 (t, 3H), 1.15-1.20 (m, 2H), 1.23-1.29 (m, 2H), 1.85-1.92 (m, 9H), 2.07-2.15 (m, 6H), 2.40 (s, 2H), 2.69-2.77 (m, 6H), 3.51 (t, 2H), 3.73-3.78 (m, 2H), 4.03 (t, 2H), 6.86 (d, 2H), 7.20 (d, 2H). HRMS ESI$^+$ m/z 389.3153 $[MH]^+$. 57% yield
172		N-methyl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)cyclohexanamine ^{1}H NMR (400MHz, CD_3OD) δ 1.02-1.14 (m, 6H), 1.53 (m, 1H), 1.60 (d, 2H), 1.69 (d, 2H), 1.81-1.87 (m, 6H), 1.91 (s, 3H), 1.99-2.03 (m, 2H), 2.14 (d, 2H), 2.48 (s, 2H), 2.61 (t, 4H), 2.69 (t, 2H), 3.48 (t, 2H), 3.72-3.76 (m, 2H), 4.03 (t, 2H), 6.89 (d, 2H), 7.24 (d, 2H). HRMS ESI$^+$ m/z 415.3314 $[MH]^+$. 61% yield

173		1-cyclopentyl-N-methyl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)methanamine ^{1}H NMR (400MHz, CD_3OD) δ 1.07-1.12 (m, 2H), 1.46-1.50 (m, 4H), 1.60-1.64 (m, 2H), 1.82-1.85 (m, 6H), 1.87-1.91 (m, 6H), 1.99-2.01 (m, 2H), 2.04 (d, 2H), 2.14 (d, 2H), 2.43 (s, 2H), 2.59-2.62 (m, 4H), 2.69 (t, 2H), 3.49 (t, 2H), 3.71-3.76 (m, 2H), 4.02 (t, 2H), 6.86 (d, 2H), 7.24 (d, 2H). HRMS ESI$^+$ m/z 415.3313 $[MH]^+$. 44% yield
174		N-methyl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)pentan-1-amine ^{1}H NMR (400MHz, CD_3OD) δ 0.86 (t, 3H), 1.08-1.13 (m, 2H), 1.20-1.28 (m, 4H), 1.62-1.68 (m, 6H), 1.92 (s, 3H), 1.97-2.01 (m, 2H), 2.08 (t, 2H), 2.14 (d, 2H), 2.44 (s, 2H), 2.60-2.64 (m, 4H), 2.70 (t, 2H), 3.49 (t, 2H), 3.71-3.76 (m, 2H), 4.02 (t, 2H), 6.89 (d, 2H), 7.25 (d, 2H). HRMS ESI$^+$ m/z 403.3313 $[MH]^+$. 30% yield
175		N-methyl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)hexan-1-amine ^{1}H NMR (400MHz, $CDCl_3$) δ 0.87 (t, 3H), 1.13-1.20 (m, 4H), 1.23-1.29 (m, 4H), 1.83-1.91 (m, 9H), 2.06-2.13 (m, 6H), 2.40 (s, 2H), 2.58-2.72 (m, 6H), 3.51 (t, 2H), 3.73-3.77 (m, 2H), 4.02 (t, 2H), 6.85 (d, 2H), 7.19 (d, 2H). HRMS ESI$^+$ m/z 417.3469 $[MH]^+$. 74% yield
176		N,3,3-trimethyl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)butan-1-amine ^{1}H NMR (400MHz, $CDCl_3$) δ 0.77 (s, 9H), 1.17 (t, 2H), 1.84-1.90 (m, 6H), 1.92 (s, 3H), 2.06-2.12 (m, 6H), 2.41 (s, 2H), 2.67-2.70 (m, 6H), 3.62 (t, 2H), 3.73-3.78 (m, 2H), 4.01 (t, 2H), 6.86 (d, 2H), 7.20 (d, 2H). HRMS ESI$^+$ m/z 417.3457 $[MH]^+$. 59% yield
177		2-[[methyl({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)amino]methyl]phenol ^{1}H NMR (400MHz, $CDCl_3$) δ 1.78 (s, 3H), 1.79-1.85 (m, 6H), 2.06-2.09 (m, 2H), 2.21 (d, 2H), 2.67-2.75 (m, 6H), 3.48-3.54 (m, 4H), 3.70-3.75 (m, 2H), 4.03 (t, 2H), 6.73 (t, 1H), 6.77 (d, 1H), 6.86 (d, 1H), 6.90 (d, 2H), 7.13 (t, 1H), 7.25 (d, 2H). HRMS ESI$^+$ m/z 439.2943 $[MH]^+$. 30% yield

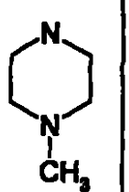
178		3-[[methyl({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)amino]methyl]phenol ^{1}H NMR (400MHz, CD_3OD) δ 1.83 (brs, 7H), 1.88-1.91 (m, 2H), 1.95-2.01 (m, 2H), 2.11-2.15 (d, 2H), 2.55 (s, 2H), 2.58-2.62 (m, 4H), 2.69 (t, 2H), 3.17 (s, 2H), 3.49 (t, 2H), 3.63-3.67 (m, 2H), 4.02 (t, 2H), 6.62 (d, 1H), 6.67 (d, 1H), 6.72 (s, 1H), 6.89 (d, 2H), 7.05 (t, 1H), 7.29 (d, 2H). HRMS ESI$^+$ m/z 439.2941 $[MH]^+$. 68% yield

Examples 179-191

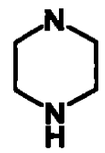
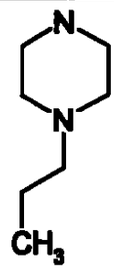
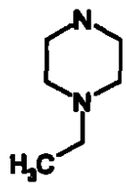
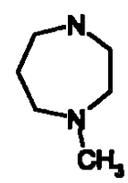
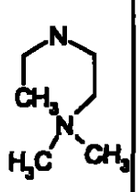
The compounds of the following tabulated Examples of the general formula

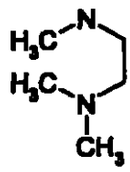
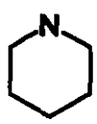
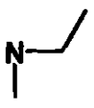


were prepared using 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carboxylic acid, the appropriate amines and O-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HBTU), O-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (TBTU) or 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (WSCDI) similarly to the procedure used for example 150.

Ex No	NR^3R^4	Analytical Data
179	NEt_2	N,N-diethyl-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxamide ^{1}H NMR (400MHz, $CDCl_3$) δ 0.64-0.74 (m, 3H), 1.04-1.12 (m, 3H), 1.79-1.82 (m, 4H), 1.91-2.03 (m, 4H), 2.23 (d, 2H), 2.54-2.58 (m, 4H), 2.65 (t, 2H), 2.88-2.94 (m, 2H), 3.27-3.35 (m, 2H), 3.77-3.89 (m, 4H), 4.01 (t, 2H), 6.86 (d, 2H), 7.15 (d, 2H). HRMS ESI$^+$ m/z 389.2789 $[MH]^+$. Microanalysis: Found: C, 69.16; H, 9.18; N, 7.05%. $C_{23}H_{36}N_2O_3$. $0.5H_2O$ requires C, 69.49; H, 9.38; N, 7.05%. 68% yield
180		1-methyl-4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}carbonyl)piperazine ^{1}H NMR (400MHz, $CDCl_3$) δ 1.76-1.81 (m, 4H), 1.97-2.03 (m, 8H), 2.15 (s, 3H), 2.19-2.22 (m, 2H), 2.50-2.54 (m, 4H), 2.62 (t, 2H), 3.26-3.44 (m, 4H), 3.78 (t, 2H), 3.87-3.90 (m, 2H), 4.02 (t, 2H), 6.86 (d, 2H), 7.15 (d, 2H). HRMS ESI$^+$ m/z 416.2908 $[MH]^+$.

153
154

		9% yield
181		1-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}carbonyl)piperazine ^{1}H NMR (400MHz, $CDCl_3$) δ 1.77-1.80 (m, 6H), 1.97-2.02 (m, 4H), 2.20 (d, 2H), 2.50-2.54 (m, 6H), 2.61 (t, 2H), 3.24-3.38 (m, 4H), 3.78 (t, 2H), 3.86-3.90 (m, 2H), 4.00 (t, 2H), 6.87 (d, 2H), 7.15 (d, 2H). HRMS ESI$^+$ m/z 402.2746 $[MH]^+$. 43% yield
182		1-propyl-4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}carbonyl)piperazine ^{1}H NMR (400MHz, $CDCl_3$) δ 0.84 (t, 3H), 1.37-1.43 (m, 2H), 1.1.69-1.77 (m, 2H), 1.84-1.86 (m, 4H), 1.96-2.07 (m, 6H), 2.14-2.19 (m, 4H), 2.66-2.69 (m, 4H), 2.74 (t, 2H), 3.26-3.40 (m, 4H), 3.78 (t, 2H), 3.87-3.89 (m, 2H), 4.02 (t, 2H), 6.86 (d, 2H), 7.15 (d, 2H). HRMS ESI$^+$ m/z 444.3196 $[MH]^+$. 71% yield
183		1-ethyl-4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}carbonyl)piperazine ^{1}H NMR (400MHz, $CDCl_3$) δ 0.97 (t, 3H), 1.76-1.83 (m, 4H), 1.98-2.01 (m, 8H), 2.18 (d, 2H), 2.25 (d, 2H), 2.51-2.55 (m, 4H), 2.62 (t, 2H), 3.20-3.40 (m, 4H), 3.77 (t, 2H), 3.85-3.88 (m, 2H), 3.98-4.03 (m, 2H), 6.85 (d, 2H), 7.13 (d, 2H). HRMS ESI$^+$ m/z 430.3047 $[MH]^+$. 81% yield
184		1-methyl-4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}carbonyl)-1,4-diazepane ^{1}H NMR (400MHz, $CDCl_3$) δ 1.75-1.81 (m, 8H), 1.98-2.03 (m, 4H), 2.14-2.29 (m, 7H), 2.51-2.54 (m, 4H), 2.62 (t, 2H), 3.12-3.24 (m, 2H), 3.54-3.65 (m, 2H), 3.77-3.88 (m, 4H), 4.01 (t, 2H), 6.88 (d, 2H), 7.16 (d, 2H). HRMS ESI$^+$ m/z 430.3057 $[MH]^+$. 68% yield
185		N-[2-(dimethylamino)ethyl]-N-ethyl-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxamide ^{1}H NMR (400MHz, $CDCl_3$) δ 0.68-0.72 (m, 3H), 1.76-1.81 (m, 4H), 1.98-2.02 (m, 8H), 2.23-2.26 (m, 6H), 2.40-2.45 (m, 2H), 2.50-2.55 (m, 4H), 2.61 (t, 2H), 2.93-3.00 (m, 2H), 3.30-3.39 (m, 2H), 3.80 (t, 2H), 3.86-3.89 (m, 2H), 4.01 (t, 2H), 6.88 (d, 2H), 7.16 (d, 2H). HRMS ESI$^+$ m/z 432.3215 $[MH]^+$. 62% yield

186		N-[2-(dimethylamino)ethyl]-N-methyl-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxamide ^{1}H NMR (400MHz, $CDCl_3$) δ 1.77-1.80 (m, 4H), 1.96-2.01 (m, 6H), 2.18-2.27 (m, 6H), 2.35-2.42 (m, 3H), 2.50-2.53 (m, 4H), 2.62 (t, 2H), 3.03 (s, 2H), 3.35-3.45 (m, 2H), 3.79 (t, 2H), 3.86-3.88 (m, 2H), 4.01 (t, 2H), 6.87 (d, 2H), 7.15 (d, 2H). HRMS ESI$^+$ m/z 418.3052 $[MH]^+$. 61% yield
187		1-(3-[4-[4-(pyrrolidin-1-ylcarbonyl)tetrahydro-2H-pyran-4-yl]phenoxy}propyl)pyrrolidine ^{1}H NMR (400MHz, $CDCl_3$) δ 1.40-1.52 (m, 3H), 1.52-1.80 (m, 3H), 1.82-2.10 (m, 6H), 2.10-2.30 (m, 2H), 2.30-2.38 (m, 2H), 2.60-3.05 (m, 6H), 3.40-3.60 (m, 2H), 3.75-3.90 (m, 4H), 4.05 (t, 2H), 6.84 (d, 2H), 7.18 (d, 2H). LRMS APCI$^+$ m/z 387 $[MH]^+$. HRMS ESI$^+$ m/z 387.2634$[MH]^+$.
188		1-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}carbonyl)piperidine ^{1}H NMR (400MHz, $CDCl_3$) δ 1.18-1.38 (m, 2H), 1.40-1.50 (m, 2H), 1.50-1.80 (m, 6H), 1.84-2.05 (m, 2H), 2.10-2.30 (m, 6H), 2.30-2.48 (m, 2H), 3.10-3.40 (m, 4H), 3.75-3.90 (m, 4H), 4.10 (t, 2H), 6.88 (d, 2H), 7.20 (d, 2H). LRMS APCI$^+$ m/z 401 $[MH]^+$. HRMS ESI$^+$ m/z 401.2670 $[MH]^+$.
189		1-(3-[4-[4-(azetidin-1-ylcarbonyl)tetrahydro-2H-pyran-4-yl]phenoxy}propyl)pyrrolidine ^{1}H NMR (400MHz, $CDCl_3$) δ 1.80-2.00 (m, 6H), 2.00-2.20 (m, 4H), 2.20-2.30 (m, 2H), 2.60-2.82 (m, 6H), 3.50-3.65(m, 2H), 3.72-3.90(m, 4H), 3.90-4.05(m, 2H), 4.08 (t, 2H), 6.90 (d, 2H), 7.20 (d, 2H). LRMS APCI$^+$ m/z 373 $[MH]^+$. HRMS ESI$^+$ m/z 373.2477$[MH]^+$.
190		N-ethyl-N-methyl-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxamide ^{1}H NMR (400MHz, $CDCl_3$) δ 1.00-1.20(m, 3H), 1.78-1.86(m, 4H), 1.92-2.08(m, 4H), 2.18-2.30(m, 2H), 2.45-2.80(m, 8H), 2.80-2.70(t, 3H), 3.22-3.50(m, 2H), 3.70-3.94 (m, 4H), 4.00 (t, 2H), 6.88 (d, 2H), 7.15 (d, 2H). LRMS APCI$^+$ m/z 375 $[MH]^+$. HRMS ESI$^+$ m/z 375.2634$[MH]^+$.
191		N,N-dimethyl-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxamide ^{1}H NMR (400MHz, $CDCl_3$) δ 1.70-1.90(m, 4H), 1.92-2.10(m, 4H), 2.20-

		2.30(m, 2H), 2.50-2.90(m, 12H), 3.70-3.82(m, 2H), 2.82-2.92(m, 2H), 4.00 (t, 2H), 6.88 (d, 2H), 7.15 (d, 2H). LRMS APCI$^+$ m/z 361 [MH]$^+$. HRMS ESI$^+$ m/z 361.2478[MH]$^+$.

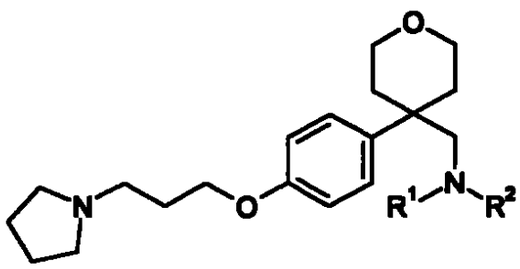
Intermediate 60: 1-(methoxyacetyl)-4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}carbonyl)piperazine

Methoxyacetyl chloride (55µl, 0.6mmol) was added dropwise at 0°C to a solution of 1-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}carbonyl)piperazine of example 181 (200mg, 0.5mmol) and *N,N*-diisopropylethylamine (100µl, 0.6mmol) in dichloromethane (3ml). The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with dichloromethane (20ml) and washed with 2N sodium hydroxide (20ml). The layers were separated and the aqueous layer was further extracted with dichloromethane (20ml). The organics were combined, dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (97:3:0.3 to 90:10:1 by volume) to provide the title compound (160mg, 67%).

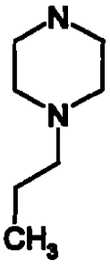
HRMS ESI$^+$ m/z 474.2952 [MH]$^+$.

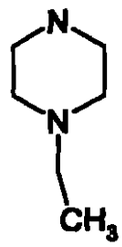
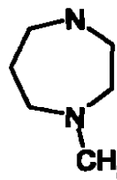
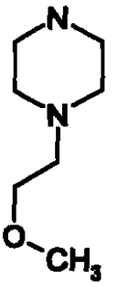
Examples 192-195

The compounds of the following tabulated Examples of the general formula



were prepared using lithium aluminium hydride, the amides of examples 182, 183, 184 and intermediate 60 similarly to the procedure used for example 142.

Ex No	NR^1R^2	Analytical Data
192 (from Ex 182)		1-propyl-4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)piperazine ^{1}H NMR (400MHz, $CDCl_3$) δ 0.85 (t, 3H), 1.40-1.46 (m, 2H), 1.77-1.80 (m, 4H), 1.84-1.91 (m, 2H), 1.98-2.03 (m, 2H), 2.08 (d, 2H), 2.18-2.22 (m, 6H), 2.24-2.28 (m, 4H), 2.36 (s, 2H), 2.51-2.54 (m, 4H), 2.63 (t, 2H), 3.51 (t, 2H), 3.72-3.75 (m, 2H), 4.01 (t, 2H), 6.84 (d, 2H), 7.20 (d, 2H). HRMS ESI$^+$ m/z 430.3410 [MH]$^+$. 98% yield

193 (from Ex 183)		1-ethyl-4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)piperazine ^{1}H NMR (400MHz, $CDCl_3$) δ 1.02 (t, 3H), 1.77-1.81 (m, 4H), 1.86-1.91 (m, 2H), 1.99-2.02 (m, 2H), 2.08 (d, 2H), 2.19-2.23 (m, 4H), 2.27-2.35 (m, 6H), 2.38 (s, 2H), 2.51-2.54 (m, 4H), 2.63 (t, 2H), 3.52 (t, 2H), 3.73-3.76 (m, 2H), 4.02 (t, 2H), 6.85 (d, 2H), 7.21 (d, 2H). HRMS ESI$^+$ m/z 416.3267 $[MH]^+$. 54% yield
194 (from Ex 184)		1-methyl-4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)-1,4-diazepane ^{1}H NMR (400MHz, $CDCl_3$) δ 1.80 (p, 2H), 1.77-1.80 (m, 4H), 1.86-1.92 (m, 4H), 1.98-2.02 (m, 2H), 2.08 (d, 2H), 2.28 (s, 3H), 2.36-2.40 (m, 2H), 2.47-2.53 (m, 8H), 2.57 (s, 2H), 2.62 (t, 2H), 3.50 (t, 2H), 3.73-3.77 (m, 2H), 4.01 (t, 2H), 6.85 (d, 2H), 7.19 (d, 2H). HRMS ESI$^+$ m/z 416.3285 $[MH]^+$. 13% yield
195 (from Int 60)		1-(2-methoxyethyl)-4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)piperazine ^{1}H NMR (400MHz, $CDCl_3$) δ 1.76-1.79 (m, 4H), 1.84-1.89 (m, 2H), 1.97-2.01 (m, 2H), 2.06 (d, 2H), 2.19-2.21 (m, 4H), 2.28-2.33 (m, 4H), 2.35 (s, 2H), 2.47 (t, 2H), 2.50-2.53 (m, 4H), 2.61 (t, 2H), 3.29 (s, 3H), 3.43 (t, 2H), 3.50 (t, 2H), 3.71-3.74 (m, 2H), 4.00 (t, 2H), 6.83 (d, 2H), 7.19 (d, 2H). HRMS ESI$^+$ m/z 446.3374 $[MH]^+$. 31% yield

Intermediate 61: 2-nitro-*N*-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}methyl)aniline

{4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (300mg, 0.94mmol), 2-fluoronitrobenzene (100µl, 0.95mmol) and potassium carbonate (150mg, 1.08mmol) were stirred together at room temperature in *N,N*-dimethylformamide (1ml) for 2 days. The reaction mixture was concentrated *in vacuo* and the residue partitioned between water (30ml) and ethyl acetate (100ml). The layers were separated and the organic phase washed with water (2x20ml), dried over sodium sulphate, filtered and concentrated *in vacuo* to give the title compound as a yellow gum (570mg, 100%).

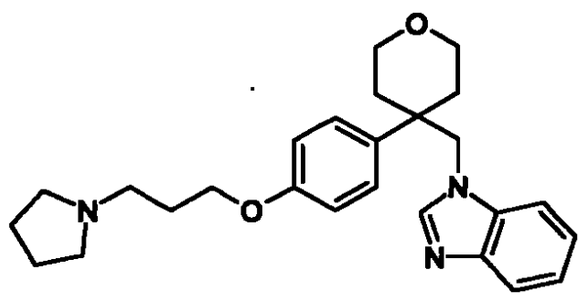
HRMS ESI$^+$ m/z 440.2537 $[MH]^+$.

Intermediate 62: *N*-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}methyl)benzene-1,2-diamine

A solution of 2-nitro-*N*-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}methyl)aniline (570mg, 1.3 mmol) in ethanol (40mL) was hydrogenated for 5 hours at room temperature at 50 psi in the presence of 10% Pd/C (60mg, 10%w/w). The reaction mixture was filtered over Arbocel® and rinsed with

ethanol. The filtrate was concentrated *in vacuo* to give the title compound as a gum, used without further purification (500mg, 94%).
HRMS ESI$^+$ m/z 410.2791 $[MH]^+$.

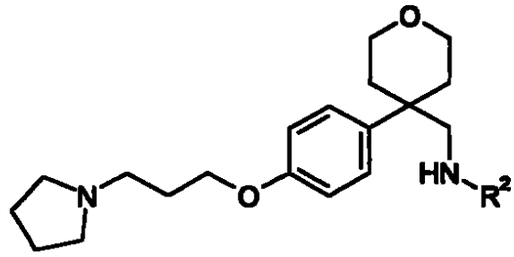
Example 196: 2-{4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}-1*H*-benzimidazole



N-({4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}methyl)benzene-1,2-diamine (500mg, 1.22mmol), trimethylorthoformate (5ml) and formic acid (0.5ml) were stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* and the residue partitioned between aqueous sodium carbonate (50ml) and ethyl acetate (100ml). The layers were separated and the organic phase washed with water (50ml), dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (98:2:0.2 to 92:8:1 by volume). The relevant fractions were evaporated and the residue taken up in diethyl ether (20ml). The unsoluble material was filtered off and the filtrate concentrated *in vacuo* to provide the title compound (150mg, 29%).
^{1}H NMR (400MHz, CD_3OD) δ 1.83-1.85 (*m*, 4H), 1.98-2.06 (*m*, 4H), 2.23 (d, 2H), 2.62 (s, 4H), 2.69 (t, 2H), 3.42 (t, 2H), 3.82 (d, 2H), 4.00 (t, 2H), 4.33 (s, 2H), 6.84 (d, 2H), 7.06 (d, 2H), 7.14-7.18 (m, 3H), 7.26 (s, 1H), 7.55 (d, 1H).
HRMS ESI$^+$ m/z 420.2637 $[MH]^+$.

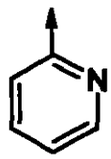
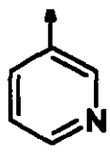
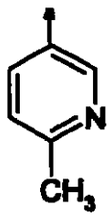
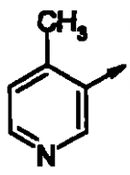
Examples 197-200

The compounds of the following tabulated Examples of the general formula

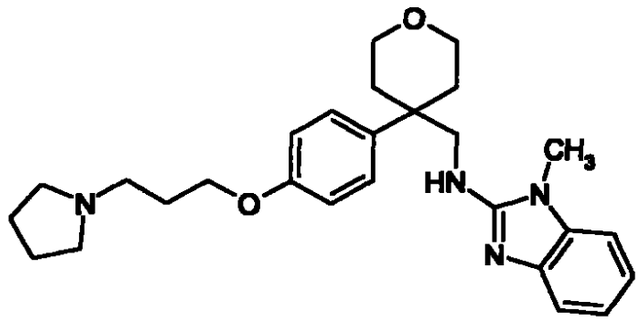


were prepared using {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine and the appropriate bromo or iodopyridines similarly to the palladium coupling procedure used for example 152.

Ex No	R^2	Analytical Data

197		N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)pyridin-2-amine ^{1}H NMR (400MHz, $CDCl_3$) δ 1.81-1.86 (m, 4H), 1.90-1.96 (m, 2H), 2.05-2.17 (m, 4H), 2.58-2.75 (m, 6H), 3.50 (d, 2H), 3.59 (t, 2H), 3.81-3.85 (m, 2H), 4.00 (t, 1H), 4.05 (t, 2H), 6.23 (d, 1H), 6.51 (t, 1H), 6.92 (d, 2H), 7.25 (d, 2H), 7.32 (t, 1H), 8.02 (d, 1H). HRMS ESI$^+$ m/z 396.2633 $[MH]^+$. 14% yield
198		N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)pyridin-3-amine ^{1}H NMR (400MHz, $CDCl_3$) δ 1.80-1.84 (m, 4H), 1.88-1.94 (m, 2H), 2.03-2.07 (m, 2H), 2.19 (d, 2H), 2.56-2.63 (m, 4H), 2.66-2.70 (m, 2H), 3.24 (s, 3H), 3.57 (t, 2H), 3.77-3.82 (m, 2H), 4.05 (t, 2H), 6.74 (d, 1H), 6.93 (d, 2H), 7.01 (t, 1H), 7.24 (d, 2H), 7.88-7.91 (m, 2H). HRMS ESI$^+$ m/z 396.2640 $[MH]^+$. 13% yield
199		6-methyl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)pyridin-3-amine ^{1}H NMR (400MHz, $CDCl_3$) δ 1.83 (d, 7H), 1.94-2.01 (m, 2H), 2.04 (t, 2H), 2.24 (d, 2H), 2.2.58-2.62 (m, 4H), 2.68 (t, 2H), 2.98 (t, 1H), 3.29 (d, 2H), 3.59 (t, 2H), 3.79-3.83 (m, 2H), 4.04 (t, 2H), 6.85 (d, 1H), 6.94 (d, 2H), 7.27 (d, 2H), 7.86 (d, 1H), 7.92 (s, 1H). HRMS ESI$^+$ m/z 410.2793 $[MH]^+$. 11% yield
200		4-methyl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)pyridin-3-amine ^{1}H NMR (400MHz, $CDCl_3$) δ 1.81-1.83 (m, 4H), 1.87-1.94 (m, 2H), 2.05 (t, 2H), 2.18 (d, 2H), 2.38 (s, 3H), 2.58-2.61 (m, 4H), 2.69 (t, 2H), 3.10 (t, 1H), 3.20 (d, 2H), 3.56 (t, 2H), 3.77-3.82 (m, 2H), 4.05 (t, 2H), 6.69 (dd, 1H), 6.87 (d, 1H), 6.93 (d, 2H), 7.24 (d, 2H), 7.78 (s, 1H). HRMS ESI$^+$ m/z 410.2793 $[MH]^+$. 13% yield

Example 201: 1-methyl-N-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)-1H-benzimidazol-2-amine



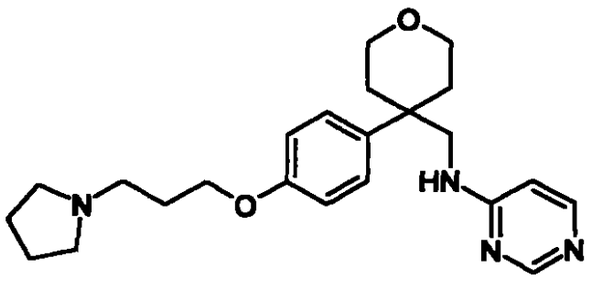
A mixture of {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (150 mg, 0.47mmol), *1-methylbenzimidazole-2-sulfonic acid* (83.4mg, 0.39mmol) and *N,N*-diisopropylethylamine (175µl, 0.98mmol) in acetonitrile (1.5ml) was heated at 155°C in the Smith Personal Synthesiser for 2400 seconds and then a further 900 seconds. The reaction mixture was partitioned between dichloromethane (10 ml) and saturated aqueous sodium bicarbonate solution (10 ml). The organic layer was dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (100:0:0 to 95:5:0.5 by volume) to provide the title compound (29mg, 14%).

^{1}H NMR (400MHz, CD_3OD) δ 1.83-1.86 (m, 4H), 1.96-2.02 (m, 4H), 2.19 (d, 2H), 2.63-2.66 (m, 4H), 2.70 (t, 2H), 3.41 (s, 3H), 3.60 (t, 2H), 3.57 (s, 2H), 3.79-3.82 (m, 2H), 3.97 (t, 2H), 6.91 (d, 2H), 6.97-7.02 (m, 2H), 7.08 (d, 1H), 7.22 (d, 1H), 7.36 (d, 2H).
LRMS APCI$^+$ m/z 449 $[MH]^+$.

Intermediate 63: 6-chloro-*N*-{[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl]methyl}pyrimidin-4-amine

A mixture of {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (100 mg, 0.31mmol), 4,6-dichloropyrimidine (46.6mg, 0.31mmol) and *N,N*-diisopropylethylamine (137µl, 0.78mmol) in isopropanol (1ml) was stirred at room temperature for 18 hours. The reaction mixture was partitioned between ethyl acetate (3x10 ml) and saturated aqueous sodium bicarbonate (10 ml). The combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (100:0:0 to 92:8:0.8 by volume) to provide the title compound (50mg, 37%).
LRMS APCI$^+$ m/z 431 $[MH]^+$.

Example 202: *N*-{[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl]methyl}pyrimidin-4-amine



A solution of 6-chloro-*N*-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}methyl)pyrimidin-4-amine (50mg, 0.12 mmol) and triethylamine (48.6µl, 0.35mmol) in ethanol (2mL) was hydrogenated for 16 hours at room temperature at 50 psi in the presence of 10% Pd/C (5mg, 10% w/w). The reaction mixture was filtered through Arbocel® and rinsed with ethanol and water. The filtrate was concentrated *in vacuo*. The residue was partitioned between ethyl acetate (20 ml) and saturated aqueous sodium carbonate (20 ml). The organic layer was dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (100:0:0 to 95:5:0.5 by volume) to provide the title compound (9mg, 20%).

^{1}H NMR (400MHz, $CDCl_3$) δ 1.78-1.81 (m, 4H), 1.85-1.90 (m, 2H), 2.00-2.05 (m, 2H), 2.09-2.16 (m, 2H), 2.53-2.60 (m, 4H), 2.66 (t, 2H), 3.54-3.58 (m, 4H); 3.79-3.83 (m, 2H), 4.02 (t, 2H), 4.44 (brs, 1H), 6.12 (d, 1H), 6.82 (d, 2H), 7.20 (d, 2H), 8.05 (d, 1H), 8.47 (s, 1H).

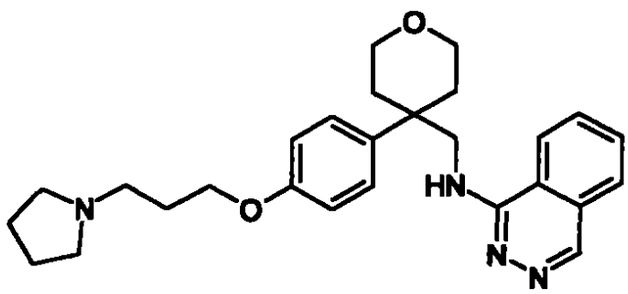
HRMS ESI$^+$ m/z 397.2598 $[MH]^+$.

Intermediate 64: 4-chloro-*N*-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}methyl)phthalazin-1-amine

A mixture of {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (300 mg, 0.94mmol), 1,4-dichlorophthalazine (188mg, 0.94mmol) and *N,N*-diisopropylethylamine (410µl, 2.36mmol) in *N,N*-dimethylformamide (1ml) was stirred at room temperature for 18 hours. More 1,4-dichlorophthalazine (188mg, 0.94mmol) was added and the reaction stirred at room temperature for 36 hours, then heated at 55°C for 18 hours. The reaction mixture was partitioned between ethyl acetate (20 ml) and saturated aqueous sodium bicarbonate solution (20 ml). The organic layer was washed with more aqueous sodium bicarbonate, brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (100:0:0 to 92:8:0.8 by volume) to provide the title compound (183mg, 61%).

LRMS APCI$^+$ m/z 481 $[M]^+$.

Example 203: *N*-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}methyl)phthalazine-1-amine

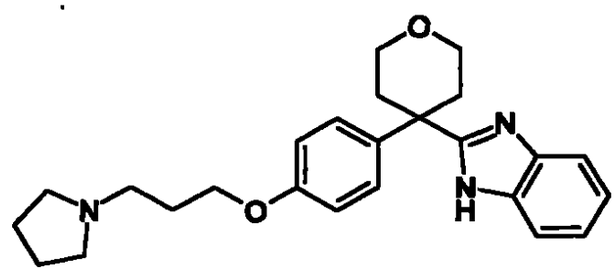


The title compound (86mg, 51%) was prepared from 4-chloro-*N*-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}methyl)phthalazin-1-amine by hydrogenation similarly to the procedure used for example 202.

^{1}H NMR (400MHz, $CDCl_3$) δ 1.80-1.84 (m, 4H), 2.01-2.08 (m, 4H), 2.15-2.20 (m, 2H), 2.55-2.60 (m, 4H), 2.66 (t, 2H), 3.61-3.66 (m, 2H), 3.86-3.92 (m, 2H), 3.96 (d, 2H), 4.07 (t, 2H), 4.62 (t, 1H), 7.00 (d, 2H), 7.32-7.36 (m, 3H), 7.66-7.77 (m, 3H), 8.69 (s, 1H).

HRMS ESI$^+$ m/z 447.2746 $[MH]^+$.

Example 204: 2-{4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}-1*H*-benzimidazole

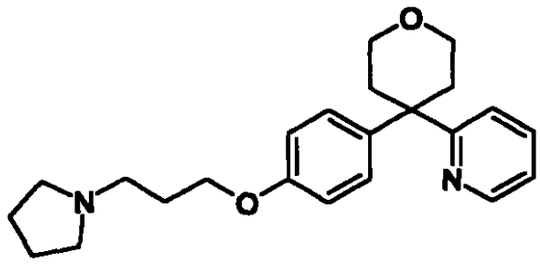


A mixture of 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carboxylic acid (400mg, 1.20mmol), 1,2-diaminobenzene (129mg, 1.20mmol) and polyphosphoric acid (2g) was heated at 130°C for 2 days. The cooled reaction mixture was partitioned between dichloromethane (20 ml) and aqueous ammonia (20 ml). The aqueous layer was further extracted with dichloromethane (2x50ml). The organic layers were combined, dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by preparative HPLC on Fraction-Lynx® eluting with water:acetonitrile:TFA (95:5:0.1) to provide the title compound (3.5mg, 1%).

^{1}H NMR (400MHz, $CDCl_3$) δ 1.92-1.96 (m, 2H), 2.06-2.21 (m, 4H), 2.40-2.46 (m, 2H), 2.96-3.00 (m, 4H), 3.05-3.09 (m, 2H), 3.16-3.20 (m, 2H), 3.57-3.65 (m, 4H), 3.93 (d, 2H), 5.45 (d, 2H), 7.06 (d, 2H), 7.45 (d, 2H), 7.71-7.74 (m, 2H).

LCMS ESI$^+$ m/z 406 $[MH]^+$.

Example 205: 2-{4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}-pyridine

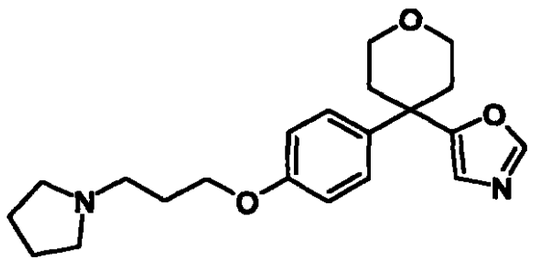


Trimethylsilylacetylene (0.9ml, 6mmol) was added at room temperature to a solution of 4-[3-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-carbonitrile (200mg, 0.6mmol) and dicarbonylcyclopentadienyl cobalt (12mg, 0.07mmol) in toluene (3ml). Tetrabutylammonium fluoride (1.54g, 6mmol) was added portionwise over 10 minutes. The reaction mixture was then stirred at room temperature under visible light under nitrogen for 12 days. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between dichloromethane (50ml) and aqueous sodium hydroxide solution (50ml). The aqueous layer was extracted again with dichloromethane (50ml). The organic layers were combined, dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by preparative HPLC on Fraction-Lynx® eluting with water:acetonitrile:TFA (95:5:0.1) to provide the title compound (4mg, 2%).

^{1}H NMR (400MHz, $CDCl_3$) δ 1.78-1.81 (m, 4H), 1.95-2.02 (m, 2H), 2.32-2.39 (m, 2H), 2.61-2.66 (m, 4H), 2.61-2.70 (m, 4H), 3.67 (t, 2H), 3.76-3.84 (m, 2H), 3.98 (d, 2H), 6.81 (d, 2H), 7.06 (t, 1H), 7.13 (d, 1H), 7.21 (d, 2H), 7.55 (t, 1H), 8.58 (d, 1H).

HRMS ESI$^+$ m/z 367.2375 $[MH]^+$.

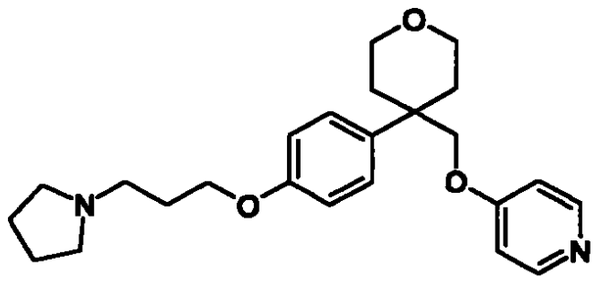
Example 206: 5-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl]-1,3-oxazole



Tosylmethyl isocyanide (370mg, 1.89mmol) was added to a solution of 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carbaldehyde (500mg, 1.58mmol) and potassium carbonate (652mg, 4.73mmol) in methanol (7ml). The reaction mixture was heated at reflux for 3 hours. The reaction mixture was partitioned between ethyl acetate (2x75ml) and water (20ml). The organic layers were combined, dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was taken up in 2N hydrochloric acid (3ml) and stirred at room temperature for 1.5 hours. The mixture was then partitioned between aqueous sodium carbonate and dichloromethane (2x75ml). The combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:5:0.5 by volume) to provide the title compound (12mg, 2%).

^{1}H NMR (400MHz, CD_3OD) δ 1.81-1.85 (m, 4H), 1.97-2.02 (m, 2H), 2.25-2.31 (m, 2H), 2.38-2.43 (m, 2H), 2.60-2.63 (m, 4H), 2.69 (t, 2H), 3.61 (t, 2H), 3.78-3.83 (m, 2H), 4.01 (t, 2H), 6.87 (d, 2H), 6.98 (s, 1H), 7.22 (d, 2H), 8.09 (s, 1H).
LRMS APCI$^+$ m/z 357 $[MH]^+$.

Example 207: 4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}methoxy)pyridine

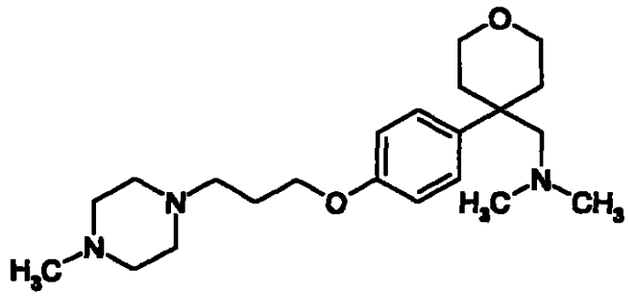


The title compound (75mg, 60%) was prepared from {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methanol and 4-bromopyridine similarly to the procedure used for example 152.
^{1}H NMR (400MHz, $CDCl_3$) δ 1.78-1.82 (m, 4H), 1.98-2.04 (m, 2H), 2.12-2.17 (m, 4H), 2.49-2.58 (m, 4H), 2.81-2.86 (*m*, 2H), 3.54-3.60 (*m*, 2H), 3.81-3.85 (*m*, 2H), 3.87 (s, 2H), 4.03 (t, 2H), 6.71 (d, 2H), 6.91 (d, 2H), 7.29 (d, 2H), 8.36 (d, 2H).
HRMS ESI$^+$ m/z 397.2479 $[MH]^+$.

Intermediate 65: 1-{4-[4-(3-chloropropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl}-*N*,*N*-dimethylmethanamine

1-Bromo-3-chloropropane (0.42ml, 4.25mmol) was added to a solution of 4-(4-dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (1.0g, 4.25mmol) and potassium carbonate (1.5g, 10.8mmol) in *N*,*N*-dimethylformamide (10ml). The reaction mixture was stirred at 45°C for 18 hours. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate (100ml) and water (50ml). The organic layer was separated, dried over sodium sulphate, filtered and concentrated *in vacuo* to provide the title compound (800mg, 60%).
LRMS APCI$^+$ m/z 412 $[MH]^+$.

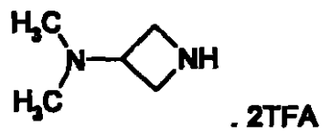
Example 208: *N*,*N*-dimethyl-1-(4-{4-[3-(4-methylpiperazin-1-yl)propoxy]phenyl}tetrahydro-2*H*-pyran-4-yl)methanamine



A mixture of 1-[4-[4-(3-chloropropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl]-*N*,*N*-dimethylmethanamine (200mg, 0.7mmol), *N*-methyl piperazine (87µl, 0.79mmol), solid sodium bicarbonate (66mg, 0.79mmol) and a catalytic amount of potassium iodide was heated at 50°C in *N*,*N*-dimethylformamide (2ml) for 18 hours. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate (2x75ml) and water (20ml). The organic layers were combined, dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (96:4:0.4 by volume) to provide the title compound (102mg, 39%).

^{1}H NMR (400MHz, $CDCl_3$) δ 1.84-1.91 (m, 2H), 1.95-1.99 (m, 8H), 2.07-2.11 (m, 2H), 2.30 (s, 3H), 2.40 (s, 2H), 2.42-2.59 (m, 10H), 3.54 (t, 2H), 3.72-3.78 (m, 2H), 4.00 (t, 2H), 6.86 (d, 2H), 7.20 (d, 2H).
HRMS ESI$^+$ m/z 376.2951 $[MH]^+$.

Intermediate 86: *N*,*N*-dimethylazetidin-3-amine ditrifluoroacetate

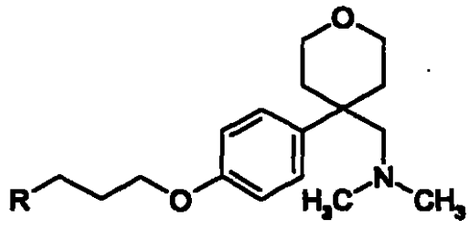


. 2TFA

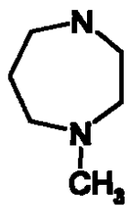
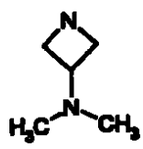
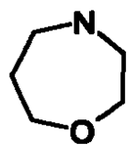
This amine was described in patent WO 2004096810 (prep 170, p240).

Examples 209-211

The compounds of the following tabulated examples of the general formula



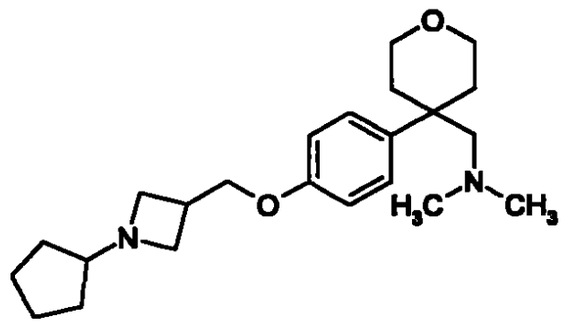
were prepared using 1-[4-[4-(3-chloropropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl]-*N*,*N*-dimethylmethanamine and the appropriate amines similarly to the procedure used for example 208.

Ex No	R	Analytical Data
209		N,N-dimethyl-1-(4-[4-[3-(4-methyl-1,4-diazepan-1-yl)propoxy]phenyl]tetrahydro-2H-pyran-4-yl)methanamine ^{1}H NMR (400MHz, $CDCl_3$) δ 1.77-1.91 (m, 6H), 1.94 (s, 6H), 2.04-2.08 (m, 2H), 2.33 (s, 3H), 2.38 (s, 2H), 2.57-2.65 (m, 6H), 2.70-2.73 (m, 4H), 3.52 (t, 2H), 3.70-3.75 (m, 2H), 3.96 (t, 2H), 6.84 (d, 2H), 7.18 (d, 2H). LRMS APCI$^+$ m/z 390 $[MH]^+$. 30% yield
210		1-[3-(4-[4-[(dimethylamino)methyl]tetrahydro-2H-pyran-4-yl]phenoxy)propyl]-N,N-dimethylazetidin-3-amine ^{1}H NMR (400MHz, $CDCl_3$) δ 1.62-1.90 (m, 6H), 1.96 (s, 6H), 2.11 (s, 6H), 2.40 (s, 2H), 2.63 (t, 3H), 2.80-2.86 (m, 3H), 3.52-3.56 (m, 4H), 3.72-3.76 (m, 2H), 3.96-3.99 (m, 2H), 6.85 (d, 2H), 7.20 (d, 2H). HRMS ESI$^+$ m/z 376.2959 $[MH]^+$. 53% yield
211		Dimethyl-[4-[4-(3-[1,4]oxazepan-4-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-amine ^{1}H NMR (400MHz, $CDCl_3$) δ 1.85-2.04 (m, 12H), 2.11 (M, 2H), 2.42 (s, 2H), 2.7-2.8 (m, 6H), 3.55 (t, 2H), 3.72-3.82 (m, 6H), 4.02 (t, 2H), 6.87 (d, 2H), 7.22 (d, 2H) HRMS ESI$^+$ m/z 377.2792 $[MH]^+$ 35% yield

Intermediate 67: 1-benzhydryl-3-chloromethyl-azetidine hydrochloride

(1-Benzhydryl-azetidin-3-yl)-methanol (3.07g, 12.1mmol) was dissolved in dichloromethane (60ml). The reaction was cooled to 0-5°C and thionyl chloride (1.07ml, 14.6mmol) was added slowly. The reaction was allowed to warm to room temperature and stirred for 18 hours. The reaction was concentrated *in vacuo* and azeotroped with toluene (3x20ml) to give the title compound (3.8g, 100%) as a pale brown solid.

Example 212: 1-(4-[4-[(1-cyclopentylazetidin-3-yl)methoxy]phenyl]tetrahydro-2*H*-pyran-4-yl)-N,N-dimethylmethanamine



Step 1:

4-(4-Dimethylaminomethyl-tetrahydro-pyran-4-yl)-phenol (1.15g, 5.65mmol), 1-benzhydryl-3-chloromethyl-azetidine hydrochloride (1.58g, 5.13mmol), *N,N*-dimethylformamide (32ml) and potassium carbonate (2.84g, 20.52mmol) were reacted together according to general procedure B. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with 2M sodium hydroxide (3x50ml), brine (3x50ml), dried over magnesium sulphate, filtered and concentrated *in vacuo* to provide 1-[4-(4-{[1-benzhydrylazetidin-3-yl]methoxy}phenyl)tetrahydro-2*H*-pyran-4-yl]-*N,N*-dimethylmethanamine (1.82g, 81%) as an off-white solid.

Step 2:

This intermediate was hydrogenated in ethanol (20ml) for 4 hours at 60°C at atmospheric pressure in the presence of 10% Pd/C (300mg). The reaction mixture was filtered through Arbocel® and rinsed with ethanol and water. The filtrate was concentrated *in vacuo*. The residue was taken up in 2N hydrochloric acid (50ml) and extracted with *tert*-butylmethyl ether (3x50ml). The aqueous layer was then basified to pH14 with 2M sodium hydroxide and extracted with dichloromethane (3x50ml). These organic layers were combined, dried over magnesium sulphate, filtered and concentrated *in vacuo* to provide 1-[4-[4-(azetidin-3-ylmethoxy)phenyl]tetrahydro-2*H*-pyran-4-yl]-*N,N*-dimethylmethanamine (850mg, 85%) as an off-white solid.

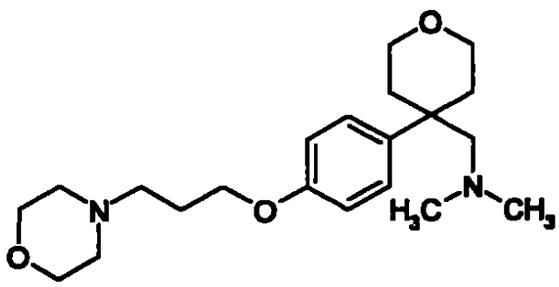
Step 3:

Cyclopentyl bromide (0.17ml, 1.54mmol) and 5M aqueous sodium hydroxide (0.34ml, 1.68mmol) were added to a solution of 1-[4-[4-(azetidin-3-ylmethoxy)phenyl]tetrahydro-2*H*-pyran-4-yl]-*N,N*-dimethylmethanamine (425mg, 1.4mmol) in acetone (9ml). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo*. The residue was taken up in 2N hydrochloric acid to reach pH 1 and extracted with *tert*-butylmethyl ether (2x15ml). The aqueous layer was then basified to pH14 with 4M sodium hydroxide (ca 40ml) and extracted with dichloromethane (3x30ml). These organic layers were combined, dried over magnesium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:4:1 by volume) to provide the title compound (55mg, 11%) as a yellow solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 1.28-1.73 (m, 8H), 1.83-1.93 (m, 2H), 1.96 (s, 6H), 2.05-2.13 (m, 2H), 2.40 (s, 2H), 2.71 (m, 1H), 2.90 (m, 1H), 3.00 (t, 2H), 3.38-3.58 (m, 4H), 3.72-3.78 (m, 2H), 4.05 (d, 2H), 6.87 (d, 2H), 7.21 (d, 2H).

LRMS ESI$^+$ m/z 373 $[MH]^+$.

Example 213: *N,N*-dimethyl-1-[4-[4-(3-morpholin-4-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl]methanamine

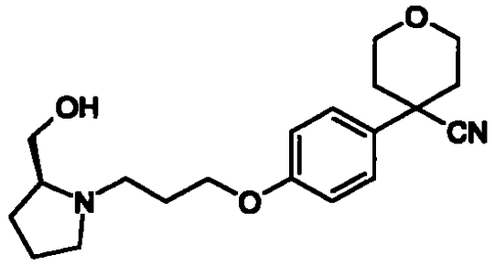


A mixture of 1-[4-[4-(3-chloropropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl]-*N*,*N*-dimethylmethanamine (100mg, 0.32mmol), morpholine (100mg, 1.1mmol) and potassium carbonate (100mg, 0.72mmol) was heated at reflux in acetonitrile (5ml) for 8 hours. Further morpholine (100mg, 1.1mmol) and potassium carbonate (100mg, 0.72mmol) were added and the reaction mixture heated at reflux for 6 hours. The reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (90:10:1 by volume) to provide the title compound (81mg, 52%).

^{1}H NMR (400MHz, CD_3OD) δ 0.81-0.87 (m, 2H), 1.04-2.01 (m, 8H), 2.13-2.18 (m, 2H), 2.48-2.50 (m, 6H), 2.66 (t, 2H), 3.50 (t, 2H), 3.68-3.77 (m, 6H), 4.03 (t, 2H), 6.90 (d, 2H), 7.27 (d, 2H).

HRMS ESI$^+$ m/z 363.2635 $[MH]^+$.

Example 214: 4-[4-[3-[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]propoxy]phenyl]tetrahydro-2*H*-pyran-4-carbonitrile



The title compound (30mg, 12%) was prepared using 4-[4-(3-chloro-propoxy)-phenyl]-tetrahydropyran-4-carbonitrile and (S)-(+)-2-pyrrolidine methanol similarly to the procedure used for example 208.

^{1}H NMR (400MHz, $CDCl_3$) δ 1.79-1.85 (m, 3H), 1.94 (m, 1H), 2.01-2.12 (m, 7H), 2.41 (m, 1H), 2.58 (m, 1H), 2.78 (m, 1H), 3.08 (m, 1H), 3.33 (m, 1H), 3.49 (m, 1H), 3.71 (d, 1H), 3.88 (t, 2H), 4.04-4.09 (m, 4H), 6.92 (d, 2H), 7.38 (d, 2H).

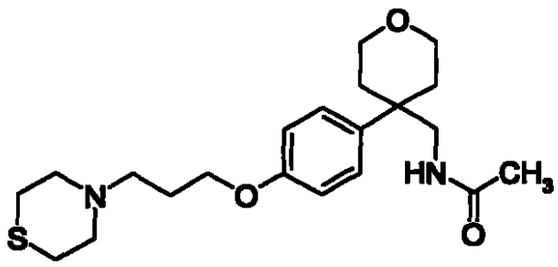
HRMS ESI$^+$ m/z 345.2167 $[MH]^+$.

Intermediate 68: 1-[4-[4-(3-thiomorpholin-4-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl]methanamine

The title compound (1.58g, 92%) was prepared using 4-[4-(3-thiomorpholin-4-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carbonitrile and lithium aluminium hydride similarly to the procedure used for intermediate 51.

LRMS APCI$^+$ m/z 351 $[MH]^+$.

Example 215: *N*-((4-[4-(3-thiomorpholin-4-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl)methyl)acetamide

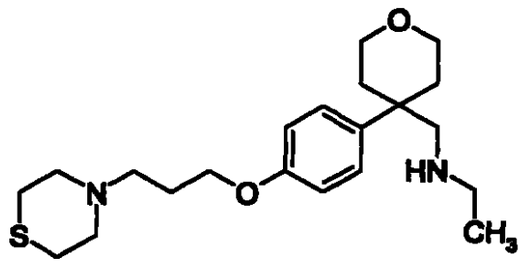


The title compound (1.16g, 100%) was prepared using 1-[4-[4-(3-thiomorpholin-4-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl]methanamine and acetic anhydride similarly to the procedure used for example 140.

^{1}H NMR (400MHz, $CDCl_3$) δ 1.82-1.86 (m, 2H), 1.87 (s, 3H), 2.00-2.04 (m, 4H), 2.58-2.85 (m, 10H), 3.45 (d, 2H), 3.56-3.61 (m, 2H), 3.79-3.84 (m, 2H), 4.02 (t, 2H), 4.97 (brs, 1H), 6.91 (d, 2H), 7.19 (d, 2H).

LRMS APCI$^+$ m/z 393 $[MH]^+$.

Example 216: *N*-((4-[4-(3-thiomorpholin-4-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl)methyl)ethanamine



The title compound (492mg, 44%) was prepared using *N*-((4-[4-(3-thiomorpholin-4-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-yl)methyl)acetamide and lithium aluminium hydride similarly to the procedure used for example 142.

^{1}H NMR (400MHz, $CDCl_3$) δ 0.96 (t, 3H), 1.88-1.98 (m, 4H), 2.11-2.15 (m, 2H), 2.49 (q, 2H), 2.55 (t, 2H), 2.68-2.74 (m, 10H), 3.55 (t, 2H), 3.74-3.79 (m, 2H), 4.00 (t, 2H), 6.89 (d, 2H), 7.22 (d, 2H).

LRMS APCI$^+$ m/z 379 $[MH]^+$.

Intermediate 89: 4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carboxylic acid

4-(4-Methoxyphenyl)-tetrahydro-2*H*-pyran-4-carbonitrile (10g, 46mmol) was heated at reflux for 18 hours in concentrated hydrochloric acid (100mL). The reaction mixture was extracted with dichloromethane (2x100mL). The combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo* to a gummy solid. This was partitioned between 2M sodium hydroxide (300ml) and ethyl acetate (300ml). The aqueous layer was then acidified with concentrated hydrochloric acid (a white precipitate formed which was dissolved by adding dichloromethane (250ml)). The layers were separated and the aqueous layer was further extracted with dichloromethane (250ml). These dichloromethane organic layers

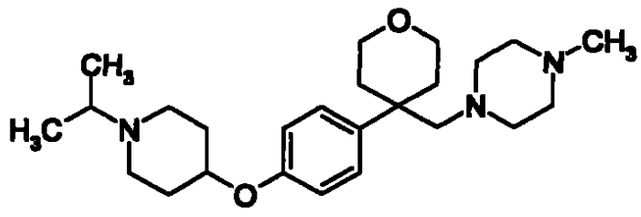
were combined, dried over sodium sulphate, filtered and concentrated *in vacuo* to provide the title compound (3.4g, 31%) as a white solid.
LRMS APCI⁻ m/z 235 [M-H]⁻.

Intermediate 70: 1-[[4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-yl]carbonyl]-4-methylpiperazine
The title compound (515mg, 77%) was prepared using 4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carboxylic acid, *N*-methyl-piperazine and O-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (TBTU) similarly to the procedure used for example 166.
HRMS ESI⁺ m/z 319.2009 [MH]⁺.

Intermediate 71: 1-[[4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-yl]methyl]-4-methylpiperazine
The title compound (428mg, 93%) was prepared using 1-[[4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-yl]carbonyl]-4-methylpiperazine and lithium aluminium hydride similarly to the procedure used for example 142.
HRMS ESI⁺ m/z 305.2220 [MH]⁺.

Intermediate 72: 4-[4-[(4-methylpiperazin-1-yl)methyl]tetrahydro-2*H*-pyran-4-yl]phenol
To a suspension of sodium thiomethoxide (660mg, 9.4mmol) in *N*,*N*-dimethylformamide (2ml) was added 1-[[4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-yl]methyl]-4-methylpiperazine (410mg, 1.3mmol) in *N*,*N*-dimethylformamide (3ml). The reaction mixture was heated to 130°C under nitrogen for 18 hours. The mixture was then allowed to cool down to room temperature and saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate (2x30ml). The combined organic extracts were dried over sodium sulphate, filtered and concentrated *in vacuo* to provide a pale brown oil. This was azeotroped with toluene and dried under high vacuum to provide the title compound (390mg, 100%) as an off-white solid.
HRMS ESI⁺ m/z 291.2082 [MH]⁺.

Example 217: 1-[(4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-yl)methyl]-4-methylpiperazine



The title compound (72mg, 14%) was prepared using 4-[4-[(4-methylpiperazin-1-yl)methyl]tetrahydro-2*H*-pyran-4-yl]phenol, 1-isopropyl-4-hydroxypiperidine (step1 of intermediate 21), PPh_3 and DIAD similarly to the procedure used for intermediate 55.
^{1}H NMR (400MHz, $CDCl_3$) δ 1.04 (d, 6H), 1.76-1.90 (m, 4H), 1.96-2.06 (m, 4H), 2.17-2.26 (m, 11H), 2.33-2.38 (m, 4H), 2.69-2.80 (m, 3H), 3.51 (t, 2H), 3.69-3.74 (m, 2H), 4.24 (m, 1H), 6.84 (d, 2H), 7.18 (d, 2H).
HRMS ESI⁺ m/z 416.3268 [MH]⁺.

170
171

Intermediate 73: 4-[[4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-yl]carbonyl]morpholine

The title compound (3.1g, 87%) was prepared using 4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-carboxylic acid, morpholine and O-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (TBTU) similarly to the procedure used for example 166.

HRMS ESI$^+$ *m/z* 306.1696 $[MH]^+$.

Intermediate 74: 4-[[4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-yl]methyl]-morpholine

The title compound (2.48g, 87%) was prepared using 4-[[4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-yl]carbonyl]morpholine and lithium aluminium hydride similarly to the procedure used for example 142.

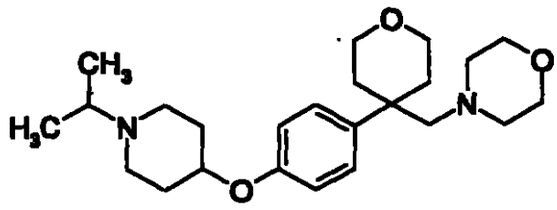
HRMS ESI$^+$ *m/z* 292.1897 $[MH]^+$.

Intermediate 75: 4-[4-(morpholin-4-ylmethyl)tetrahydro-2*H*-pyran-4-yl]phenol

The title compound (1.70g, 75%) was prepared using 4-[[4-(4-methoxyphenyl)tetrahydro-2*H*-pyran-4-yl]methyl]-morpholine and sodium thiomethoxide similarly to the procedure used for intermediate 72.

HRMS ESI$^+$ *m/z* 278.1740 $[MH]^+$.

Example 218: 4-[[4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl]tetrahydro-2*H*-pyran-4-yl]methyl]-morpholine



The title compound (52mg, 12%) was prepared using 4-[4-(morpholin-4-ylmethyl)tetrahydro-2*H*-pyran-4-yl]phenol, 1-isopropyl-4-hydroxypiperidine (step1 of intermediate 21), PPh_3 and DIAD similarly to the procedure used for intermediate 55.

^{1}H NMR (400MHz, CD_3OD) δ 1.09 (d, 6H), 1.74-1.80 (m, 2H), 1.83-1.90 (m, 2H), 1.98-2.04 (m, 2H), 2.12-2.18 (m, 6H), 2.40 (s, 2H), 2.47 (t, 2H), 2.75 (m, 1H), 2.80-2.85 (m, 2H), 3.47-3.54 (m, 6H), 3.71-3.77 (m, 2H), 4.36 (m, 1H), 6.90 (d, 2H), 7.28 (d, 2H).

HRMS ESI$^+$ *m/z* 403.2951 $[MH]^+$.

Intermediate 76: 4-[[4-(4-[[1-(benzhydryl)azetidin-3-yl]methoxy]phenyl) tetrahydro-2*H*-pyran-4-yl]methyl]-morpholine

The title compound (1.09g, 66%) was prepared using 4-[4-(morpholin-4-ylmethyl)tetrahydro-2*H*-pyran-4-yl]phenol, (1-benzhydryl-azetidin-3-yl)-methanol, PPh_3 and DIAD similarly to the procedure used for intermediate 55.

HRMS ESI$^+$ *m/z* 513.3103 $[MH]^+$.

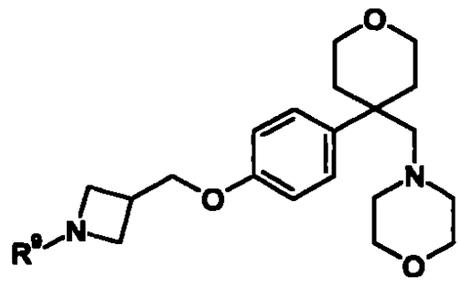
Intermediate 77: 4-[[4-[4-(azetidin-3-ylmethoxy)phenyl]tetrahydro-2*H*-pyran-4-yl]methyl]-morpholine

A solution of 4-[[4-(4-[[1-(benzhydryl)azetidin-3-yl]methoxy]phenyl)tetrahydro-2*H*-pyran-4-yl]methyl]-morpholine (1.0g, 1.95 mmol) in ethanol (10mL) was hydrogenated for 16 hours at room temperature at 60 psi in the presence of $Pd(OH)_2/C$ (150mg, 15% w/w). 2N Hydrochloric acid (few drops) was added and the reaction mixture hydrogenated for 16 hours at 60°C at 60 psi. The reaction mixture was basified with aqueous sodium carbonate and the mixture filtered over Arbocel® and rinsed with ethanol. The filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (98:4:0.4 to 90:10:1 by volume) to provide the title compound (210mg, 31%).

HRMS ESI$^+$ m/z 347.2323 $[MH]^+$.

Examples 219-221:

The compounds of the following tabulated examples of the general formula



were prepared using 4-([4-[4-(azetidin-3-ylmethoxy)phenyl]tetrahydro-2*H*-pyran-4-yl]methyl)-morpholine, the appropriate ketones and sodium triacetoxyborohydride similarly to the procedure used for example 54.

Ex No	R^9	Analytical Data
219	cyclopentyl	4-[(4-[4-[(1-cyclopentylazetidin-3-yl)methoxy]phenyl]tetrahydro-2H-pyran-4-yl)methyl]morpholine ^{1}H NMR (400MHz, $CDCl_3$) δ 1.32-1.37 (m, 2H), 1.49-1.53 (m, 2H), 1.58-1.69 (m, 4H), 1.83-1.89 (m, 2H), 2.08-2.15 (m, 6H), 2.38 (s, 2H), 2.74 (m, 1H), 2.91 (m, 1H), 3.03 (t, 2H), 3.45 (t, 2H), 3.49-3.54 (m, 6H), 3.72-3.76 (m, 2H), 4.04 (d, 2H), 6.84 (d, 2H), 7.22 (d, 2H). HRMS ESI$^+$ m/z 415.2946 $[MH]^+$. 92% yield
220	isopropyl	4-[(4-[4-[(1-isopropylazetidin-3-yl)methoxy]phenyl]tetrahydro-2H-pyran-4-yl)methyl]morpholine ^{1}H NMR (400MHz, $CDCl_3$) δ 0.92 (d, 6H), 1.83-1.90 (m, 2H), 2.09-2.14 (m, 6H), 2.31 (m, 1H), 2.38 (s, 2H), 2.85 (m, 1H), 3.03 (t, 2H), 3.41 (t, 2H), 3.49-3.54 (m, 6H), 3.72-3.76 (m, 2H), 4.06 (d, 2H), 6.85 (d, 2H), 7.22 (d, 2H). HRMS ESI$^+$ m/z 389.2791 $[MH]^+$. 61% yield
221	cyclobutyl	4-[(4-[4-[(1-cyclobutylazetidin-3-yl)methoxy]phenyl]tetrahydro-2H-pyran-4-yl)methyl]morpholine ^{1}H NMR (400MHz, $CDCl_3$) δ 1.62-1.75 (m, 2H), 1.82-1.90 (m, 4H), 1.93-

172
173

		1.99 (m, 2H), 2.09-2.15 (m, 6H), 2.38 (s, 2H), 2.86 (m, 1H), 3.07 (t, 2H), 3.14 (m, 1H), 3.40 (t, 2H), 3.49-3.55 (m, 6H), 3.72-3.77 (m, 2H), 4.07 (d, 2H), 6.85 (d, 2H), 7.22 (d, 2H). HRMS ESI$^+$ m/z 401.2791 [MH]$^+$. 50% yield

Intermediate 78: 4-[4-(methylthio)phenyl]tetrahydro-2*H*-pyran-4-carbonitrile

The title compound (5.5g, 77%, solid after trituration in pentane) was prepared using 4-(methylthio)phenylacetonitrile, bis(2-bromoethyl)ether, sodium hydride and potassium iodide similarly to the procedure used for intermediate 56.

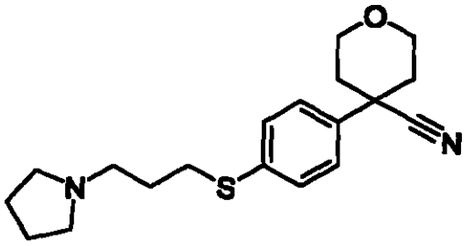
Microanalysis: Found: C, 66.62; H, 6.46; N, 5.97%. $C_{13}H_{15}NOS$ requires C, 66.92; H, 6.48; N, 6.00%.

Intermediate 79: 4-[4-(methylsulfinyl)phenyl]tetrahydro-2*H*-pyran-4-carbonitrile

A solution of *meta*-chloroperbenzoic acid (5.08g, 22.66mmol) in dichloromethane (30ml) was added dropwise over 15 minutes at 0°C to a solution of 4-[4-(methylthio)phenyl]tetrahydro-2*H*-pyran-4-carbonitrile (4.8g, 20.6mmol) in dichloromethane (40ml). The reaction mixture was warmed to room temperature over 4 hours. The mixture was then diluted with dichloromethane (180ml), washed with sodium sulphite solution and 10% aqueous sodium carbonate. The organic layer was separated, dried over sodium sulphate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (100:0:0 to 95:5:0.5 by volume) to provide the title compound (4.55g, 89%) as an off-white solid.

LRMS APCI$^+$ m/z 250 [MH]$^+$.

Example 222: 4-[4-[(3-pyrrolidin-1-ylpropyl)thio]phenyl]tetrahydro-2*H*-pyran-4-carbonitrile



2,6-Lutidine (3.33ml, 28.6mmol) was added to a solution of 4-[4-(methylsulfinyl)phenyl]tetrahydro-2*H*-pyran-4-carbonitrile (2.3g, 9.23mmol) in acetonitrile (70ml). The mixture was cooled in an ice-acetone bath and trifluoroacetic anhydride (3.87ml, 27.69mmol) added slowly. The solution was stirred at this temperature under nitrogen for 3 hours. The reaction mixture was then concentrated *in vacuo* and the residue taken up in methanol (7ml). Triethylamine (7ml) was added at 0°C and the mixture stirred at 0°C for 30 minutes. *N,N*-Dimethylformamide (10ml) was added at 0°C, followed by potassium carbonate (2.8g, 20.31mmol) and 1-(3-chloro-propyl)-pyrrolidine (2.72g, 18.46mmol) in *N,N*-dimethylformamide (10ml). The mixture was then warmed to room temperature and stirred for 18 hours. The reaction mixture was concentrated *in vacuo*. The residue was taken up in water (50ml) and extracted with ethyl acetate (2x150ml). The organic layers were combined, dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with

dichloromethane:methanol:ammonia (97:3:0.3 to 95:5:0.5 by volume) to provide the title compound (2.62g, 86%) as a solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 1.77-1.80 (m, 4H), 1.84-1.91 (m, 2H), 2.01-2.14 (m, 4H), 2.48-2.52 (m, 4H), 2.58 (t, 2H), 2.99 (t, 2H), 3.89 (t, 2H), 4.06-4.10 (m, 2H), 7.34-7.39 (m, 4H).

LRMS APCI$^+$ m/z 331 $[MH]^+$.

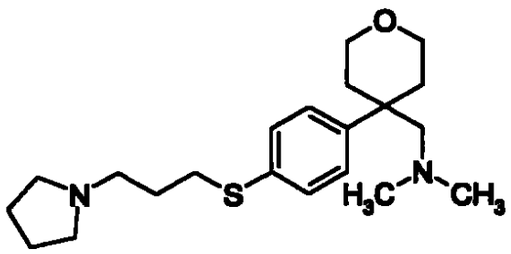
Intermediate 80: 1-(4-[4-[(3-pyrrolidin-1-ylpropyl)thio]phenyl}tetrahydro-2*H*-pyran-4-yl)methanamine

The title compound (2.42g, 91%) was prepared using 4-{4-[(3-pyrrolidin-1-ylpropyl)thio]phenyl}tetrahydro-2*H*-pyran-4-carbonitrile and lithium aluminium hydride similarly to the procedure used for intermediate 51.

LRMS APCI$^+$ m/z 335 $[MH]^+$.

Microanalysis: Found: C, 64.08; H, 8.79; N, 7.447%. $C_{19}H_{30}N_2OS.0.33DCM$ requires C, 64.04; H, 8.52; N, 7.73%.

Example 223: *N,N*-dimethyl-1-(4-[4-[(3-pyrrolidin-1-ylpropyl)thio]phenyl}tetrahydro-2*H*-pyran-4-yl)methanamine

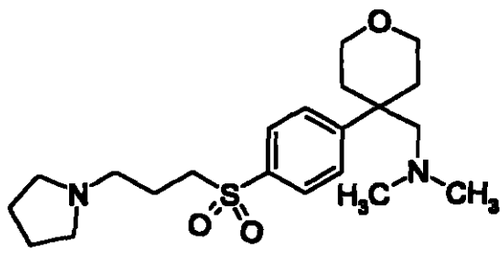


Formaldehyde (37%w/w solution in water, 650µl, 7.58mmol) was added to a solution of 1-(4-[4-[(3-pyrrolidin-1-ylpropyl)thio]phenyl}tetrahydro-2*H*-pyran-4-yl)methanamine (1.0g, 3.03mmol) in tetrahydrofuran (10ml). Acetic acid (173µl, 3.03mmol) was then added and the mixture stirred at room temperature for 10 minutes. The mixture was cooled to 0°C and sodium triacetoxyborohydride (1.6g, 7.57mmol) was added in 2 portions. The mixture was then warmed to room temperature and stirred for 18 hours. The reaction was quenched with water and concentrated *in vacuo*. The residue was taken up in sodium bicarbonate until the aqueous layer pH reached 8. The aqueous layer was then extracted with dichloromethane (2x100ml). The organic extracts were combined, dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (97:3:0.3 to 90:10:1 by volume) to provide the title compound (139mg, 13%) as an oil which crystallised on standing.

^{1}H NMR (400MHz, CD_3OD) δ 1.77-1.91 (m, 8H), 1.95 (s, 6H), 2.13-2.18 (m, 2H), 2.49 (s, 2H), 2.51-2.54 (m, 4H), 2.60 (t, 2H), 2.96 (t, 2H), 3.50 (t, 2H), 3.73-3.78 (m, 2H), 7.31-7.36 (m, 4H).

HRMS ESI$^+$ m/z 363.2462 $[MH]^+$.

Example 224: *N,N*-dimethyl-1-(4-[4-[(3-pyrrolidin-1-ylpropyl)sulphonyl]phenyl}tetrahydro-2*H*-pyran-4-yl)methanamine



N,N-Dimethyl-1-(4-[4-[(3-pyrrolidin-1-ylpropyl)thio]phenyl}tetrahydro-2*H*-pyran-4-yl)methanamine (70mg, 0.19mmol) was dissolved in acetone (2ml) and water (0.5ml). The mixture was cooled to 0°C and a solution of Oxone® (131mg, 0.21mmol) in water (0.5ml) added dropwise. The reaction mixture was stirred at room temperature for 18 hours. The mixture was then diluted with more water, basified with 10% aqueous sodium carbonate and extracted with dichloromethane (2x20ml). The organic layers were combined, dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (96:4:0.4 by volume) to provide the title compound (23mg, 30%) as an oil.

^{1}H NMR (400MHz, $CDCl_3$) δ 1.72-1.75 (m, 4H), 1.90-1.99 (m, 10H), 2.10-2.14 (m, 2H), 2.40-2.44 (m, 4H), 2.48-2.52 (m, 4H), 3.20 (t, 2H), 3.52 (t, 2H), 3.75-3.80 (m, 2H), 7.52 (d, 2H), 7.86 (d, 2H).
HRMS ESI$^+$ m/z 395.2363 $[MH]^+$.

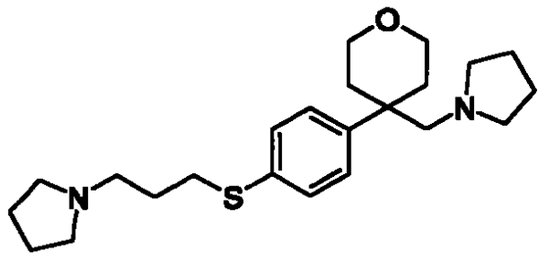
Intermediate 81: 4-[4-[(3-pyrrolidin-1-ylpropyl)thio]phenyl}tetrahydro-2*H*-pyran-4-carboxylic acid

4-[4-[(3-Pyrrolidin-1-ylpropyl)thio]phenyl}tetrahydro-2*H*-pyran-4-carbonitrile (1g, 3.03mmol) was heated at reflux in concentrated hydrochloric acid (10ml) for 18 hours. More hydrochloric acid (11ml) was added and the mixture heated at reflux for a further 18 hours. The reaction mixture was then concentrated *in vacuo* to a solid. This was taken up in dichloromethane and triethylamine (4ml) added. The reaction mixture was then concentrated *in vacuo*. This was repeated twice to provide the title compound (2.03g) as a solid containing triethylamine hydrochloride.
LRMS APCI$^+$ m/z 350 $[MH]^+$.

Intermediate 82: 1-[3-({4-[4-(pyrrolidin-1-ylcarbonyl)tetrahydro-2*H*-pyran-4-yl]phenyl}thio)propyl]pyrrolidine

The title compound (228mg, 40%) was prepared using 4-{4-[(3-pyrrolidin-1-ylpropyl)thio]phenyl}tetrahydro-2*H*-pyran-4-carboxylic acid and pyrrolidine similarly to the procedure used for example 149.
HRMS ESI$^+$ m/z 403.2403 $[MH]^+$.

Example 225: 1-[3-({4-[4-(pyrrolidin-1-ylmethyl)tetrahydro-2*H*-pyran-4-yl]phenyl}thio)propyl]pyrrolidine



The title compound (58mg, 27%) was prepared using 1-[3-({4-[4-(pyrrolidin-1-ylcarbonyl)tetrahydro-2*H*-pyran-4-yl]phenyl}thio)propyl]pyrrolidine and lithium aluminium hydride similarly to the procedure used for example 142.

^{1}H NMR (400MHz, $CDCl_3$) δ 1.54-1.57 (m, 4H), 1.75-1.79 (m, 4H), 1.84-1.94 (m, 4H), 2.08-2.10 (m, 2H), 2.18-2.22 (m, 4H), 2.47-2.50 (m, 4H), 2.57 (t, 2H), 2.63 (s, 2H), 2.98 (t, 2H), 3.54 (t, 2H), 3.73-3.78 (m, 2H), 7.22 (d, 2H), 7.29 (d, 2H).

HRMS ESI$^+$ m/z 389.2615 $[MH]^+$.

Intermediate 83: 1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexanecarboxylic acid

The title compound (contaminated with ammonium chloride) was prepared using 1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexanecarbonitrile and concentrated hydrochloric acid similarly to the procedure used for intermediate 60.

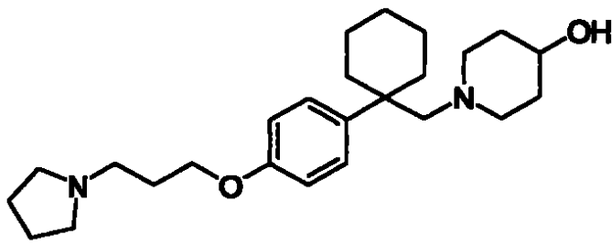
LRMS ESI$^+$ m/z 332 $[MH]^+$.

Intermediate 84: 1-({1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl}carbonyl)piperidin-4-ol

The title compound (200mg, 16%) was prepared using 1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexanecarboxylic acid and 4-hydroxypiperidine similarly to the procedure used for example 149.

HRMS ESI$^+$ m/z 415.2943 $[MH]^+$.

Example 226: 1-({1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl}methyl)piperidin-4-ol

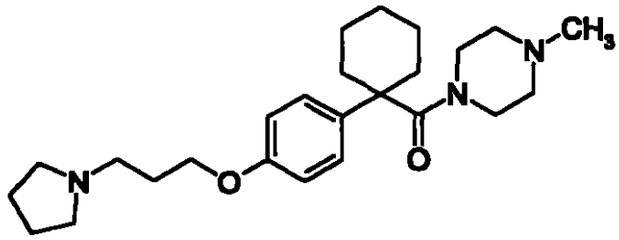


The title compound (90mg, 46%) was prepared using 1-({1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl}carbonyl)piperidin-4-ol and lithium aluminium hydride similarly to the procedure used for example 142.

^{1}H NMR (400MHz, $CDCl_3$) δ 1.29-1.55 (m, 10H), 1.64-1.69 (m, 2H), 1.77-1.81 (m, 4H), 1.90-2.06 (m, 4H), 2.10-2.13 (m, 2H), 2.23 (s, 2H), 2.26-2.30 (m, 2H), 2.51-2.54 (m, 4H), 2.62 (t, 2H), 3.51 (m, 1H), 4.01 (t, 2H), 6.83 (d, 2H), 7.25 (d, 2H).

HRMS ESI$^+$ m/z 401.3154 $[MH]^+$.

Example 227: 1-methyl-4-({1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl}carbonyl)piperazine



The title compound (10mg, 8%) was prepared using 1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexanecarboxylic acid and 1-methylpiperazine similarly to the procedure used for example 149.

^{1}H NMR (400MHz, CD_3OD) δ 1.32 (*m*, 1H), 1.64-1.69 (*m*, 7H), 1.81-1.85 (m, 4H), 1.98-2.03 (m, 2H), 2.05-2.13 (m, 4H), 2.15 (s, 3H), 2.25-2.28 (m, 2H), 2.59-2.62 (m, 4H), 2.69 (t, 2H), 3.33-3.42 (m, 4H), 4.01 (t, 2H), 6.90 (d, 2H), 7.16 (d, 2H).

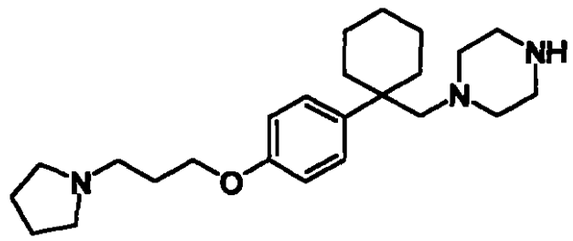
HRMS ESI$^+$ m/z 414.3107 $[MH]^+$.

Intermediate 86: 1-({1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl}carbonyl)piperazine

The title compound (351mg, 19%) was prepared using 1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexanecarboxylic acid and piperazine similarly to the procedure used for example 149.

LRMS APCI$^+$ m/z 400 $[MH]^+$.

Example 228: 1-({1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl}methyl) piperazine

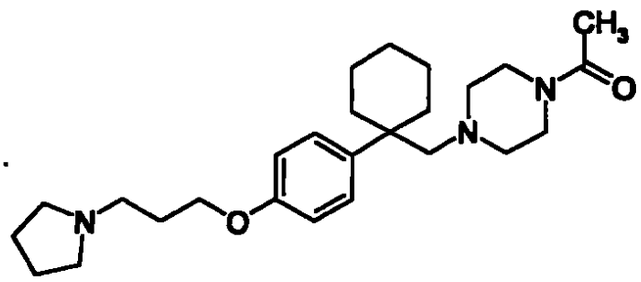


The title compound (167mg, 69%) was prepared using 1-({1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl}carbonyl)piperazine and lithium aluminium hydride similarly to the procedure used for example 142.

^{1}H NMR (400MHz, $CDCl_3$) δ 1.30-1.33 (m, 3H), 1.46-1.54 (m, 4H), 1.78-1.81 (m, 4H), 1.98-2.05 (m, 4H), 2.09-2.12 (m, 6H), 2.23 (s, 2H), 2.53-2.57 (*m*, 4H), 2.62-2.71 (m, 6H), 4.01 (t, 2H), 6.83 (d, 2H), 7.26 (d, 2H).

LRMS APCI$^+$ m/z 386 $[MH]^+$.

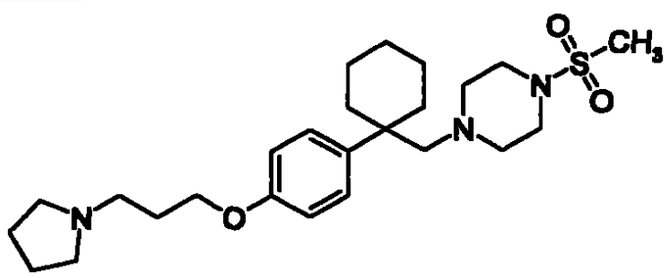
Example 229: 1-acetyl-4-({1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl}methyl)piperazine



The title compound (73mg, 73%) was prepared using 1-({1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl}methyl) piperazine and acetic anhydride similarly to the procedure used for example 166.

^{1}H NMR (400MHz, $CDCl_3$) δ 1.31-1.34 (m, 3H), 1.48-1.53 (m, 5H), 1.82-1.85 (m, 4H), 1.99 (s, 3H), 2.02-2.07 (m, 4H), 2.13-2.17 (m, 4H), 2.28 (s, 2H), 2.58-2.64 (m, 4H), 2.70 (t, 2H), 3.20 (t, 2H), 3.41-3.43 (m, 2H), 4.01 (t, 2H), 6.83 (d, 2H), 7.25 (d, 2H).
HRMS ESI$^+$ m/z 428.3264 $[MH]^+$.

Example 230: 1-(methylsulfonyl)-4-({1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl}methyl)piperazine



Methanesulphonic acid anhydride (49mg, 0.28mmol) was added at 0°C to a solution of 1-({1-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]cyclohexyl}methyl) piperazine (90mg, 0.23mmol) and pyridine (47µl, 0.58mmol) in dichloromethane (1ml). The reaction was stirred at 0 °C for 10 minutes, then allowed to warm up to room temperature and stirred for 18 hours. The reaction mixture was concentrated under reduced pressure and partitioned between dichloromethane (20ml) and aqueous sodium carbonate (20ml). The layers were separated. The organic layer was dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (96:4:0.4 by volume) to provide the title compound (61mg, 56%).
^{1}H NMR (400MHz, $CDCl_3$) δ 1.29-1.36 (m, 3H), 1.45-1.52 (m, 5H), 1.85-1.90 (m, 4H), 2.08-2.15 (m, 4H), 2.22 (t, 4H), 2.32 (s, 2H), 2.67-2.79 (m, 9H), 3.00-3.03 (m, 4H), 4.02 (t, 2H), 6.83 (d, 2H), 7.24 (d, 2H).
HRMS ESI$^+$ m/z 484.2931 $[MH]^+$.

Intermediate 86: tert-butyl bis(2-chloroethyl)carbamate

Bis-(2-chloroethyl)amine hydrochloride (10g, 56mmol) was stirred vigourously in a mixture of dichloromethane (150ml) and aqueous 10% sodium hydroxide (50ml). Di-tert-butyldicarbonate (12.2g, 56mmol) as a solution in dichloromethane (75ml) was then added dropwise. The reaction mixture was stirred at room temperature for 5 hours. TLC showed the reaction was not complete so more di-tert-

178
179

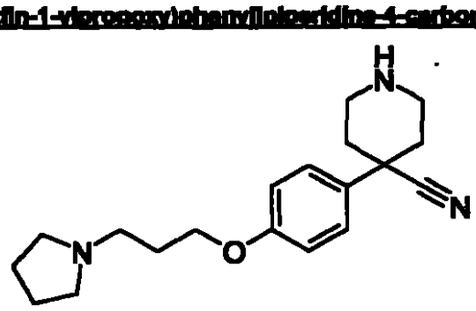
butyldicarbonate (4g, 18.3mmol) was added. The mixture was stirred vigourously for 18 hours at room temperature. The layers were then separated and the aqueous layer extracted with more dichloromethane (2x50ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (99:1 to 80:20 by volume) to provide the title compound (7.9g, 58%).

Intermediate 87: *tert*-butyl 4-cyano-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl] piperidine-1-carboxylate

The title compound (1.8g, 53%) was prepared using [4-(3-pyrrolidin-1-ylpropoxy)phenyl]acetonitrile, *tert*-butyl bis(2-chloroethyl)carbamate, sodium hydride and potassium iodide similarly to the procedure used for intermediate 56.

LRMS APCI$^+$ m/z 414 $[MH]^+$ and m/z 245 $[SMH]^+$.

Example 231: 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]piperidine-4-carbonitrile

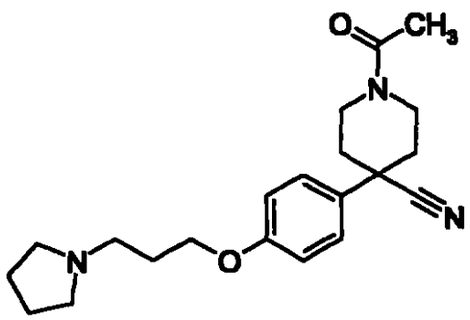


tert-Butyl 4-cyano-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl] piperidine-1-carboxylate (500mg, 1.24mmol) was stirred for 1 hour in trifluoroacetic acid (1.91ml, 24.8mmol) and dichloromethane (30ml). More trifluoroacetic acid (3ml) was added and the reaction stirred at room temperature for another hour. The reaction mixture was quenched with saturated aqueous sodium carbonate solution (15ml) and the layers separated. The organic layer was dried over sodium sulphate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:5:0.5 to 90:10:1 by volume) to provide the title compound (450mg, 18% over 2 steps).

^{1}H NMR (400MHz, CD_3OD) δ 1.81-1.85 (m, 4H), 1.91-2.09 (m, 6H), 2.59-2.62 (m, 4H), 2.69 (t, 2H), 2.99 (t, 2H), 3.12-3.15 (m, 2H), 4.04 (t, 2H), 6.96 (d, 2H), 7.42 (d, 2H).

HRMS ESI$^+$ m/z 314.2227 $[MH]^+$.

Example 232: 1-acetyl-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]piperidine-4-carbonitrile

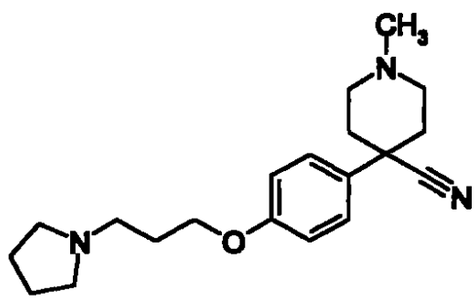


Acetyl chloride (27µl, 0.37mmol) was added dropwise to a solution of 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]piperidine-4-carbonitrile (90mg, 0.28mmol) and triethylamine (78µl, 0.56mmol) in dichloromethane (3ml). The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with dichloromethane (15ml) and washed with water (15ml). The layers were separated and the aqueous layer was further extracted with dichloromethane (2x10ml). The organics were combined, washed with brine, dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with ethyl acetate:methanol:ammonia (95:5:0.5 by volume) to provide the title compound (28mg, 28%).

^{1}H NMR (400MHz, CD_3OD) δ 1.82-1.85 (m, 4H), 1.89-2.18 (m, 9H), 2.60-2.63 (m, 4H), 2.69 (t, 2H), 3.00 (t, 1H), 3.50 (t, 1H), 4.03-4.12 (m, 3H), 4.70 (d, 1H), 6.97 (d, 2H), 7.44 (d, 2H).

HRMS ESI$^+$ m/z 366.2329 $[MH]^+$.

Example 233: 1-methyl-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]piperidine-4-carbonitrile



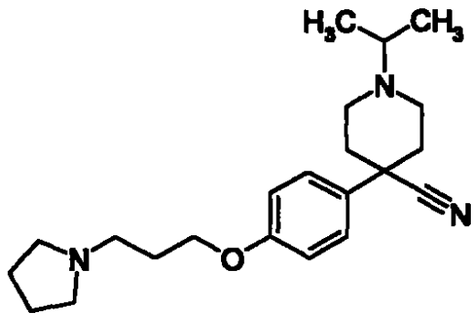
The title compound (80mg, 76%) was prepared from 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]piperidine-4-carbonitrile, formaldehyde and sodium triacetoxyborohydride similarly to the procedure used for example 54.

^{1}H NMR (400MHz, CD_3OD) δ 1.81-1.85 (m, 4H), 1.97-2.15 (m, 6H), 2.37 (s, 3H), 2.45 (t, 2H), 2.58-2.62 (m, 4H), 2.68 (t, 2H), 2.99 (d, 2H), 4.04 (t, 2H), 6.96 (d, 2H), 7.42 (d, 2H).

LRMS APCI$^+$ m/z 328 $[MH]^+$.

Microanalysis: Found: C, 73.01; H, 8.94; N, 12.81%. $C_{20}H_{29}N_3O$ requires C, 73.36; H, 8.93; N, 12.83%.

Example 234: 1-isopropyl-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]piperidine-4-carbonitrile

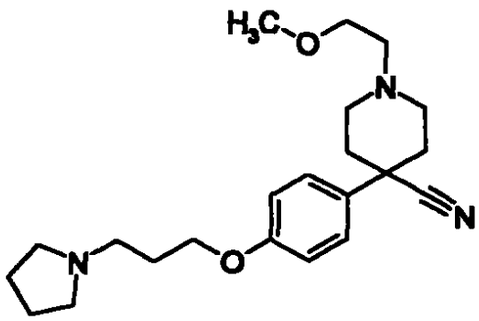


The title compound (45mg, 58%) was prepared from 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]piperidine-4-carbonitrile, acetone and sodium triacetoxyborohydride similarly to the procedure used for example 54.

180

^{1}H NMR (400MHz, CD_3OD) δ 1.12 (d, 6H), 1.81-1.84 (m, 4H), 1.98-2.14 (m, 6H), 2.58-2.69 (m, 8H), 2.82 (m, 1H), 3.02 (d, 2H), 4.04 (t, 2H), 6.96 (d, 2H), 7.42 (d, 2H).
HRMS ESI$^+$ m/z 356.2691 $[MH]^+$.

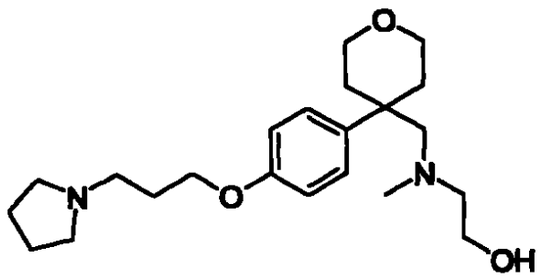
Example 238: 1-(2-methoxyethyl)-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]piperidine-4-carbonitrile



A mixture of 4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]piperidine-4-carbonitrile (68mg, 0.22mmol), 2-bromoethylmethylether (21µl, 0.22mmol), solid sodium bicarbonate (84mg, 1.0mmol) and potassium iodide (5mg, catalytic) was heated at 50°C in acetonitrile (1ml) for 18 hours. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between dichloromethane (2x50ml) and 10% aqueous sodium carbonate (20ml). The organic layers were combined, dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (97:3:0.3 to 95:5:0.5 by volume) to provide the title compound (46mg, 61%).

^{1}H NMR (400MHz, CD_3OD) δ 1.83-1.87 (m, 4H), 2.01-2.10 (m, 6H), 2.45-2.52 (m, 2H), 2.65-2.69 (m, 6H), 2.75 (t, 2H), 3.09 (d, 2H), 3.35 (s, 3H), 3.56 (t, 2H), 4.04 (t, 2H), 6.86 (d, 2H), 7.42 (d, 2H).
HRMS ESI$^+$ m/z 372.2639 $[MH]^+$.

Example 239: 2-[methyl([4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl]methyl)amino]ethanol



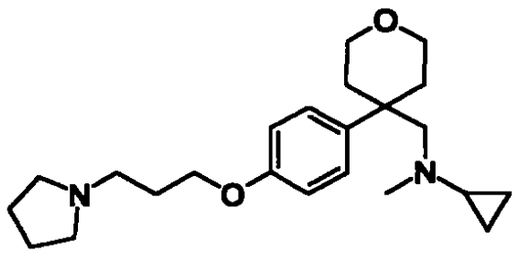
A solution of methyl-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]-tetrahydropyran-4-ylmethyl]amine (350 mg, 1.05 mmol), glycolaldehyde dimer (130 mg, 1.05 mmol) and AcOH (0.15 ml, 2.1 mmol) in DCM (5 ml) was stirred at room temperature for 18 hours. Saturated aqueous sodium carbonate (10 ml) and DCM (10 ml) were added and the mixture was shaken and partitioned. The aqueous phase was extracted with DCM (2x10 ml) and the combined organics dried (K_2CO_3), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with

dichloromethane:methanol:ammonia (92:8:1) to provide the title compound as a clear colourless oil (223 mg, 0.59 mmol, 56%).

^{1}H NMR (400MHz, $CDCl_3$) δ 1.70-1.90 (m, 6H), 1.96 (s, 3H), 2.00 (quintet, 2H), 2.14 (m, 2H), 2.37 (t, 2H), 2.40-2.60 (m, 6H), 2.65 (t, 2H), 3.35 (t, 2H), 3.50 (m, 2H), 3.76 (m, 2H), 4.01 (t, 2H), 6.89 (d, 2H), 7.19 (d, 2H).

HRMS ESI$^+$ m/z 377.2796 $[MH]^+$.

Example 237: N-methyl-N-{(4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl)methyl}cyclopropanamine

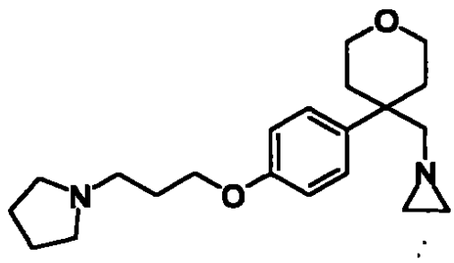


A mixture of methyl-{4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]-tetrahydropyran-4-ylmethyl}amine (115 mg, 0.35 mmol), (1-Ethoxy-cyclopropoxy)-trimethylsilane (360 mg, 2.0 mmol), AcOH (0.2 ml, 3.5 mmol), $NaCNBH_3$ (110 mg, 1.75 mmol) and 4Å molecular sieves (100 mg) in MeOH (5 ml) was heated to reflux for 18 hours. The mixture was cooled, concentrated *in vacuo* and partitioned between 2M NaOH (10 ml) and DCM (10 ml). The organic phase was separated and the aqueous phase extracted with DCM (2x10 ml). The combined organic phases were concentrated *in vacuo* and purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (92:8:1) to provide the title compound as a clear colourless oil (20 mg, 0.054 mmol, 15%).

^{1}H NMR (400MHz, $CDCl_3$) δ 0.15 (m, 2H), 0.29 (m, 2H), 1.68 (m, 1H), 1.70-1.90 (m, 6H), 1.85 (s, 3H), 2.00-2.10 (m, 4H), 2.60 (m, 4H), 2.65 (s, 2H), 2.68 (m, 2H), 3.50 (t, 2H), 3.76 (m, 2H), 4.01 (t, 2H), 6.85 (d, 2H), 7.16 (d, 2H).

HRMS ESI$^+$ m/z 373.2844 $[MH]^+$.

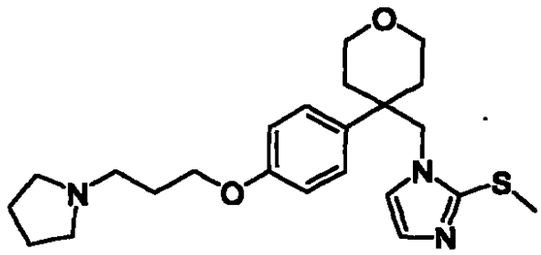
Example 238: 1-(3-{4-[4-(aziridin-1-ylmethyl)tetrahydro-2H-pyran-4-yl]phenoxy}propyl)pyrrolidine



A mixture of {4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (482 mg, 1.50 mmol), 1,2-dibromoethane (0.13 ml, 1.50 mmol) and K_2CO_3 (420 mg, 3.0 mmol) in acetonitrile (50 ml) was heated to 70°C for 3 days. The mixture was concentrated *in vacuo* and purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (93:7:1 to 91:9:1) to provide the title compound as a clear colourless oil (51 mg, 0.15 mmol, 10%).

^{1}H NMR (400MHz, $CDCl_3$) δ 0.71 (m, 2H), 1.48 (m, 2H), 1.78 (m, 4H), 2.00 (m, 4H), 2.19 (m, 2H), 2.30 (s, 2H), 2.54 (m, 4H), 2.63 (t, 2H), 3.64 (m, 2H), 3.78 (m, 2H), 4.01 (t, 2H), 6.86 (d, 2H), 7.21 (d, 2H).
HRMS ESI$^+$ m/z 345.2534 $[MH]^+$.

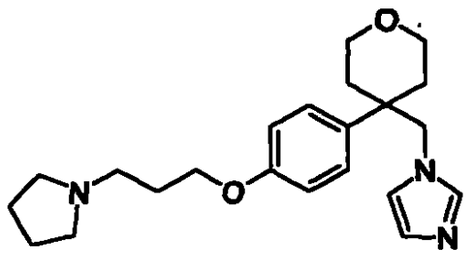
Example 238: 2-(methylthio)-1-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)-1H-imidazole



A solution of {4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (159 mg, 0.50 mmol) and dimethyl 2,2-diethoxyethyldithioimido-carbonate (120 mg, 0.50 mmol, ARKIVOC 2001, viii, 34-39) in AcOH (5 ml) was heated at reflux for 8 h. The mixture was concentrated *in vacuo* and partitioned between saturated aqueous sodium bicarbonate (10 ml) and DCM (10 ml). The aqueous phase was extracted with DCM (2x10 ml) and the combined organics dried (K_2CO_3), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (90:10:1) to provide the title compound as a clear colourless gum (90 mg, 0.22 mmol, 43%).

^{1}H NMR (400MHz, $CDCl_3$) δ 1.80-2.00 (m, 6H), 2.12 (m, 2H), 2.21 (quintet, 2H), 2.48 (s, 3H), 2.80-3.00 (m, 6H), 3.45 (m, 2H), 3.83 (m, 2H), 3.98 (s, 2H), 4.06 (t, 2H), 6.10 (s, 1H), 6.85 (d, 2H), 6.87 (s, 1H), 7.01 (d, 2H).
LRMS APCI$^+$ m/z 416 $[MH]^+$.

Example 239: 1-{4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl}-1H-imidazole



To a solution of 2-(methylthio)-1-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)-1H-imidazole (80 mg, 0.22 mmol) in EtOH (4 ml) and water (1ml) was added Raney Nickel (50% slurry in water) in 200 mg aliquots every 30 min. After 3 h all starting material had been consumed. The mixture was filtered through Arbocel® with EtOH (200 ml) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (90:10:1) to provide the title compound as a yellow oil (29 mg, 0.078 mmol, 36%).

183 of

^{1}H NMR (400MHz, $CDCl_3$) δ 1.80-2.00 (m, 6H), 2.10 (m, 4H), 2.70-2.90 (m, 6H), 3.50 (t, 2H), 3.81 (m, 2H), 3.97 (s, 2H), 4.04 (t, 2H), 6.32 (s, 1H), 6.80-6.90 (m, 4H), 6.98 (d, 2H).
HRMS ESI$^+$ m/z 370.2485 $[MH]^+$.

Intermediate 89: 4-[4-[[tert-butyl(dimethyl)silyl]oxy]phenyl]tetrahydro-2H-pyran-4-carbonitrile
A solution of 4-(4-hydroxy-phenyl)-tetrahydro-pyran-4-carbonitrile (5g, 25mmol), t-butyldimethylsilyl chloride (4.46g, 29mmol) and imidazole (2.34g, 34mmol) were stirred in DMF (15ml) at room temperature. After 30 minutes, a yellow suspension was observed. The reaction was partitioned between ether (75ml) and water (100ml). The ether was then washed further with water (4x50ml), dried over sodium sulphate, filtered and concentrated *in vacuo*. The title compound was isolated as a pale orange waxy solid (7g, 90%).

Intermediate 90: 1-[4-(4-[[tert-butyl(dimethyl)silyl]oxy]phenyl]tetrahydro-2H-pyran-4-yl]methanamine
To a stirred solution of 4-(4-[[tert-butyl(dimethyl)silyl]oxy]phenyl)tetrahydro-2H-pyran-4-carbonitrile (3.5g, 11mmol) in THF (35ml) at 0°C was added dropwise lithium aluminium hydride (1M solution in ether, 44ml, 44mmol). The reaction was allowed to warm up to room temperature and stirred for 4 hours until complete. The reaction mixture was cooled to 0°C, water (1.66 mL) was added followed by NaOH (2.0M, 1.66 mL) and water (4.97 mL). The mixture was filtered through a short pad of celite, eluting with dichloromethane:methanol (97:3, 150ml) and concentrated *in vacuo*. Solid obtained was partitioned between ethyl acetate (50ml) and sodium bicarbonate (50ml). The organic layer was then dried over sodium sulphate, filtered and concentrated *in vacuo* to give the title compound (2.04g, 58%).

LRMS APCI$^+$ m/z 322 $[MH]^+$.

Intermediate 90: N-[[4-(4-[[tert-butyl(dimethyl)silyl]oxy]phenyl]tetrahydro-2H-pyran-4-yl]methyl]pyridin-2-amine
1-[4-(4-[[tert-butyl(dimethyl)silyl]oxy]phenyl)tetrahydro-2H-pyran-4-yl]methanamine (3.65g, 11.4mmol), 2-bromopyridine (910µl, 9.48mmol), tris(dibenzylideneacetone)dipalladium(0) (471mg, 0.455mmol), 2,2'-bis(diphenylphosphino)1,1'-binaphyl (567mg, 0.910mmol) and sodium *tert*-butoxide (1.29g, 13.0mmol) were stirred in toluene (50ml) at 70°C under nitrogen for 24 hours. The toluene was removed *in vacuo* and the residue partitioned between dichloromethane (50ml) and saturated sodium bicarbonate solution (50ml). The organic layer was separated and dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with ether:pentane (80:20 by volume) to provide the title compound (2.10g, 46%) as a yellow solid.
LRMS APCI$^+$ m/z 399 $[MH]^+$.

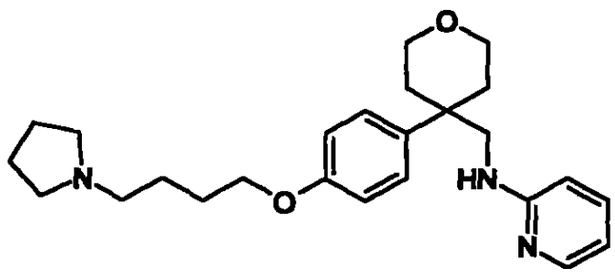
Intermediate 91: 4-[4-[(pyridin-2-ylamino)methyl]tetrahydro-2H-pyran-4-yl]phenol
N-[[4-(4-[[tert-butyl(dimethyl)silyl]oxy]phenyl)tetrahydro-2H-pyran-4-yl]methyl]pyridin-2-amine (2.099g, 5.27mmol) and tetrabutylammonium fluoride (1M solution in THF, 5.80ml, 5.80mmol) were stirred in THF (20ml) at room temperature for 24 hours until complete. THF was removed *in vacuo* and the residue

partitioned between dichloromethane (75ml) and sodium bicarbonate (50ml). The organic layer was washed further with sodium bicarbonate (2x50ml), then separated and dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on Biotage® silica gel eluting with dichloromethane:methanol:ammonia (100:0:0 to 90:10:1 by volume) to give the title compound (662mg, 58%) as a solid.
LRMS APCI$^+$ m/z 285 $[MH]^+$.

Intermediate 92: N-({4-[4-(4-chlorobutoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)pyridin-2-amine

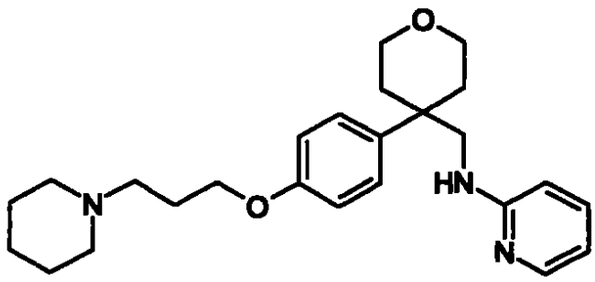
4-{4-[(pyridin-2-ylamino)methyl]tetrahydro-2H-pyran-4-yl}phenol (220mg, 0.775mmol), 1-bromo-4-chlorobutane (146mg, 0.852mmol) and potassium carbonate (118mg, 0.852mmol) were stirred in DMF (1ml) at 60°C for 24 hours until complete. Reaction was partitioned between ethyl acetate (50ml) and water (75ml). The organic layer was separated and washed further with water (2x30ml), then dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude compound was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (100:0:0 to 98:2:0.2 by volume) to give the title compound (184mg, 63%) as a yellow solid.
LRMS APCI$^+$ m/z 375 $[MH]^+$.

Example 241: N-({4-[4-(4-pyrrolidin-1-ylbutoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)pyridin-2-amine



A mixture of N-({4-[4-(4-chlorobutoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)pyridin-2-amine (180mg, 0.481mmol), pyrrolidine (80µl, 0.963mmol), sodium carbonate (102mg, 0.963mmol) and sodium iodide (4mg, 0.024mmol) were stirred in butanol (5ml) at 100°C for 24 hours until complete. Butanol was removed *in vacuo* and the residue partitioned between ethyl acetate (40ml) and water (40ml). Organic layer was dried over sodium sulphate, filtered and concentrated *in vacuo* to give a brown solid. Solid was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (98:2:02 to 96:4:0.4 by volume), followed by recrystallisation from ether (1.5ml) to give the title compound (56.6mg, 29%).
^{1}H NMR (400MHz, $CDCl_3$) δ 1.78-2.00 (m, 12H), 2.08-2.20 (m, 2H), 2.54-2.90 (m, 4H), 3.50 (d, 2H), 2.54-2.63 (m, 2H), 3.79-3.88 (m, 2H), 3.96-4.08 (m, 2H), 6.23 (d, 1H), 6.50 (t, 1H), 6.90 (d, 2H), 7.25 (d, 2H), 7.32 (t, 1H), 8.01 (d, 1H).
LRMS APCI$^+$ m/z 410 $[MH]^+$.

Example 242: N-({4-[4-(3-piperidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)pyridin-2-amine

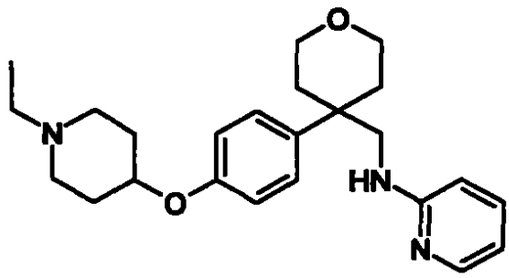


4-{4-[(pyridin-2-ylamino)methyl]tetrahydro-2H-pyran-4-yl}phenol (200mg, 0.704mmol), 3-chloropropylpiperidine hydrochloride (152mg, 0.775mmol) and potassium carbonate (204mg, 1.48mmol) were stirred in DMF (1ml) at 45°C for 24 hours until complete. The reaction was then partitioned between ethyl acetate (40ml) and water (40ml). The organic layer was separated, dried over sodium sulphate and concentrated *in vacuo* to give a solid. The solid was purified by preparative HPLC to give the title compound (220mg, 76%) as a white solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 1.44-1.55 (m, 2H), 1.64-1.78 (m, 4H), 1.85-2.00 (m, 2H), 2.08-2.18 (m, 4H), 2.52-2.70 (m, 6H), 3.48 (d, 2H), 3.62-3.82 (m, 2H), 3.76-3.85 (m, 2H), 4.02 (t, 2H), 6.21 (d, 1H), 6.60 (t, 1H), 6.90 (d, 2H), 7.24 (d, 2H), 7.34 (t, 1H), 8.01 (d, 1H).

LRMS APCI$^+$ m/z 410 $[MH]^+$.

Example 243: N-[(4-{4-[(1-ethylpiperidin-4-yl)oxy]phenyl}tetrahydro-2H-pyran-4-yl)methyl]pyridin-2-amine



To a solution of 4-{4-[(pyridin-2-ylamino)methyl]tetrahydro-2H-pyran-4-yl}phenol (250mg, 0.881mmol), 1-ethylpiperidin-4-ol (103mg, 0.8mmol) and triphenylphosphine (231mg, 0.881mmol) in THF (5ml) at 0°C under nitrogen was added dropwise diisopropyl azodicarboxylate (95% solution, 183µl, 0.881mmol). Reaction was stirred for 10 minutes then warmed to room temperature for 72 hours until complete. THF was removed *in vacuo* and the residue partitioned between ethyl acetate (50ml) and saturated sodium bicarbonate solution (50ml). The organic layer was separated, dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude product was purified by flash chromatography eluting with

dichloromethane:methanol:ammonia (100:0:0 to 96:4:0.4 by volume) to give the title compound (8.2mg, 23%) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) δ 1.05 (t, 3H), 1.80-1.96 (m, 4H), 2.00-2.18 (m, 4H), 2.28-2.42 (m, 2H), 2.44-2.54 (q, 2H), 2.72-2.86 (m, 2H), 3.50 (d, 2H), 3.55-3.62 (m, 2H), 3.78-3.86 (m, 2H), 4.00-4.08 (m, 1H), 4.30-4.39 (m, 1H), 6.22 (d, 1H), 6.50 (t, 1H), 6.90 (d, 2H), 7.23 (d, 2H), 7.30 (t, 1H), 8.01 (d, 1H).

LRMS APCI$^+$ m/z 396 $[MH]^+$.

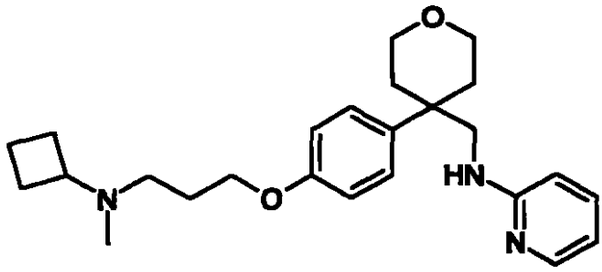
HRMS ESI$^+$ m/z 396.2841$[MH]^+$.

Intermediate 93: N-(3-chloropropyl)-N-methylcyclobutanamine

To a solution of N-methylcyclobutanamine (1g, 3.89mmol) and potassium carbonate (1.18g, 8.56mmol) in acetonitrile (20ml) at 0°C was added 1-bromo-3-chloropropane (383µl, 3.89mmol). Reaction was warmed to room temperature and stirred for 24 hours. Solid removed by filtration and filtrate concentrated *in vacuo* to give the title compound (241mg, 38%) as an oil. No purification was performed.

LRMS APCI$^+$ m/z 162 $[MH]^+$.

Example 344: N-[[4-[4-[3-[cyclobutyl(methyl)amino]propoxy]phenyl]tetrahydro-2H-pyran-4-yl]methyl]pyridin-2-amine



4-[4-[(pyridin-2-ylamino)methyl]tetrahydro-2H-pyran-4-yl]phenol (386mg, 1.36mmol), N-(3-chloropropyl)-N-methylcyclobutanamine (241mg, 1.496mmol) and potassium carbonate (280mg, 2.03mmol) were stirred in DMF (2ml) at 45°C for 24 hours until complete. Reaction was partitioned between ethyl acetate (40ml) and saturated sodium bicarbonate solution (50ml), then the organic layer washed with water (50ml). Organic layer separated and dried over sodium sulphate, filtered and concentrated *in vacuo*. Crude product purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (100:0:0 to 90:10:1 by volume) to give the title compound (165mg, 30%).

^{1}H NMR (400MHz, $CDCl_3$) δ 1.55-1.72 (m, 2H), 1.80-1.99 (m, 6H), 2.00-2.09 (m, 2H), 2.10-2.20 (m, 4H), 2.40 (t, 2H), 2.80 (quintet, 1H), 3.50 (d, 2H), 3.54-3.62 (m, 2H), 3.78-3.86 (m, 2H), 4.00 (m, 3H), 6.20 (d, 1H), 6.50 (t, 1H), 6.92 (d, 2H), 7.22 (d, 2H), 7.32 (t, 1H), 8.00 (d, 1H).

LRMS APCI$^+$ m/z 410 $[MH]^+$.

HRMS ESI$^+$ m/z 410.2794$[MH]^+$.

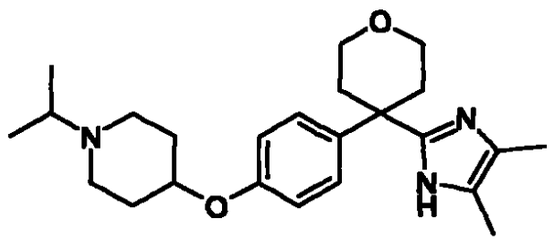
Intermediate 94: 4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl]tetrahydro-2H-pyran-4-carbaldehyde

To a cooled solution of 4-[4-[(1-isopropylpiperidin-4-yl)oxy]phenyl]tetrahydro-2H-pyran-4-carbonitrile (1.16g, 3.53mmol) in dichloromethane (12ml) at -78°C under nitrogen, was added dropwise

187
188

diisobutylaluminium hydride (1M solution in dichloromethane, 12.38ml, 12mmol) keeping the temperature below -60°C. Reaction stirred at -78°C for 40 minutes, then at -20°C for 1 hour before allowing to warm to room temperature. After 1 hour, reaction cooled and quenched with 2M HCl (13.2ml) and basified with sodium carbonate to pH 8, and filtered though a short pad of celite eluting with dichloromethane:methanol (99:1 by volume). Reaction then partitioned between dichloromethane (50ml) and water (50ml), and organic layer washed with a further portion of water (50ml) before being separated, dried over sodium sulphate, filtered and concentrated *in vacuo*. Purified by flash chromatography eluting with dichloromethane:methanol (99:1 to 92:8 by volume) to give the title compound (318mg, 27%).
LRMS APCI$^+$ m/z 332 $[MH]^+$.

Example 245: 4-{4-[4-(4,5-dimethyl-1H-imidazol-2-yl)tetrahydro-2H-pyran-4-yl]phenoxy}-1-isopropylpiperidine



4-{4-[(1-Isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2H-pyran-4-carbaldehyde (50mg, 0.151mmol), ammonium acetate (116mg, 1.51mmol) and 2,3-butanedione (13mg, 0.151mmol) in acetic acid (1ml) heated in a Smith Personal Synthesiser microwave for 900 seconds at 180°C. Acetic acid removed *in vacuo* and residue partitioned between ethyl acetate (20ml) and saturated sodium bicarbonate solution (20ml). Organic layer was seperated, dried over sodium sulphate and concentrated *in vacuo*. Purified by flash chromatography eluting with dichloromethane:methanol:ammonia (100:0:0 to 95:5:0.5 by volume) to give the title compound (25.6mg, 43%) as a brown oil.
^{1}H NMR (400MHz, $CDCl_3$) δ1.08 (d, 6H), 1.76-1.88 (m, 2H), 1.98-2.07 (m, 2H), 2.10 (s, 6H), 2.19-2.28 (m, 2H), 2.39-2.50 (m, 4H), 2.72-2.87 (m, 3H), 3.67-3.84 (m, 4H), 4.20-4.34 (m, 1H), 6.83 (d, 2H), 7.14 (d, 2H).
LRMS APCI$^+$ m/z 398 $[MH]^+$.

Intermediate 95: (3-Nitro-pyridin-4-yl)-{4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl}-amine

To a stirred solution of {4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (390mg, 1.2mmol) in acetonitrile (~5mL), was added Hunig's base (230µL, 1.35mmol, 1.1eq.) and 4-ethoxy-3-nitropyridine hydrogen chloride (250mg, 1.2mmol, 1eq.) and the mixture stirred at reflux for 72 hours. To this a further portion of 4-ethoxy-3-nitropyridine hydrogen chloride (50mg, 0.24mmol, 0.2eq.) was added and the mixture stirred at reflux for a further 24 hours. The reaction mixture was then concentrated *in vacuo* to give a dark yellow oily residue. This was partitioned between 2M NaOH (30mL) and DCM (2 x

30mL). The organics were combined, dried over sodium sulphate, filtered and concentrated *in vacuo* to give a dark yellow oil. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (98:2:0.2 to 90:10:1, by volume) to provide the title compound (205mg, 38%).

HRMS ESI$^+$ *m/z* 441.2486 $[MH]^+$.

Intermediate 96: (3-Nitro-pyridin-2-yl)-[4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-amine

To a stirred solution of {4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (320mg, 1.0mmol) *in* acetonitrile (~5mL), was added Hunig's base (190µL, 1.1mmol, 1.1eq.) and 2-chloro-3-nitropyridine (175mg, 1.1mmol, 1.1eq.) and the mixture stirred at reflux for 4 hours. The reaction mixture was then concentrated *in vacuo* and partitioned between saturated $NaHCO_3$ solution (20mL) and DCM (2 x 20mL). The organics were combined, dried over sodium sulphate, filtered and concentrated *in vacuo* to give the title compound (475mg, 100%) as a yellow oil.

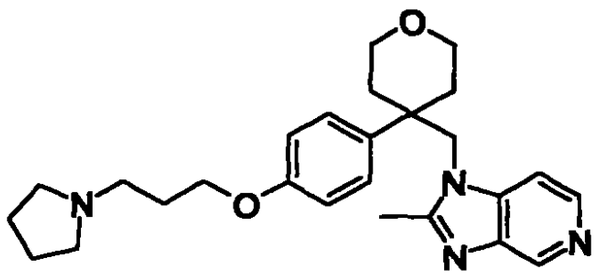
LRMS APCI$^+$ *m/z* 441 $[MH]^+$.

Intermediate 97: N*4*-[4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-pyridine-3,4-diamine

A solution of (3-Nitro-pyridin-4-yl)-[4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-amine (200mg, 0.45 mmol) in ethanol (~5mL) was hydrogenated for 4 hours at room temperature at 40 psi in the presence of 10% Pd/C (20mg, 10%w/w). The reaction mixture was filtered over Arbocel® and rinsed with ethanol. The filtrate was concentrated *in vacuo* to give a brown oily residue. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (94:6:0.6, by volume) to provide the title compound (68mg, 36%).

HRMS ESI$^+$ m/z 411.2750 $[MH]^+$.

Example 248: 2-Methyl-1-[4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-1H-Imidazo[4,5-c]pyridine



N*4*-[4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-pyridine-3,4-diamine (60mg, 0.15mmol) and acetic anhydride (~1mL) were stirred at reflux for 18 hours. The reaction mixture was quenched with ~1mL water, then basified with dilute sodium carbonate solution then extracted with DCM (2 x 20mL). The organics were combined, dried over sodium sulphate, filtered and concentrated *in vacuo* to give a brown oil. The crude product was purified by flash chromatography on silica gel eluting with

dichloromethane:methanol:ammonia (95:5:0.5 to 90:10:1 by volume) to provide the title compound as a brown oil (19mg, 30%).

^{1}H NMR (400MHz, $CDCl_3$) δ 1.78-1.82 (m, 6H), 1.97-2.10 (m, 5H), 2.23 (m, 2H), 2.54 (m, 4H), 2.62 (t, 2H), 3.40 (m, 2H), 3.82 (m, 2H), 4.00 (t, 2H), 4.07 (s, 2H), 6.80-6.88 (m, 4H), 7.00 (d, 1H), 8.30 (d, 1H), 8.92 (s, 1H).

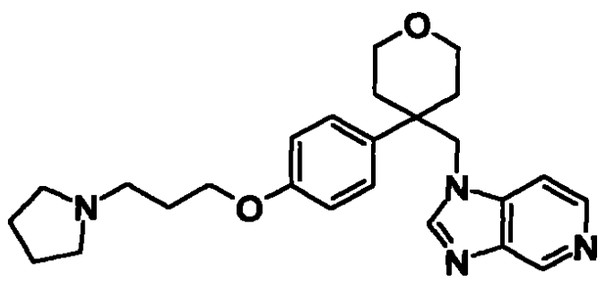
LRMS ESI$^+$ m/z 435 $[MH]^+$.

Intermediate 98: N*2*-[4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-pyridine-2,3-diamine

A solution of (3-Nitro-pyridin-2-yl)-[4-[4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-amine (465mg, 1.06 mmol) in ethanol (~10mL) was hydrogenated for 4 hours at room temperature at 40 psi in the presence of 10% Pd/C (45mg, 10%w/w). The reaction mixture was filtered over Arbocel® and rinsed with ethanol (30mL), 2M HCl (20mL) and EtOH (30mL). The filtrate was concentrated *in vacuo* to give the title compound (385mg, 84%).

HRMS ESI$^+$ m/z 411.2750 $[MH]^+$.

Example 247: 1-[[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl]methyl]-1H-imidazo[4,5-c]pyridine

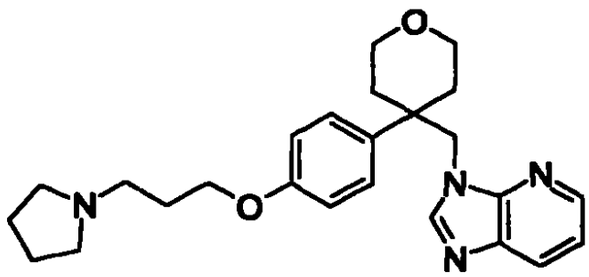


N*4*-[4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-pyridine-3,4-diamine (280mg, 0.66mmol), trimethylorthoformate (5mL) and formic acid (0.5mL) were stirred at 40°C for 18 hours then at 60°C for 24 hours, then at 80°C for 24 hours. The reaction mixture was concentrated *in vacuo* and the residue partitioned between 2M NaOH (30mL) and DCM (2 x 30mL). The organics were combined, dried over sodium sulphate, filtered and concentrated *in vacuo* to give a brown oil. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:5:0.5 to 90:10:1 by volume) to provide the title compound as a clear viscous oil (185mg, 65%).

^{1}H NMR (400MHz, $CDCl_3$) δ 1.78-1.82 (m, 4H), 1.91-2.03 (m, 4H), 2.15-2.20 (m, 2H), 2.52 (m, 4H), 2.61 (t, 2H), 3.44 (m, 2H), 3.82 (m, 2H), 4.00 (t, 2H), 4.19 (s, 2H), 6.82 (d, 2H), 6.86-6.93 (m, 3H), 7.08 (s, 1H), 8.30 (d, 1H), 9.01 (s, 1H).

HRMS ESI$^+$ m/z 421.2590 $[MH]^+$.

Example 248: 3-[[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl]methyl]-3H-imidazo[4,5-b]pyridine

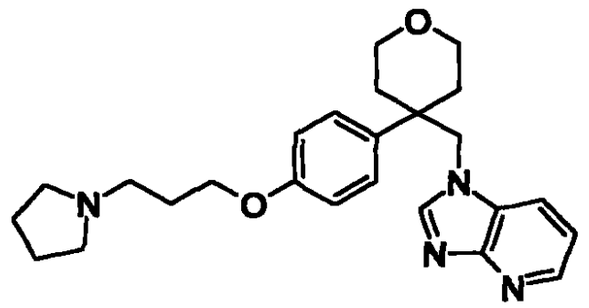


N*2*-[4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-ylmethyl]-pyridine-2,3-diamine (350mg, 0.85mmol), trimethylorthoformate (5mL) and formic acid (0.5mL) were stirred at 40°C for 3 hours. The reaction mixture was concentrated *in vacuo* and the residue partitioned between saturated $NaHCO_3$ solution (40mL) and DCM (2 x 40mL). The organics were combined, dried over sodium sulphate, filtered and concentrated *in vacuo* to give a brown oil. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (97:3:0.3 to 93:7:0.7 by volume) to provide the title compound as a brown oil (255mg, 71%).

^1H NMR (400MHz, $CDCl_3$) δ 1.78-1.82 (*m*, 4H), 1.99-2.10 (*m*, 6H), 2.57 (*m*, 4H), 2.84 (t, 2H), 3.58 (*m*, 2H), 3.92 (m, 2H), 4.03 (t, 2H), 4.40 (s, 2H), 6.82 (s, 1H), 6.90 (d, 2H), 7.02 (d, 2H), 7.20 (m, 1H), 7.99 (d, 1H), 8.38 (d, 1H).

HRMS ESI$^+$ m/z 421.2586 $[MH]^+$.

Example 249: 1-([4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl]methyl)-1H-imidazo[4,5-b]pyridine



Step 1:

Trifluoro-methanesulfonic acid 2-nitro-pyridin-3-yl ester (1.1g, 4.1mmo), {4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (1.3g, 4.1mmol) and Hunig's base (1.7mL, 9.8mmol) were stirred at 60°C for 72 hours. The mixture was diluted with DCM (30mL) and washed with water (10mL). The DCM layer was dried over sodium sulphate, filtered and concentrated *in vacuo* to give a dark brown oil. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (98:2:0.2 to 90:10:1, by volume) to give a green oily residue after concentration *in vacuo*.

Step 2:

To a solution of this residue in methanol (10mL) was added methyl viologen dichloride hydrate (5mg, 0.02mmol) and a solution of sodium dithionite (1.07g, 6.13mmol) and $NaHCO_3$ (940mg, 11.2mmol) in

water (10mL). The mixture was stirred at room temperature for 10 minutes and then extracted with DCM (2 x 30mL). The organics were dried over sodium sulphate, filtered and concentrated *in vacuo* to give a dark green oil. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (94:6:0.6 to 90:10:1, by volume) to give a dark green solid after concentration *in vacuo*.

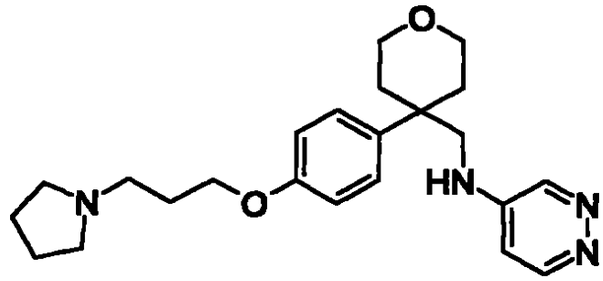
Step 3:

This green solid, trimethylorthoformate (5mL) and formic acid (0.5mL) were stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* and the residue partitioned between saturated 2M NaOH solution (20mL) and DCM (2 x 20mL). The organics were combined, dried over sodium sulphate, filtered and concentrated *in vacuo* to give an orange oil. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (96:4:0.4 to 90:10:1 by volume) to provide the title compound as a pale yellow oil (95mg, 6%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (m, 4H), 1.90-2.02 (m, 4H), 2.17 (m, 2H), 2.52 (m, 4H), 2.61 (t, 2H), 3.41 (t, 2H), 3.80 (m, 2H), 3.98 (t, 2H), 4.16 (s, 2H), 6.78 (d, 2H), 6.90 (d, 2H), 7.02 (m, 1H), 7.17 (d, 1H), 7.31 (s, 1H), 8.43 (m, 1H)

LRMS APCI$^+$ *m/z* 421 $[MH]^+$.

Example 250: N-{[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl]methyl}pyridazin-4-amine



Step 1:

A mixture of {4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (500mg, 1.67mmol), 3,4,5-Trichloro-pyridazine (403mg, 2.20mmol) and potassium carbonate (240mg, 1.73mmol) in acetonitrile (5mL) were stirred at room temperature for 72 hours. The mixture was concentrated *in vacuo* and partitioned between water (30mL) and DCM (2 x 30mL). The combined organics were dried over sodium sulphate, filtered and concentrated *in vacuo* to give a deep red oil. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (96:4:0.4 to 93:70:7, by volume) to give a deep red oil after concentration *in vacuo*.

Step 2:

A solution of this oil and sodium hydroxide (110mg, 2.7mmol) in ethanol (~5mL) was hydrogenated for 18 hours at room temperature at 50 psi in the presence of 10% Pd/C (80mg, 10%w/w). The reaction mixture was filtered over Arbocel® and rinsed with ethanol. The filtrate was concentrated *in vacuo* to give an oily residue. The crude product was purified by flash chromatography on silica gel eluting with

dichloromethane:methanol:ammonia (94:6:0.6 to 90:10:1, by volume) to provide the title compound (230mg, 37%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (m, 4H), 1.88 (m, 2H), 2.01 (m, 2H), 2.20 (m, 2H), 2.55 (m, 4H), 2.63 (t, 2H), 3.25 (d, 2H), 3.55 (m, 2H), 3.80 (m, 2H), 3.90 (t, 1H), 4.02 (t, 2H), 6.33 (m, 1H), 6.96 (d, 2H), 7.20 (d, 2H), 8.40 (d, 1H), 8.57 (d, 1H)

HRMS ESI$^+$ m/z 397.2591 $[MH]^+$.

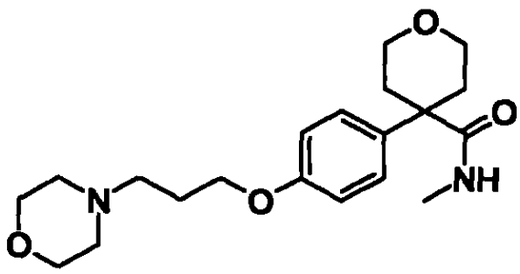
Intermediate 99: 4-[4-(3-Morpholin-4-yl-propoxy)-phenyl]-tetrahydro-pyran-4-carboxylic acid hydrochloride

A solution of 4-[4-(3-morpholino-4-ylpropoxy)phenyl]tetrahydropyran-4-carbonitrile (2.0g, 6.05mmol) in concentrated hydrochloric acid (30mL, 10vol) was heated at reflux for 16h. The solution was cooled to room temperature affording a precipitate. This was filtered, washed with water (~5mL) and diethyl ether (~10mL) and then dried to give the title compound (1.34g, 57%) as a pale orange solid.

LRMS (APCI$^-$) 348 $(M-H^+)^-$.

Microanalysis: Found: C, 58.16; H, 7.30; N, 3.45%. $C_{19}H_{28}NO_5Cl$. $0.3H_2O$ requires C, 58.32; H, 7.37; N, 3.58%.

Example 251: N-methyl-4-[4-(3-morpholin-4-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxamide

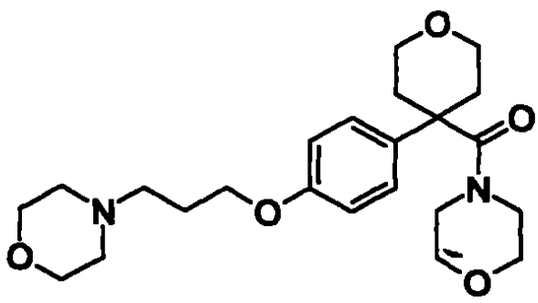


O-(1*H*-Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (640mg, 1.7mmol) was added to a solution of 4-[4-(3-Morpholin-4-yl-propoxy)-phenyl]-tetrahydro-pyran-4-carboxylic acid hydrochloride (500mg, 1.3mmol), methylamine hydrogen chloride (130mg, 1.9mmol) and Hunig's base (790µL, 4.5mmol) in *N*,*N*-dimethylformamide (5mL). The mixture was stirred at room temperature for 2 hours and then concentrated *in vacuo*. The residue was partitioned between 2M NaOH solution (20mL) and DCM (2x20mL). The organics were combined, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:5:0.5 to 90:10:1, by volume) to provide the title compound (355mg, 76%) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93-2.00 (m, 2H), 2.01-2.08 (m, 2H), 2.37-2.40 (m, 2H), 2.48 (m, 4H), 2.50 (t, 2H), 2.70 (d, 3H), 3.67-3.80 (m, 8H), 4.02 (t, 2H), 6.88 (d, 2H), 7.22 (d, 2H).

LRMS APCI$^+$ m/z 363 $[MH]^+$.

Example 252: 4-{3-[4-[4-(morpholin-4-ylcarbonyl)tetrahydro-2H-pyran-4-yl]phenoxy]propyl}morpholine

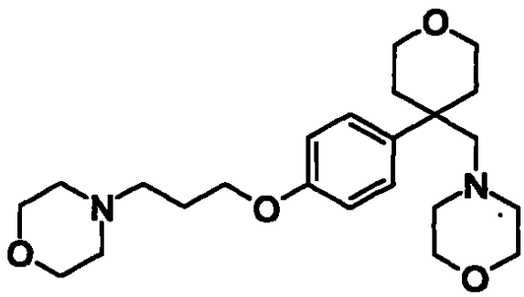


O-(1*H*-Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (200mg, 0.5mmol) was added to a solution of 4-[4-(3-Morpholin-4-yl-propoxy)-phenyl]-tetrahydro-pyran-4-carboxylic acid hydrochloride (160mg, 0.4mmol), morpholine (54 µL, 0.6mmol) and Hunig's base (180µL, 1mmol) in *N,N*-dimethylformamide (2mL). The mixture was stirred at room temperature for 3 hours and then concentrated *in vacuo*. The residue was partitioned between 2M NaOH solution (20mL) and DCM (2x20mL). The organics were combined, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:5:0.5 to 90:10:1, by volume) to provide the title compound (182mg, 100%) as a pale brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93-2.04 (m, 4H), 2.20 (m, 2H), 2.42-2.55 (m, 6H), 3.22-3.43 (br m, 8H), 3.72 (t, 4H), 3.79 (m, 2H), 3.90 (m, 2H), 4.00 (t, 2H), 6.88 (d, 2H), 7.17 (d, 2H).

LRMS APCI$^+$ m/z 419 $[MH]^+$.

Example 283: 4-(3-[4-[4-(morpholin-4-ylmethyl)tetrahydro-2H-pyran-4-yl]phenoxy}propyl)morpholine

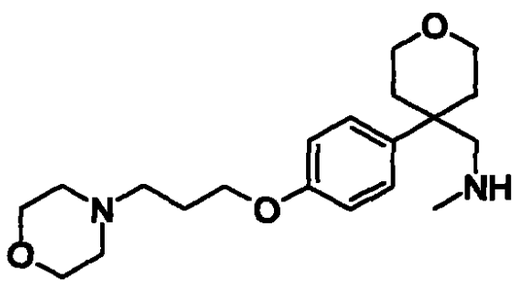


To a stirred solution of 4-(3-[4-[4-(morpholin-4-ylcarbonyl)tetrahydro-2H-pyran-4-yl]phenoxy}propyl)morpholine (160mg, 0.38 mmol) in THF (4 mL) at 0°C was added dropwise a solution of $LiAlH_4$ (1.0M solution in Et_2O, 1.15 mL, 1.15 mmol). The reaction mixture was stirred at 0°C for 20mins then heated at reflux for 1.5 hours. The reaction was then cooled to 0°C, water (0.10 ml) was added dropwise followed by sodium hydroxide (2.0M, 0.10 ml) and water (0.30 ml). The mixture was filtered through a short pad of celite, eluting with 1% methanol in dichloromethane (15 ml) and the organic washings concentrated *in vacuo*. The crude compound was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:ammonia, 97:3:0.3 to 92:8:0.8, to give the title compound as a clear oil (125 mg, 81%).

194
195

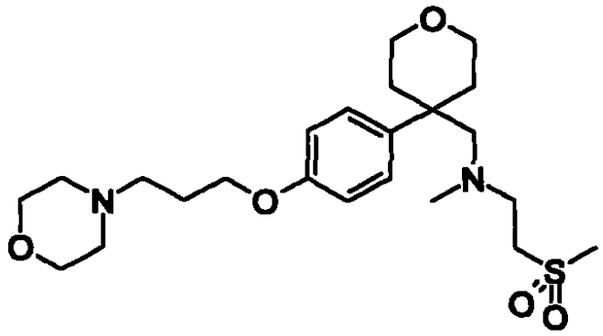
^{1}H NMR (400MHz, $CDCl_3$) δ 1.83 (m, 2H), 1.95 (m, 2H), 2.07-2.16 (m, 6H), 2.40 (s, 2H), 2.43-2.50 (m, 4H), 2.52 (t, 2H), 3.51 (m, 6H), 3.76 (m, 6H), 4.01(t, 2H), 6.82 (d, 2H), 7.21 (d, 2H).
HRMS ESI$^+$ m/z 405.2742 $[MH]^+$.

Example 254: N-methyl-1-[4-[4-(3-morpholin-4-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl]methanamine



The title compound (252mg, 77%) was prepared from N-methyl-4-[4-(3-morpholin-4-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxamide and a solution of $LiAlH_4$ (1.0M solution in Et_2O) similarly to the procedure used for 4-(3-[4-[4-(morpholin-4-ylmethyl)tetrahydro-2H-pyran-4-yl]phenoxy]propyl)morpholine.
^{1}H NMR (400 MHz, CD_3OD) δ 1.85-2.00 (m, 6H), 2.12 (m, 2H), 2.24 (s, 3H), 2.45 (m, 4H), 2.53 (t, 2H), 2.63 (s, 2H), 3.57 (m, 2H), 3.70-3.80 (m, 6H), 4.01 (t, 1H), 6.88 (d, 2H), 7.20 (d, 2H).
HRMS ESI$^+$ m/z 349.2477 $[MH]^+$.

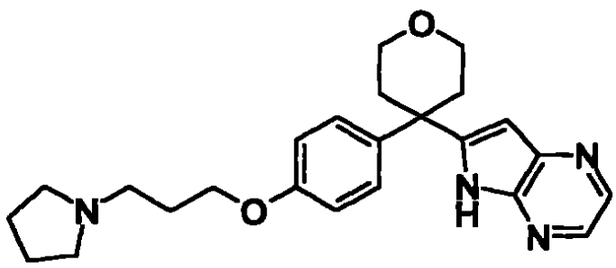
Example 255: N-methyl-2-(methylsulfonyl)-N-([4-[4-(3-morpholin-4-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl]methyl)ethanamine



To a stirred solution of N-methyl-1-[4-[4-(3-morpholin-4-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl]methanamine (230mg, 0.66mmol) in methanol (2mL) was added methanesulfonyl-ethene (64μL, 0.72mmol) and the mixture stirred at room temperature for 18 hours. The mixture was concentrated *in vacuo* and triturated with diethyl ether to give the title compound as a white solid (274mg, 91%).
^{1}H NMR (400MHz, $CDCl_3$) δ 1.81 (m, 2H), 1.97 (m, 2H), 2.04 (s, 3H), 2.13 (m, 2H), 2.42-2.58 (m, 8H), 2.62 (t, 2H), 2.74 (s, 3H), 2.81 (t, 2H), 3.50 (m, 2H), 3.70-3.80 (m, 6H), 4.00 (t, 2H), 6.86 (d, 2H), 7.20 (d, 2H).
HRMS ESI$^+$ m/z 455.2570 $[MH]^+$.
Microanalysis: Found: C, 60.61; H, 8.47; N, 6.09%. $C_{23}H_{38}N_2O_5S$ requires C, 60.76; H, 8.42; N, 6.16%.

195
196

Example 256: 6-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl]-6H-pyrrolo[2,3-b]pyrazine

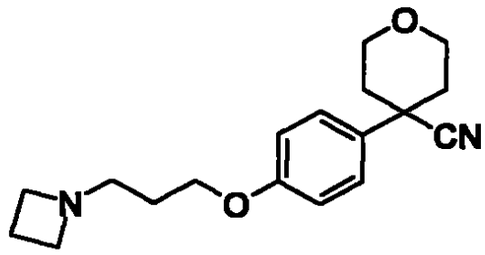


A solution of 2-methyl-pyrazine (580µL, 6.4mmol) in THF (4mL) was added to 4.7mL of 1.5M lithium diisopropylamide : THF complex in hexanes at –40°C and the resulting deep red solution stirred at –40°C for 0.5 hours. A solution of 4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-carbonitrile (1.00g, 3.2mmol) in THF (5mL) was added at –40°C and the reaction mixture stirred at this temperature for 0.5 hours, then at room temperature for 18 hours. A further 1 equivalent of lithium diisopropylamide complex was then added and the reaction mixture stirred at reflux for 24 hours.. The mixture was cooled to room temperature, water (10mL) added and the mixture concentrated *in vacuo*. The residue was partitioned between water (80mL) and DCM (2 x 80mL). The organics were combined, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:5:0.5 to 90:10:1, by volume) to provide the title compound (65mg, 6%) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74-1.80 (m, 6H), 2.00 (m, 2H), 2.42-2.55 (m, 6H), 2.60 (t, 2H), 3.80 (m, 4H), 4.00 (t, 2H), 6.60 (s, 1H), 6.86 (d, 2H), 7.21 (d, 2H), 8.05 (d, 1H), 8.39 (d, 1H).

HRMS ESI$^+$ m/z 407.2437 $[MH]^+$.

Example 257: 4-[4-(3-azetidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carbonitrile

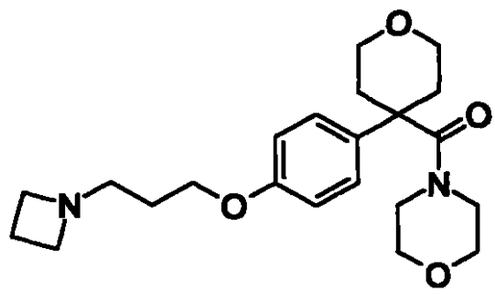


A mixture of 4-[4-(3-chloro-propoxy)-phenyl]-tetrahydropyran-4-carbonitrile and 4-[4-(3-bromo-propoxy)-phenyl]-tetrahydropyran-4-carbonitrile (7.5g, 27mmol), K_2CO_3 (9.6g, 70mmol) and azetidine hydrochloride (4.0g, 43mmol) in acetonitrile (80mL) was heated at 40°C for 18 hours. The mixture was concentrated *in vacuo* then partitioned between water (150mL) and ethyl acetate (150mL). The organic layer was extracted with 2M HCl solution (2 x 100mL) and the combined acid layers basified with 40% potassium hydroxide solution, then extracted with DCM (2 x 150mL). The DCM layers were combined, dried over sodium sulphate, filtered and concentrated under reduced pressure to give the title compound (1.1g, 57%) as a clear, viscous oil.

196
197

^{1}H NMR (400 MHz, DMSO) δ 1.80 (quintet, 2H), 2.00-2.14 (m, 6H), 2.58 (t, 2H), 3.20 (t, 4H), 3.88 (m, 2H), 4.00-4.11 (m, 4H), 6.90 (d, 2H), 7.38 (d, 2H);
LRMS (APCI$^+$) m/z 301 $(MH)^+$.

Example 268: 4-({4-[4-(3-azetidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}carbonyl)morpholine



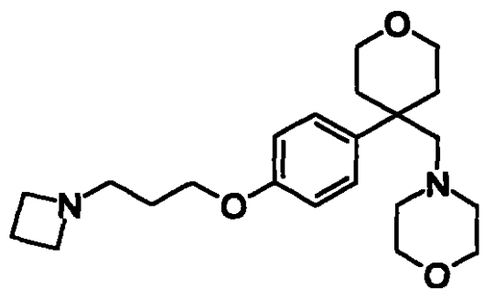
Step 1:

A solution of 4-[4-(3-azetidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carbonitrile (1.1g, 3.7*mmol*) *in* concentrated hydrochloric acid (15mL, 10vol) was heated and stirred at reflux for 24 hours. The solution was cooled to room temperature and then concentrated *in vacuo* affording a brown oily solid. Hunig's base (6mL) was added and the mixture concentrated *in vacuo* to give a brown oily residue.

Step2:

O-(1*H*-Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (1.7g, 4.5mmol) was added to a solution of this residue, morpholine (600µL, 6.9mmol) and Hunig's base (780µL, 4.5mmol) in *N,N*-dimethylformamide (5mL). The mixture was stirred at room temperature for 72 hours and then concentrated *in vacuo*. The residue was partitioned between water (50mL) and DCM (2 x 50mL). The organics were combined, dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:5:0.5 to 90:10:1, by volume) to provide the title compound (128mg, 9%) as a pale pink foam after trituration with diethyl ether.
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93-2.04 (m, 4H), 2.20 (m, 2H), 2.51-2.60 (*m*, 2H), 3.22-3.45 (br m, 10H), 3.78 (m, 2H), 3.86 (m, 2H), 4.02 (t, 2H), 4.13 (t, 4H), 6.88 (d, 2H), 7.18 (d, 2H).
HRMS ESI$^+$ m/z 389.2426 $[MH]^+$.

Example 269: 4-({4-[4-(3-azetidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)morpholine



To a stirred solution of 4-({4-[4-(3-azetidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}carbonyl)morpholine (120mg, 0.31mmol) in THF (1 mL) at 0°C was added dropwise a solution of $LiAlH_4$ (1.0M solution in Et_2O, 1.00mL, 1.00mmol). The reaction mixture was stirred at 0°C for 20mins then heated at reflux for 3 hours. The reaction was then cooled to 0°C, water (0.10 ml) was added dropwise followed by sodium hydroxide (2.0M, 0.10 ml) and water (0.30 ml). The mixture was filtered through a short pad of celite, eluting with 1% methanol in dichloromethane (15 ml) and the organic washings concentrated *in vacuo*. The crude compound was purified by column chromatography on silica gel, eluting with dichloromethane:methanol:ammonia, 97:3:0.3 to 94:6:0.6, to give the title compound as a clear oil (25 mg, 22%).

^{1}H NMR (400MHz, $CDCl_3$) δ 1.78-1.90 (m, 8H), 2.08 (m, 2H), 2.13 (m, 4H), 2.38 (s, 2H), 2.59 (t, 2H), 3.20 (t, 2H), 3.51 (m, 6H), 3.76 (m, 2H), 4.00 (t, 2H), 6.82 (d, 2H), 7.21 (d, 2H).
LRMS APCI$^+$ m/z 375 $[MH]^+$.

Intermediate 100: 4-(4-{[1-(diphenylmethyl)azetidin-3-yl]methoxy}phenyl)tetrahydro-2H-pyran-4-carbonitrile

4-(4-Hydroxy-phenyl)-tetrahydro-pyran-4-carbonitrile (6.18g, 30.4mmol), (1-benzhydryl-azetidin-3-yl)-methanol (7g, 28mmol), PPh_3 (8g, 30.4mmol), and DIAD (69mL, 30.4mmol), were reacted together similarly to general procedure C. The crude material was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate:diethylamine (50:45:5 to 0:95:5) to provide the title compound (5.03g, 41%) as a yellow solid.

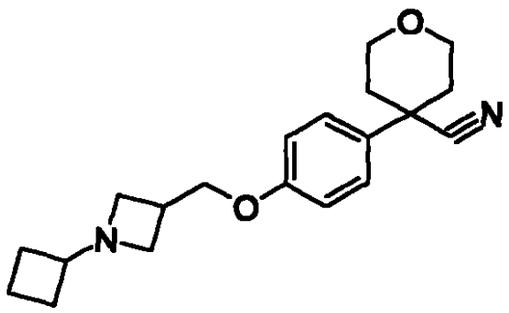
LRMS APCI$^+$ m/z 439 $[MH]^+$.

Intermediate 101: 4-[4-(azetidin-3-ylmethoxy)phenyl]tetrahydro-2H-pyran-4-carbonitrile

4-(4-{[1-(diphenylmethyl)azetidin-3-yl]methoxy}phenyl)tetrahydro-2H-pyran-4-carbonitrile (0.605g, 1.38mmol), palladium hydroxide (0.06g), concentrated hydrochloric acid (0.115mL, 1.38mmol), and ethanol (6mL) were combined and hydrogenated for 18 hours at 40°C at 40psi. The mixture was filtered through Arbocel® and rinsed with ethanol. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM (50mL) and washed with 10% aqueous sodium carbonate (20mL). The organics were dried over sodium sulphate, filtered and concentrated *in vacuo* to provide a green oil. This was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:5:0.5 to 90:10:1) to provide the title compound (0.145g, 39%) as a yellow oil.

LRMS APCI$^+$ m/z 273 $[MH]^+$.

Example 260: 4-{4-[(1-cyclobutylazetidin-3-yl)methoxy]phenyl}tetrahydro-2H-pyran-4-carbonitrile

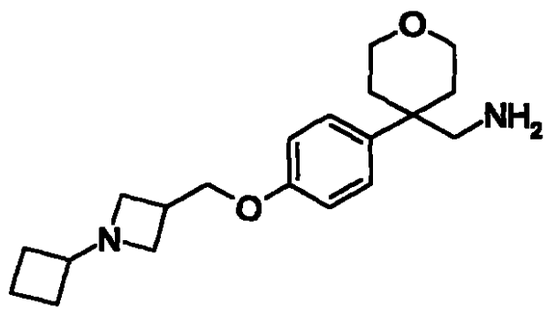


4-[4-(azetidin-3-ylmethoxy)phenyl]tetrahydro-2H-pyran-4-carbonitrile (0.2g, 0.73mmol) was dissolved in THF (2mL). Cyclobutanone (0.06mL, 0.80mmol) and acetic acid (0.042mL, 0.73mmol) were added. The mixture was stirred at room temperature for 30 minutes. Sodium triacetoxyborohydride (0.311g, 1.47mmol) was added. The mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with 10% aqueous sodium carbonate (5mL) then extracted with DCM (2 x 50mL). The organics were combined, dried over sodium sulphate, filtered and concentrated *in vacuo* to provide a clear oil. This was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (96:4:0.4 to 95:5:0.5) to provide the title compound (0.184g, 81%) as a clear oil.

^{1}H NMR (400MHz, $CDCl_3$) δ 1.60-1.70 (m, 2H), 1.70-1.80 (m, 2H), 1.80-1.90 (m, 2H), 1.95-2.00 (m, 2H), 2.0-2.15 (m, 2H), 2.9 (m, 1H), 3.1 (t, 2H), 3.16 (m, 1H), 3.4 (t, 2H), 3.9 (m, 2H), 4.10 (m, 4H), 6.90 (d, 2H), 7.40 (d, 2H)

HRMS ESI$^+$ m/z 327.2059 $[MH]^+$.

Example 261: 1-{4-[4-[(1-cyclobutylazetidin-3-yl)methoxy]phenyl]tetrahydro-2H-pyran-4-yl}methanamine



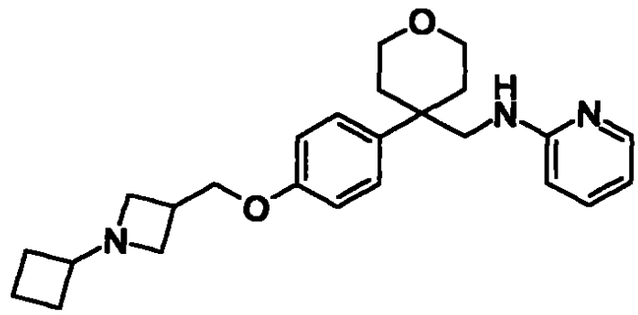
4-{4-[(1-cyclobutylazetidin-3-yl)methoxy]phenyl}tetrahydro-2H-pyran-4-carbonitrile (0.29g, 0.89mmol), was dissolved in THF (5mL). The solution was cooled to 0°C under nitrogen. Lithium aluminiumhydride (2.7mL, 1.0M solution in diethyl ether) was added dropwise. The reaction was stirred at 0°C for 30 minutes, then warmed up to ambient temperature for 4 hours under a nitrogen atmosphere until complete. The reaction was cooled to 0°C, water (0.1mL) was added dropwise followed by sodium hydroxide (2.0M, 0.1mL) and water (0.3mL). The mixture was filtered (using dichloromethane:methanol (90:10)) through celite. The organics were dried over sodium sulphate, filtered and concentrated *in vacuo* to provide a

199
200

clear oil. This was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (96:4:0.4 to 90:10:1) to provide the title compound (0.175g, 59%) as a clear colourless oil.

^{1}H NMR (400MHz, $CDCl_3$) δ 1.60-1.70 (m, 2H), 1.70-1.85 (m, 2H), 1.85-1.95 (m, 2H), 1.95-2.06 (m, 2H), 2.1-2.18 (m, 2H), 2.79 (s, 2H), 2.9 (m, 1H), 3.1 (t, 2H), 3.2 (m, 1H), 3.48 (m, 2H), 3.54 (m, 2H), 3.8 (m, 2H), 4.10 (d, 2H), 6.9 (d, 2H), 7.2 (d, 2H)
HRMS ESI$^+$ m/z 331.2374 $[MH]^+$.

Example 282: N-[(4-{4-[(1-cyclobutylazetidin-3-yl)methoxy]phenyl}tetrahydro-2H-pyran-4-yl)methyl]pyridin-2-amine



1-(4-{4-[(1-cyclobutylazetidin-3-yl)methoxy]phenyl}tetrahydro-2H-pyran-4-yl)methanamine (0.175g, 0.53mmol) was dissolved in toluene (5mL), 2-bromopyridine (0.051mL, 0.53mmol), 2,2'-bis(diphenylphosphino)-1,1'binaphthyl (0.013g, 0.02mmol) and sodium *tert*-butoxide (0.078g, 0.79mmol) were added. The reaction mixture was purged with nitrogen, tris(dibenzylideneacetone)dipalladium(0) (0.011g, 0.01mmol) was added. The mixture was heated under nitrogen at 70°C for 16 hours. The reaction mixture was diluted with water (20mL) and extracted with DCM (2 x 30mL). The combined organics were dried over sodium sulphate, filtered and concentrated *in vacuo* to provide a yellow oil. This was purified by HPLC eluting with methanol: 10nM ammonium formate (aq) (1:1), fractions were combined and concentrated *in vacuo* to leave a clear oil. This was dissolved in DCM (50mL) and washed with saturated sodium hydrogen carbonate solution in water (10mL). The organic was dried over sodium sulphate, filtered and concentrated *in vacuo* to provide the title compound (0.016g, 7%) as a clear colourless oil.

^{1}H NMR (400MHz, $CDCl_3$) δ 1.60-1.70 (m, 2H), 1.70-1.80 (m, 2H), 1.80-1.92 (m, 2H), 1.92-2.0 (m, 2H), 2.18 (m, 2H), 2.90 (m, 1H), 3.10 (t, 2H), 3.15 (m, 1H), 3.40 (t, 2H), 3.50 (d, 2H), 3.60 (m, 2H), 3.80 (m, 2H), 4.0 (m, 1H), 4.10 (d, 2H), 6.22 (d, 1H), 6.50 (d, 1H), 6.90 (d, 2H), 7.28 (d, 2H), 7.32 (t, 1H), 8.0 (d, 1H)

HRMS ESI$^+$ m/z 408.2641 $[MH]^+$.

200

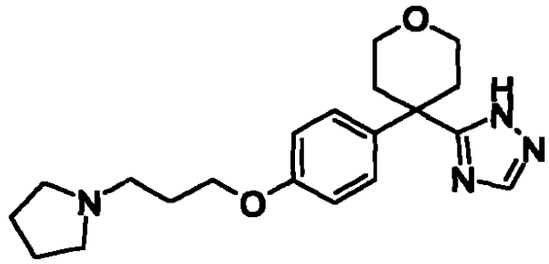
Intermediate 192: N-[(dimethylamino)methylene]-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxamide

4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxylic acid amide (0.561g, 1.69mmol) and *N,N*-dimethylformamide dimethyl acetal (5mL) were combined and heated at reflux for 4 hours. The reaction mixture was concentrated *in vacuo* and azeotroped with toluene (2 x 10mL) to provide the title compound (0.655g, 100%) as a brown solid.

^{1}H NMR (400MHz, $CDCl_3$) δ 1.80-1.85 (*m*, 4H), 1.85-1.95 (*m*, 2H), 2.0-2.10 (m, 2H), 2.6-2.78 (m, 8H), 3.0 (s, 3H), 3.05 (s, 3H), 3.60 (m, 2H), 3.90 (m, 2H), 4.0 (t, 2H), 6.80 (d, 2H), 7.35 (d, 2H), 8.30 (s, 1H)

LRMS APCI$^+$ m/z 388 $[MH]^+$.

Example 283: 3-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl]-1H-1,2,4-triazole

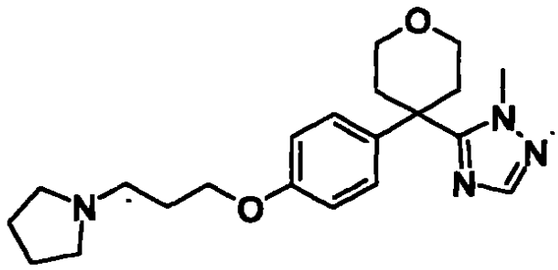


N-[(dimethylamino)methylene]-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxamide (0.15g, 0.39mmol), hydrazine hydrate (0.048mL, 0.98mmol) and acetic acid (1mL) were combined and heated at 100°C for 1.5 hours. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in dichloromethane (100mL) and washed with 10% aqueous sodium carbonate (20mL). The organic was dried over sodium sulphate and evaporated to provide a clear oil. This was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (92:8:0.8 to 90:10:1) to produce a clear oil which was triturated with diethyl ether (3mL), a white solid was isolated as the title compound (0.034g, 24%).

^{1}H NMR (400MHz, $CDCl_3$) δ 1.82-1.95 (m, 4H), 2.0-2.10 (m, 2H), 2.30 (m, 2H), 2.60-2.70 (m, 2H), 2.70-2.80 (*m*, 8H), 3.62 (t, 2H), 3.89 (*m*, 2H), 3.95 (t, 2H), 6.80 (d, 2H), 7.20 (d, 2H), 7.95 (d, 1H)

HRMS ESI$^+$ *m/z* 357.2279 $[MH]^+$.

Example 284: 1-methyl-5-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl]-1H-1,2,4-triazole



N-[(dimethylamino)methylene]-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carboxamide (0.34g, 0.88mmol), methyl hydrazine (0.116mL, 2.19mmol) and acetic acid (1mL) were combined and heated at 100°C for 2 hours. The reaction mixture was diluted with water (10mL), solid sodium carbonate was added until the mixture was pH9. Dichloromethane (2 x 50mL) was used to extract. The combined organics were dried over sodium sulphate, filtered and concentrated *in vacuo* to provide a yellow oil. This was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (96:4:0.4 to 90:10:1) to produce the title compound (0.065g, 20%) as a white solid.

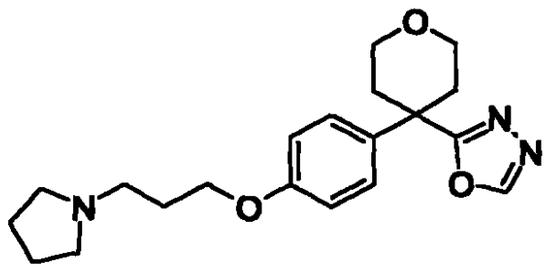
^{1}H NMR (400MHz, $CDCl_3$) δ 1.83-1.93 (m, 4H), 2.05-2.16 (m, 2H), 2.30 (m, 2H), 2.48 (m, 2H), 2.60-2.85 (m, 8H), 3.37 (s, 3H), 3.80 (m, 2H), 3.90 (m, 2H), 4.0 (t, 2H), 6.85 (d, 2H), 7.07 (d, 2H), 7.88 (s, 1H)

HRMS ESI$^+$ m/z 371.2434 $[MH]^+$.

Intermediate 103: N'-formyl-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carbohydrazide

4-[4-(3-Pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2*H*-pyran-4-carboxylic acid (0.75g, 0.225mmol), formic hydrazide (0.162g, 0.27mmol), 1-hydroxybenzotriazole (0.304g, 0.225mmol), diisopropylethylamine (1.18mL, 0.88mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.431g, 0.225mmol) in dichloromethane (10mL) was stirred at room temperature for 18 hours. The reaction mixture was diluted with dichloromethane (100mL) and washed with water (2 x 20mL) The organics were dried over sodium sulphate, filtered and concentrated *in vacuo* to provide a cream solid. This was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:5:0.5 to 90:10:1) to provide the title compound (0.145g, 17%) as a clear oil.
LRMS ESI$^+$ m/z 376 $[MH]^+$, ESI$^-$ m/z 374 $[M-H^+]$

Example 265: 2-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl]-1,3,4-oxadiazole



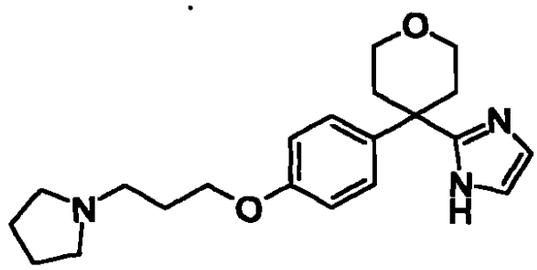
Triphenylphosphine (0.203g, 0.78mmol), iodine (0.198g, 0.78mmol) and triethylamine (0.217mL, 1.56mmol) were dissolved in dichloromethane (5mL). The mixture was stirred at room temperature for 10 minutes. *N'*-formyl-4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carbohydrazide (0.145g, 0.39mmol) in dichloromethane (5mL) was added. The mixture was stirred at room temperature for 18 hours. The reaction mixture was diluted with dichloromethane (100mL) and washed with water (25mL). The organic was dried over sodium sulphate, filtered and concentrated *in vacuo* to provide a yellow oil. This was purified using preparative HPLC on Fraction-Lynx® eluting with water:acetonitrile:trifluoroacetic acid (95:5:0.1) to provide the title compound (0.028g, 20%) as a clear oil.

^{1}H NMR (400MHz, $CDCl_3$) δ1.78-1.85 (m, 4H), 2.05 (m, 2H), 2.30 (m, 2H), 2.58-2.60 (m, 4H), 2.60-2.70 (m, 4H), 3.59 (m, 2H), 3.90-4.05 (m, 4H), 6.90 (d, 2H), 7.20 (d, 2H), 8.30 (s, 1H).
HRMS ESI$^+$ m/z 358.2117 $[MH]^+$.

Intermediate 194: 2-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl]-4,5-dihydro-1H-imidazole

4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-carbonitrile (0.5g, 3.1mmol), ethylenediamine (1.5mL, 22mmol), copper (II) acetate (0.07g, 0.3mmol) and N-methylpyrrolidinone (1.5mL) were combined and subjected to microwave (Smith Personal Synthesiser) irradiation at 220°C for 1 hour. The reaction mixture was concentrated *in vacuo* to provide a brown oil. This was columned by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (94:6:0.6 to 85:15:1.5) to provide the title compound (0.157g, 31%) as a yellow oil.
LRMS ESI$^+$ m/z 358 $[MH]^+$.

Example 286: 2-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl]-1H-imidazole



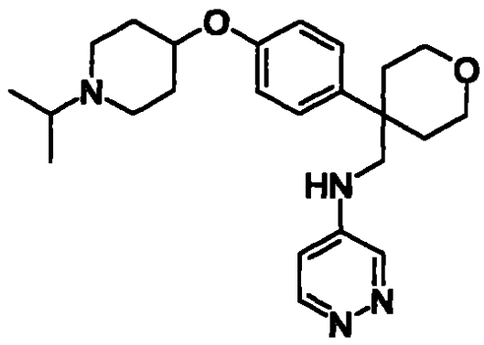
Dimethylsulphoxide (0.156mL, 2.19mmol) and dichloromethane (15mL) were combined and cooled to –78°C under nitrogen, oxalyl chloride (0.191mL, 2.19mmol) was added and the reaction mixture was stirred at –78°C under nitrogen for 1 hour. A solution of 2-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-

pyran-4-yl)-4,5-dihydro-1H-imidazole (0.314g, 0.88mol) in dichloromethane (15mL) was added slowly. The reaction was stirred at –78°C for 1 hour. Triethylamine (0.611mL, 4.4mmol) was then added and the reaction was stirred for a further hour. The reaction mixture allowed to warm to room temperature for 1 hour. The reaction mixture was diluted with dichloromethane (100mL) and washed with an aqueous ammonia solution (20mL). The organic was dried over sodium sulphate, filtered and concentrated *in vacuo* to provide a yellow oil. This was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (96:4:0.4 to 90:10:1) to provide a yellow oil, which was triturated with diethyl ether. A cream solid was filtered to provide the title compound (0.07g, 22%)

^{1}H NMR (400MHz, $CDCl_3$) δ 1.80 (m, 4H), 2.05 (m, 2H), 2.30 (m, 2H), 2.50 (m, 2H), 2.60-2.78 (m, 6H), 3.73 (m, 2H), 3.83 (m, 2H) (4.0 (t, 2H), 6.85 (d, 2H), 6.95 (s, 2H), 7.15 (d, 2H)

HRMS ESI$^+$ m/z 356.2327 $[MH]^+$.

Example 297: N-[(4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2H-pyran-4-yl)methyl]pyridazin-4-amine



Step 1:

(4-{4-[(1-isopropylpiperidin-4-yl)oxy]phenyl}tetrahydro-2*H*-pyran-4-yl)methylamine (0.5g, 1.5mmol), 3,4,5-trichloropyridazine (0.275g, 1.5mmol), potassium carbonate (0.690g, 5mmol) and acetonitrile (5mL) were combined and stirred at room temperature for 20 hours. The reaction mixture was partitioned between water (20mL) and dichloromethane (2 x 50 mL). The combined organics were dried over sodium sulphate, filtered and concentrated *in vacuo* to provide an orange oil. This was purified by flash chromatography eluting with dichloromethane:methanol:ammonia (100:0:0 to 90:10:1) to provide a brown oil.

Step 2:

The product from step 1 (0.162g, 0.34mmol) and sodium hydroxide (0.033g, 0.82mmol) were dissolved in ethanol (3mL). 10% Palladium on charcoal (0.02g) was added. The mixture was hydrogenated for 18 hours at room temperature at 50 psi. The reaction mixture was filtered through Arbocel®, the filtrate was concentrated *in vacuo* to provide a yellow oil. This was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (94:6:0.6 to 90:10:1) to provide the title compound (0.08g, 60%) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) δ 1.08 (d, 6H), 1.78-1.90 (m, 4H), 2.05 (m, 2H), 2.20 (m, 2H), 2.43 (m, 2H), 2.72-2.82 (m, 3H), 3.28 (d, 2H), 3.55 (m, 2H), 3.78 (m, 2H), 4.30 (m, 1H), 4.35 (m, 1H), 6.25 (d, 1H), 6.90 (d, 2H), 7.20 (d, 2H), 8.40 (s, 1H), 8.48 (d, 1H)
HRMS ESI$^+$ *m/z* 411.2749 [MH]$^+$.

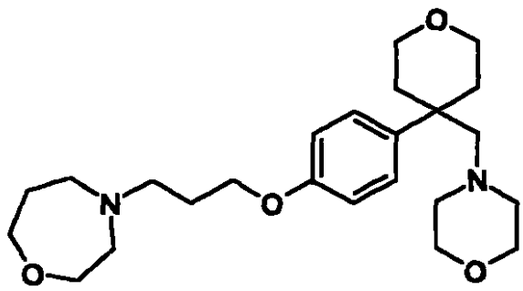
Intermediate 195: 4-[4-(3-[1,4]Oxazepan-4-yl-propoxy)-phenyl]-tetrahydro-pyran-4-carbonitrile

4-[4-(3-Chloro-propoxy)-phenyl]-tetrahydro-pyran-4-carbonitrile (5.3 g, 19 mmol) was taken in acetonitrile (30 ml), to which was added Hunig's base (8 g, 47 mmol) and homo-morpholine hydrogen chloride (2.8 g, 20 mmol). This solution was heated at reflux for 18 hours. The solvent was removed *in vacuo* and the residue purified by silica gel column chromatography, eluting with a gradient of DCM:MeOH:NH_3 (from 98:2:0.2 to 94:6:0.6) to afford the title compound as a yellow oil (3.35 g, 51%).
HRMS ESI$^+$ m/z 345.2166 [MH]$^+$

Intermediate 196: C-[4-[4-(3-[1,4]Oxazepan-4-yl-propoxy)-phenyl]-tetrahydro-pyran-4-yl]-methylamine

4-[4-(3-[1,4]Oxazepan-4-yl-propoxy)-phenyl]-tetrahydro-pyran-4-carbonitrile (900 mg, 26 mmol) was dissolved in THF (5ml) and cooled to 0°C under nitrogen. Lithium aluminium hydride (1M in EtO_2, 7.8 ml, 78mmol) was added dropwise and left to stir for 10 minutes before heating to reflux for 18 hours. The solution was cooled to 0°C before quenching with water (0.78 ml), followed by sodium hydroxide (2M, 0.78ml) and finally water (2.4 ml). The resulting slurry was filtered through Arbocel®, washing through with DCM (2 x 10ml). The filtrate was concentrated *in vacuo* to afford the title compound as a colourless oil (650 mg, 72%).
HRMS ESI$^+$ m/z 349.2480 [MH]$^+$

Example 268: 4-(3-[4-[4-(morpholin-4-ylmethyl)tetrahydro-2H-pyran-4-yl]phenoxy]propyl)-1,4-oxazepane

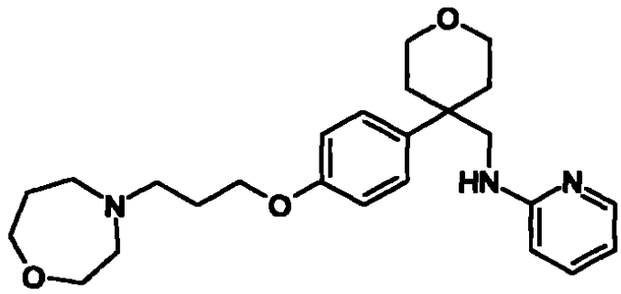


C-[4-[4-(3-[1,4]Oxazepan-4-yl-propoxy)-phenyl]-tetrahydro-pyran-4-yl]-methylamine (150 mg, 0.43 mmol) and 1-Bromo-2-(2-bromo-ethoxy)-ethane (110 mg, 0.47 mmol) were dissolved in acetonitrile (10 ml) and K_2CO_3 (130 mg, 0.95 mmol) was added. The solution was heated at 60°C for 18 hours before filtering the solution to remove to the solid K_2CO_3. The filtrate was concentrated *in vacuo* before purifying using column chromatography, eluting with a gradient of DCM:MeOH:NH_3 (from 99:1:0.1 to 90:10:1) to afford the title compound as a colourless oil (75 mg, 42%).

205
206

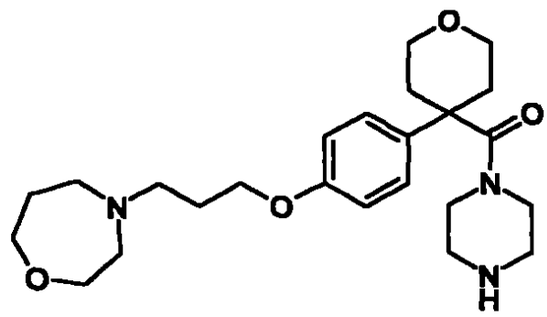
^{1}H NMR (400MHz, CD_3OD) δ 1.80-2.00 (m, 8H), 2.11-2.20 (m, 6H), 2.41 (s, 2H), 2.69-2.79 (m, 6H), 3.48 (m, 6H), 3.72-3.80 (m, 6H), 4.02 (t, 2H)6.87 (d, 2H), 7.15 (d, 2H)
HRMS ESI$^+$ m/z 419.2896 $[MH]^+$

Example 269: N-[(4-[4-[3-(1,4-oxazepan-4-yl)propoxy]phenyl]tetrahydro-2H-pyran-4-yl)methyl]pyridin-2-amine



C-[4-[4-(3-[1,4]Oxazepan-4-yl-propoxy)-phenyl]-tetrahydro-pyran-4-yl]-methylamine (210 mg, 0.48 mmol) was added to a solution of 2-bromopyridine (70 mg, 0.42 mmol), $Pd_2(dba)_3$ (91 mg, 0.1 mmol), BINAP (126 mg, 2 mmol) and sodium *tert*-butoxide (56 mg, 5.7 mmol) in toluene (3 ml). This solution was heated in the microwave (Smith Personal Synthesiser) at 110°C for 15 minutes. The solution was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography, eluting with a gradient of DCM:MeOH:NH_3 (from 99:1:0.1 to 95:5:0.5) to afford the title compound as a yellow oil (120 mg, 59%).
^{1}H NMR (400MHz, CD_3OD) δ 1.88-2.00 (m, 6H), 2.17 (m, 2H), 2.68-2.79 (m, 6H), 3.43 (s, 2H), 3.50 (m, 2H), 3.76 (m, 2H), 3.80 (m, 4H), 4.03 (t, 2H), 6.39 (d, 1H), 6.44 (t, 1H), 6.91 (d, 2H), 7.33 (m, 3H), 7.81 (d, 1H)
HRMS ESI$^+$ m/z 426.2741 $[MH]^+$

Example 270: 4-(3-[4-[4-(piperazin-1-ylcarbonyl)tetrahydro-2H-pyran-4-yl]phenoxy]propyl)-1,4-oxazepane



Step1:
4-[4-(3-[1,4]Oxazepan-4-yl-propoxy)-phenyl]-tetrahydro-pyran-4-carbonitrile (1 g, 29 mmol) was dissolved in concentrated hydrochloric acid (15ml) and heated at 90°C for 24 hours, and the solvent was then removed *in vacuo*. 2-tert butyl 1,1,2,2 tetramethyl guanidine (2 ml) and water (1ml) was then added to the

residue and concentrated *in vacuo* and azeotroped with toluene (2 x 4ml) to afford crude 4-[4-(3-[1,4]Oxazepan-4-yl-propoxy)-phenyl]-tetrahydro-pyran-4-carboxylic acid guanidine salt (3 g) an orange oil.

Step 2:

4-[4-(3-[1,4]Oxazepan-4-yl-propoxy)-phenyl]-tetrahydro-pyran-4-carboxylic acid guanidine (1.2 g, 0.88 mmol of free acid) was dissolved in DMF (5 ml), to which was added N-BOC piperidine (200 mg, 1.06 mmol), HBTU (400 mg, 1.06 mmol) and Hunig's base (129 mg, 1.06 mmol). The reaction was stirred at room temperature for 3 hours before adding saturated sodium bicarbonate solution (15ml) and extracting the product into EtOAc (15 ml). The organic layer was washed with brine (15 ml), dried over Na_2SO_4 and concentrated *in vacuo* before purifying the residue by column chromatography, eluting with a gradient of DCM:MeOH:NH_3 (from 99:1:0.1 to 92:8:0.8). This afforded 4-[4-[4-(3-[1,4]Oxazepan-4-yl-propoxy)-phenyl]-tetrahydro-pyran-4-carbonyl]-piperazine-1-carboxylic acid tert-butyl ester as a colourless oil that became a white solid (260 mg, 55%) on standing overnight.

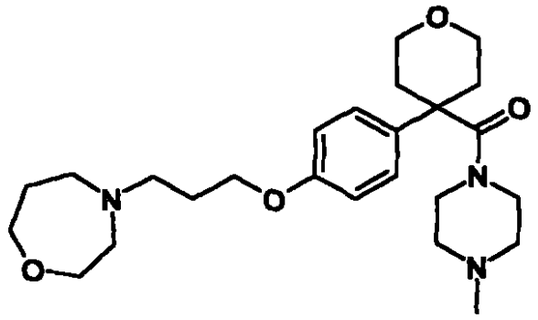
Step 3:

4-[4-[4-(3-[1,4]Oxazepan-4-yl-propoxy)-phenyl]-tetrahydro-pyran-4-carbonyl]-piperazine-1-carboxylic acid tert-butyl ester (260 mg, 0.48 mmol) was dissolved in a solution of hydrogen chloride in dioxane (4M, 5 ml) and was stirred at room temperature for 2 hours. The solvent was removed *in vacuo* and the residue dissolved in DCM (10 ml) and washed with saturated sodium bicarbonate solution (15 ml). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* before purifying the residue using column chromatography, eluting with a gradient of DCM:MeOH:NH_3 (from 99:1:0.1 to 92:8:0.8) to afford the title compound as a white solid (80 mg, 37%).

^{1}H NMR (400MHz, d_6-DMSO) δ 1.70-1.88 (m, 6H), 2.08 (m, 2H), 2.52-2.63 (m, 6H), 3.04-3.35 (m, 8H), 3.58 (m, 4H), 3.64 (m, 2H), 3.72 (m, 2H), 3.98 (t, 2H), 6.92 (d, 2H), 7.12 (d, 2H)

LRMS ESI$^+$ m/z 432 [MH]$^+$

Example 271: 4-[3-[4-[4-[(4-methylpiperazin-1-yl)carbonyl]tetrahydro-2H-pyran-4-yl]phenoxy]propyl]-1,4-oxazepane



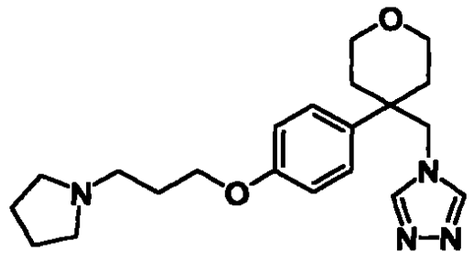
4-(3-[4-[4-(piperazin-1-ylcarbonyl)tetrahydro-2H-pyran-4-yl]phenoxy]propyl)-1,4-oxazepane (45 mg, 0.1 mmol) was dissolved in DCM (3 ml), to which was added formaldehyde (37% w/w in H_2O, 12 mg, 0.12 mmol) and acetic acid (8 mg, 0.12 mmol) and was stirred at room temperature for 30 minutes before adding STAB (25 mg, 0.12 mmol). The solution was allowed to stir for a further 45 minutes before washing the solution with saturated sodium bicarbonate (10 ml), followed by brine (10 ml). The organic

layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford the title compound as a white solid (25 mg, 56%).

^{1}H NMR (400MHz, d_6-DMSO) δ 1.76-2.13 (m, 11H), 2.55-2.78 (m, 6H), 3.16-3.39 (m, 8H), 3.50-3.62 (m, 4H), 3.63 (m, 2H), 3.72 (M, 2H), 3.99 (t, 2H), 6.92 (d, 2H), 7.12 (d, 2H).

LRMS ESI$^+$ m/z 448 $[MH]^+$

Example 272: 4-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)-4H-1,2,4-triazole



A mixture of {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl} methylamine (200mg, 0.63mmol), *N*-[(1*E*)-(dimethylamino)methylene]-*N*,*N*-dimethylhydrazonoformamide (300mg, 2.11mmol) and p-toluenesulphonic acid monohydrate (10mg, 0.05mmol), was heated at reflux in toluene (2ml) for 24 hours. The reaction mixture was concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (95:5:0.5 to 80:20:2 by volume) to provide 160mg of beige gum. This gum was triturated with diethyl ether (3ml) to give the title compound as a white powder (120mg, 51%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.46 (s, 2H), 6.97 (d, 2H), 6.89 (d, 2H), 4.02 (m, 4H), 3.82 (m, 2H), 3.43-3.52 (m, 2H), 2.62 (t, 2H), 2.51 (m, 4H), 2.12 (m, 2H), 2.02 (m, 2H), 1.84 (m, 2H), 1.80 (m, 4H).

LRMS ESI$^+$ m/z 371 $[M+H]^+$

HRMS ESI$^+$ m/z 371.2433 $[M+H]^+$

Intermediate 107: (1-isopropylazetidin-3-yl)methanol hydrochloride

A mixture of (1-benzhydrylazetidin-3-yl)methanol (4.0g, 15.8mmol), acetone (20ml), 2-propanol (80ml), c.HCl (1.5ml) and $Pd(OH)_2$ was hydrogenated at 50psi/50° for 18 hours. The reaction mixture was filtered through Arbocel® and concentrated *in vacuo*, the residue was triturated with diisopropyl ether (50ml) to give the title compound as a pale green hygroscopic powder (2.6g, 99%)

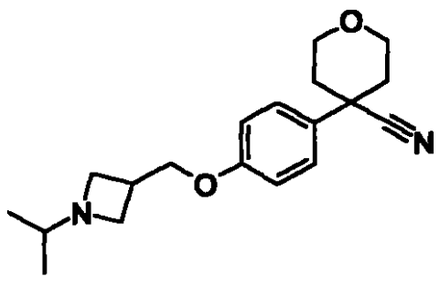
LRMS ESI$^+$ m/z 130 $[M+H]^+$

Intermediate 108: 3-(chloromethyl)-1-isopropylazetidine hydrochloride

(1-isopropylazetidin-3-yl)methanol hydrochloride (2.6g, 15.7mmol) was dissolved in dichloromethane (50ml) and cooled to 0°C. Thionyl chloride (1.4ml, 19.2mmol) was added dropwise over 5 min. The reaction mixture was then stirred whilst warming to ambient temperature. Stirred at ambient temperature for 48 hours. The reaction mixture was concentrated *in vacuo* and azeotroped with toluene (40ml) to give the title compound as a biege hygroscopic powder (2.8g, 99%).

LRMS ESI$^+$ m/z 148/150 $[M+H]^+$ (Cl isotopes)

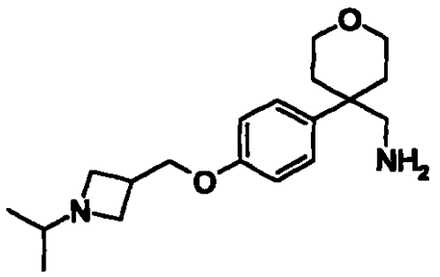
Example 273: 4-[4-[(1-isopropylazetidin-3-yl)methoxy]phenyl]tetrahydro-2H-pyran-4-carbonitrile



3-(chloromethyl)-1-isopropylazetidine hydrochloride (2.8g, 15.2mmol), 4-(4-hydroxyphenyl)tetrahydropyran-4-carbonitrile (3.1g, 15.2mmol) and potassium carbonate (8.5g, 61.6mmol) were combined in DMF (40ml) and stirred at 50° for 2 hours. Potassium iodide (0.5g 3.0mmol) was added and the mixture was stirred at 50° for 18 hours then at 90-95° for a further 5 hours. The reaction mixture was concentrated *in vacuo* then partitioned between ethyl acetate (80ml) and water (50ml). The ethyl acetate was washed with saturated NaCl (50ml) then dried over Na_2SO_4 and concentrated *in vacuo* to give a brown semi-crystalline material which was triturated with diisopropyl ether (25ml) to give the title compound as a beige powder (2.9g, 60%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.38 (d, 2H), 6.91 (d, 2H), 4.08 (m, 4H), 3.89 (m, 2H), 3.41 (t, 2H), 3.02 (t, 2H), 2.87 (m, 1H), 2.31 (m, 1H), 2.15-2.00 (m, 4H), 0.94 (d, 6H).

Example 274: 1-[4-[4-[(1-isopropylazetidin-3-yl)methoxy]phenyl]tetrahydro-2H-pyran-4-yl]methanamine

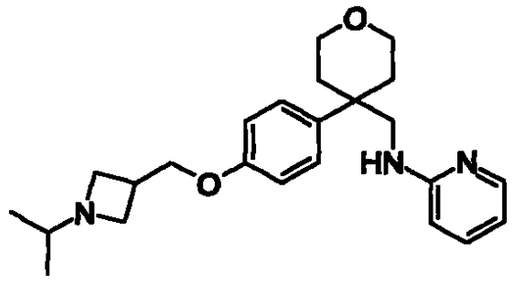


A solution of 4-[4-[(1-isopropylazetidin-3-yl)methoxy]phenyl]tetrahydro-2H-pyran-4-carbonitrile (1.8g, 5.73mmol) in THF (80ml) was cooled to 0°C under an atmosphere of nitrogen. A solution of lithium aluminium hydride (1.0M solution in Et_2O, 17ml, 17mmol) was added dropwise over 5 min. The mixture was stirred whilst warming to ambient temperature over 18 hours. The reaction was cooled to 0°C and quenched with water (0.5ml) then 2M NaOH (0.5ml) and then water (1.5ml). Celite® (3g) was added and the mixture stirred at ambient temperature for 0.5 hour. Diluted with ethyl acetate (50ml), filtered and concentrated *in vacuo* to give a colourless oil (1.8g). The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (97:3:0.3 to 88:12:1.2 by volume) to give the title compound as a white crystalline solid (1.55g, 85%).

^{1}H NMR (400MHz, $CDCl_3$) δ 7.18 (d, 2H), 6.89 (d, 2H), 4.18 (d, 2H), 3.77 (m, 2H), 3.54 (m, 2H), 3.41 (t, 2H), 3.02 (t, 2H), 2.88 (m, 1H), 2.75 (s, 2H), 2.31 (quintet, 1H), 2.11 (m, 2H), 1.80 (m, 2H), 0.95 (d, 6H).

LRMS ESI$^+$ m/z 319 $[M+H]^+$
HRMS ESI$^+$ m/z 319.2375 $[MH]^+$

Example 275: N-[(4-{4-[(1-isopropylazetidin-3-yl)methoxy]phenyl}tetrahydro-2H-pyran-4-yl)methyl]pyridin-2-amine

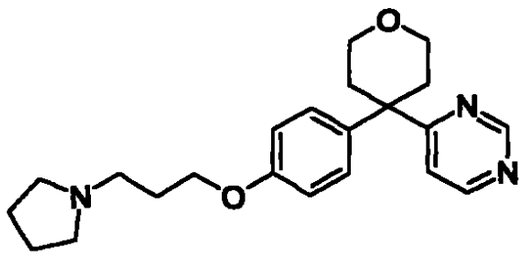


1-(4-{4-[(1-isopropylazetidin-3-yl)methoxy]phenyl}tetrahydro-2H-pyran-4-yl)methanamine was stirred with 2-bromopyridine (60µl, 0.63mmol), tris(dibenzylideneacetone)dipalladium(0) (15mg, 0.018mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (19mg, 0.036mmol) and sodium *tert*-butoxide (90mg, 0.94mmol) and heated at 80°C in toluene (5ml) for 3 hours under nitrogen. The reaction mixture was partitioned between aqueous sodium hydroxide (50ml) and ethyl acetate (50ml). The organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (97:3:0.3 to 90:10:1 by volume) to give the product which required further purification by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (96:4:0.4 to 94:6:0.6 by volume) to give a pale yellow oil which crystallized on standing, this was triturated with diethyl ether (2ml) to give the title compound as a pale yellow powder (65mg, 26%).
^{1}H NMR (400MHz, $CDCl_3$) δ 8.02 (d, 1H), 7.31 (t, 1H), 7.25 (d, 2H), 6.91 (d, 2H), 6.60 (t, 1H), 6.20 (d, 1H), 4.09 (d, 2H), 3.99 (t, 1H), 3.82 (m, 2H), 3.59 (m, 2H), 3.48 (d, 2H), 3.45 (m, 2H), 3.03 (m, 2H), 2.88 (m, 1H),2.33 (m, 1H), 2.13 (m, 2H), 1.92 (m, 2H), 0.93 (d, 6H).
LRMS ESI$^+$ m/z 396 $[M+H]^+$
HRMS ESI$^+$ m/z 396.2639 $[M+H]^+$

Intermediate 109: 1-[4-{4-(3-pyrrolidin-1-ylpropoxy)phenyl}tetrahydro-2H-pyran-4-yl]ethanone

To a solution of 4-[4-(3-Pyrrolidin-1-ylpropoxy)-phenyl]tetrahydropyran-4-carbonitrile (2.0g, 6.37mmol) in diethyl ether (30ml) and THF (5ml) was added methyl lithium/lithium bromide complex (1.5M solution in diethyl ether, 4.5ml, 6.75mmol), the reaction mixture was stirred at ambient temperature for 18 hours. The reaction mixture was quenched by adding water (5ml) and concentrated *in vacuo*. The residue was partitioned between DCM (100ml) and water (30ml), the organics were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a crude product which was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (98:2:0.2 to 92:8:0.8 by volume) to provide a colourless gum (500mg, 24%).
LRMS ESI$^+$ m/z 332 $[M+H]^+$

Example 276: 4-[4-{4-(3-pyrrolidin-1-ylpropoxy)phenyl}tetrahydro-2H-pyran-4-yl]pyrimidine



Step 1.

1-{4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}ethanone (500mg, 1.51mmol) was dissolved in dimethylformamide dimethylacetal (3ml) and heated in a sealed tube microwave reactor (Smiths Personal Synthesizer) at 150°C for 1800 seconds then at 170°C for 2400 seconds. The reaction mixture concentrated *in vacuo* to give a crude product (3-Dimethylamino-1-{4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl}propenone, 500mg) which was used without purification in the next step.

Step 2.

The crude intermediate was dissolved in ethanol (10ml), formamidine acetate (320mg, 3.07mmol) and sodium ethoxide (21% w/v solution in ethanol, 1.0ml, 3.09mmol) were added and the mixture stirred at ambient temperature for 1.5 hours then heated at 70°C for 2 hours. Formamidine acetate (500mg, 4.80mmol) was added and stirred at 70°C for 18 hours. Formamidine acetate (500mg, 4.80mmol) and potassium carbonate (2.0g, 14.5mmol) were added and stirred at reflux for 5 hours. Formamidine acetate (500mg, 4.80mmol) was added and stirred at reflux for 18 hours. The reaction mixture was partitioned between DCM (80ml) and 10% Na_2CO_3 (50ml), the organics were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a black solid. The crude product was purified by flash chromatography on silica gel eluting with dichloromethane:methanol:ammonia (100:0:0 to 94:6:0.6 by volume) to give the title compound as a brown oil (45mg, 8%).

^{1}H NMR (400MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.53 (d, 1H), 7.20 (d, 2H), 7.08 (d, 1H), 6.83 (d, 2H), 3.96 (t, 2H), 3.78 (m, 2H), 3.66 (m, 2H), 2.68-2.55 (m, 2H), 2.50 (m, 4H), 2.33 (m, 2H), 1.96 (m, 4H), 1.76 (m, 4H).

LRMS ESI$^+$ m/z 368 $[M+H]^+$

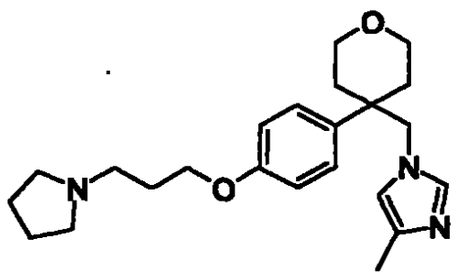
Intermediate 110: 4-methyl-1-({4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl}methyl)-1H-imidazole-2-thiol

2-Aminopropionaldehyde dimethyl acetal (0.2g, 1.7mmol), thiocarbonyldiimidazole (0.36g, 2.0mmol) and triethylamine (0.23ml, 1.7mmol) were stirred in DMF (2.0ml) at ambient temperature for 30 minutes before heating to 50°C for 18 hours. {4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydropyran-4-yl}methylamine (540mg, 1.7mmol) was added and stirred at ambient temperature for 4 hours. 2M HCl (6ml) was added, stirred at 70°C for 18 hours, then c.HCl (1.0ml) was added and the mixture stirred at 110°C for 18 hours. The reaction mixture was cooled and partitioned between ethyl acetate (100ml) and dilute aqueous sodium carbonate (50ml). The organics were dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound as a grey solid (600mg, 84%).

LRMS ESI$^+$ m/z 416 $[M+H]^+$

277

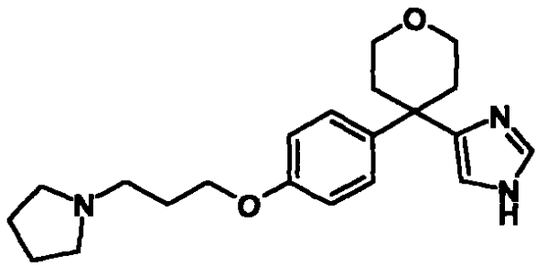
Example 277: 4-methyl-1-((4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazole



4-methyl-1-((4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl)methyl)-1H-imidazole-2-thiol (0.6g, 1.44mmol) was dissolved in ethanol (20mL), water (5mL) was added, and the mixture was cooled in ice. Raney nickel (4g) was added, the reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction mixture was filtered though Arbocel® and concentrated *in vacuo* to provide a brown oil. This was purified by flash chromatography on silica gel eluting with ethyl acetate:diethylamine (95:5) to provide the title compound (0.066, 16%) as a clear oil.

^{1}H NMR (400 MHz $CDCl_3$) δ 1.80-1.90 (m, 6H), 2.08-2.18 (m, 7H), 2.65-2.80 (m, 6H), 3.50 (t, 2H), 3.80 (m, 2H), 3.90 (s, 2H), 4.05 (t, 2H), 6.10 (s, 1H), 6.70 (s, 1H), 6.89 (d, 2H), 7.0 (d, 2H).
LRMS ESI$^+$ *m/z* 384 $[MH]^+$

Example 278: 4-[4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-yl]-1H-imidazole



Step 1:

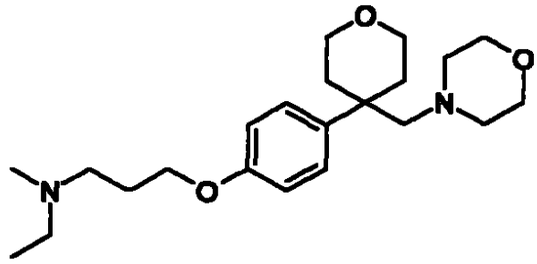
4-[4-(3-pyrrolidin-1-ylpropoxy)phenyl]tetrahydro-2H-pyran-4-carbaldehyde (500 mg, 1.6 mmol) and TosMIC (340 mg, 1.7 mmol) were dissolved in EtOH (20 ml), to which NaCN (12 mg, 0.25 mmol) was added. The solution immediately turned pale yellow and was allowed to stir for 2 hours at room temperature. The solvent was removed *in vacuo* and the residue was taken up in DCM (10 ml) and washed with saturated sodium bicarbonate solution (15 ml), followed by brine (15 ml). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford 5-[4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-yl]-4-(toluene-4-sulfonyl)-4,5-dihydro-oxazole as a pale brown foam (500 mg).
LRMS ESI$^+$ *m/z* 513 $[MH]^+$

Step 2:

The 5-[4-[4-(3-Pyrrolidin-1-yl-propoxy)-phenyl]-tetrahydro-pyran-4-yl]-4-(toluene-4-sulfonyl)-4,5-dihydro-oxazole (500 mg) was dissolved in EtOH saturated with ammonia (7ml) before heating in a bomb at 110°C for 18 hours. The solvent was removed *in vacuo* and the residue was taken up in DCM (10 ml) and washed with saturated sodium bicarbonate solution (15 ml), followed by brine (15 ml). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*, before purifying by column chromatography, eluting with a gradient of DCM:MeOH:NH_3 (from 99:1:0.1 to 90:10:1), but this failed to separate the product from a close running impurity. The residue was therefore purified using column chromatography a second time, eluting with an isocratic solution of cyclohexane:DCM:Et_2O:MeOH:NH_3 (10:5:3:2:0.2) to afford the title compound as a colourless solid (70 mg, 12%).

^{1}H NMR (400MHz, $CDCl_3$) δ 1.8 (m, 4H), 1.93-2.05 (m, 2H), 2.24-2.39 (m, 4H), 2.57 (m, 4H), 2.63 (t, 2H), 3.67 (m, 2H), 3.79 (m, 2H), 4.00 (t, 2H), 6.77 (s, 1H), 6.81 (d, 2H), 7.18 (d, 2H), 7.38 (s, 1H)
LRMS ESI$^+$ m/z 356 $[MH]^+$, 354 $[M-H^+]$

Example 279: 4-[4-(4-{3-[ethyl(methyl)amino]propoxy}phenyl)tetrahydro-2H-pyran-4-ylmethyl]-morpholine



Step 1:

A mixture of 4-[4-(3-chloro-propoxy)-phenyl]-tetrahydropyran-4-carbonitrile (3.0 g, 10.7 mmol), potassium iodide (100 mg, 0.60 mmol) and ethylmethylamine (5.0 ml, 58.3 mmol) in acetonitrile (30 mL) was heated to 60°C overnight. The mixture was cooled, concentrated *in vacuo* and partitioned between dilute Na_2CO_3 solution (40 ml) and ethyl acetate (80 ml). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the crude material was carried out with flash chromatography (silica gel, ethyl acetate/methanol/aqueous ammonia 98:2:0.2 to 85:15:1.5) to afford 4-(4-{3-[ethyl(methyl)amino]propoxy}phenyl)tetrahydro-2H-pyran-4-carbonitrile as a pale yellow oil (2.0 g, 6.6 mmol, 62%).

^{1}H NMR (400 MHz $CDCl_3$) δ 1.08 (t, 3H), 1.91-2.00 (m, 2H), 2.00-2.14 (m, 4H), 2.25 (s, 3H), 2.40-2.50 (m, 2H), 2.63 (t, 2H), 3.89 (m, 2H), 4.00-4.11 (m, 4H), 6.91 (d, 2H), 7.38 (d, 2H).
LRMS ESI$^+$ m/z 303 $[MH]^+$

Step 2:

Lithium aluminium hydride (9.93 ml of a 1M solution in tetrahydrofuran, 9.93 mmol) was added to a solution of 4-(4-{3-[ethyl(methyl)amino]propoxy}phenyl)tetrahydro-2H-pyran-4-carbonitrile (2.0 g, 6.6 mmol) in tetrahydrofuran (10 ml) at 0°C under N_2. The reaction mixture was warmed to room temperature over 18 h and then quenched by the sequential addition of water (0.4 ml), 2M NaOH solution (0.4 ml) and water (0.4 ml). The mixture was filtered through arbocel and concentrated *in vacuo* to yield 3-[4-[4-

(aminomethyl)tetrahydro-2H-pyran-4-yl]phenoxy}-N-ethyl-N-methylpropan-1-amine as a pale yellow oil (1.93 g, 6.3 mmol, 95%).

^{1}H NMR (400 MHz $CDCl_3$) δ 1.02-1.08 (t, 3H), 1.73-1.83 (m, 2H), 1.90-2.00 (m, 2H), 2.06-2.16 (m, 2H), 2.23 (s, 3H), 2.40-2.48 (q, 2H), 2.50-2.58 (t, 2H), 2.75 (s, 2H), 3.48-3.58 (m, 2H), 3.70-3.80 (m, 2H), 3.98-4.04 (t, 2H), 6.89 (d, 2H), 7.19 (d, 2H).

LRMS APCI$^+$ m/z 307 $[MH]^+$

Step 3:

To a stirred solution of 3-{4-[4-(aminomethyl)tetrahydro-2H-pyran-4-yl]phenoxy}-N-ethyl-N-methylpropan-1-amine (500 mg, 1.6 mmol) and bis(2-bromoethyl)ether (345 mg, 1.5 mmol) in anhydrous acetonitrile (50 mL) was added potassium carbonate (450 mg, 3.3 mmol). The mixture was heated to 60°C overnight then concentrated *in vacuo*. The crude product was partitioned between dichloromethane (50 ml) and water (50 ml), the aqueous phase was extracted with dichloromethane (25 ml) and the combined organics were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the crude material was carried out with flash chromatography (silica gel, dichloromethane/methanol/aqueous ammonia 100:0:0 to 96:4:0.4) to afford the title compound as a clear colourless oil (315 mg, 0.84 mmol, 52%).

^{1}H NMR (400 MHz $CDCl_3$) δ 1.05 (t, 3H), 1.82-1.93 (m, 2H), 1.92-2.00 (m, 2H), 2.06-2.20 (m, 6H), 2.25 (s, 3H), 2.39 (s, 2H), 2.40-2.50 (q, 2H), 2.50-2.59 (m, 2H), 3.48-3.60 (m, 6H), 3.70-3.80 (m, 2H), 4.00 (t, 2H), 6.86 (d, 2H), 7.20 (d, 2H).

LRMS APCI$^+$ m/z 377 $[MH]^+$

HRMS ESI$^+$ m/z 377.2792 $[MH]^+$

<u>H_3 Cell Based Functional Assay</u>

Compounds were evaluated using a cell based functional assay measuring cAMP through β-lactamase reporter gene activity. A stable cell line was generated from HEK-293 cells expressing a CRE β-lactamase reporter gene and transfected with human histamine H_3 receptor cDNA. Cells were seeded at a density of 500,000 cells/ml, and grown overnight in MEM (Invitrogen) supplemented with 1% dialysed FBS (Sigma), 2mM glutamine (Sigma), 1mM sodium pyruvate (Sigma), 0.1mM non essential amino acids (Invitrogen) and 25mM HEPES (Sigma) in poly D lysine coated 384 well plates (BD Biosciences). H_3 receptor agonist imetit (Tocris) dose dependently inhibited 10μM forskolin (Calbiochem) stimulated synthesis of cAMP measured after 4.5hours by β-lactamase cleavage of CCF4-AM dye (Invitrogen). For IC_{50} determination, test compounds were prepared in PBS (Sigma) and DMSO (Sigma) at a dose response of $5x10^{-10}$ to $5x10^{-5}$M with a final DMSO concentration in the assay of 0.5%. Cells were incubated for 15 minutes plus/minus compound and their ability to permit 10μM forskolin-stimulated cAMP synthesis in the presence of 1nM imetit was measured as described above. Functional K_i values were calculated from the IC_{50} of compounds tested as antagonists based on an experimentally determined imetit EC_{80} (represented in the equation as K_d) of 350pM, and an imetit concentration [L] of 1nM, according to the Cheng-Prussoff equation where $K_i = (IC_{50})/(1+([L]/K_d))$.

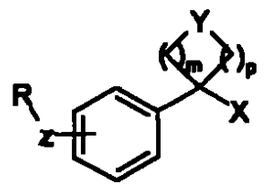
All the examples were tested in the assay described above and found to have a K_i value of less than 5 μM. Most of the examples have a K_i value of less than 100 nM.

The data for some of said preferred compounds are given below by way of example:

Example Number	K_i (H3 cell based assay – nM)	Example Number	K_i (H3 cell based assay – nM)	Example Number	K_i (H3 cell based assay – nM)
29	0.4	190	2.4	249	9.7
133	12.4	191	10.3	250	4.8
136	3.9	196	0.6	254	1.3
156	1.0	205	5.8	266	9.7
158	2.0	208	12.9	267	5.8
160	1.5	213	2.6	268	6.5
187	7.3	220	2.2	276	8.2
188	6.8	247	3.9	272	10.8
189	14.3	248	0.3		

CLAIMS

1. A compound of the formula (1) :



(1)

or a pharmaceutically acceptable salt and/or solvate (including hydrate) thereof wherein :

the substituent of formula –Z-R is in the meta or para position of the phenyl group;

X is selected from -CN, $-CH_2OH$, $-CH_2-O-(C_1-C_4)$alkyl, $-C(O)OH$, $-C(O)O(C_1-C_4)$alkyl, $-CH_2-NR^1R^2$, $-C(O)NR^3R^4$, $-CH_2-O$-het^2, $-CH_2$-het^1 and het^1, the group het^1 in both $-CH_2$-het^1 and het^1 being optionally substituted by one or two substituents independently selected from halo, cyano, (C_1-C_4)alkyl, -S-(C_1-C_4)alkyl and (C_1-C_4)alkoxy;

R^1 is hydrogen or (C_1-C_4)alkyl optionally substituted by (C_3-C_8)cycloalkyl;

R^2 is selected from the group consisting of :

hydrogen,

(C_1-C_8)alkyl optionally substituted by one or two substituents independently selected from (C_3-C_8)cycloalkyl, hydroxy, -S-(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, $-SO_2-(C_1-C_4)$alkyl, -SO-(C_1-C_4)alkyl, halo, het^1, amino, (C_1-C_4)alkylamino, $[(C_1-C_4)alkyl]_2$amino and phenyl, said phenyl being optionally substituted by one or two substituents independently selected from halo, hydroxy, cyano, (C_1-C_4)alkyl and (C_1-C_4)alkoxy,

(C_3-C_8)cycloalkyl,

het^2, optionally substituted by one or two substituents independently selected from halo, cyano, (C_1-C_4)alkyl, NH_2 and (C_1-C_4)alkoxy,

$-SO_2-R^5$ wherein R^5 is selected from the group consisting of (C_1-C_4)alkyl, amino, (C_1-C_4)alkylamino, $[(C_1-C_4)alkyl]_2$amino, phenyl and $-(C_1-C_4)$alkyl-phenyl, said phenyl being optionally substituted by one or two substituents independently selected from halo, cyano, (C_1-C_4)alkyl and (C_1-C_4)alkoxy, and

$-C(O)-R^6$ wherein R^6 is selected from the group consisting of (C_1-C_4)alkyl, amino, (C_1-C_4)alkylamino, $[(C_1-C_4)alkyl]_2$amino, phenyl and $-(C_1-C_4)$alkyl-phenyl, said phenyl being optionally substituted by one or two substituents independently selected from halo, cyano, (C_1-C_4)alkyl and (C_1-C_4)alkoxy;

or R^1 and R^2 form together with the N atom to which they are attached a 3-, 4-, 5-, 6- or 7-membered saturated heterocycle wherein one C atom may be replaced by N, O, S, SO or SO_2 and wherein said saturated heterocycle is optionally substituted by one or two groups independently selected from hydroxy,

halo, =O, (C_1-C_4)alkyl, -(C_1-C_4)alkyl(C_3-C_8)cycloalkyl, (C_1-C_4)alkoxy, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, -$SO_2(C_1-C_4)$alkyl, -C(O)(C_1-C_4)alkyl, [(C_1-C_4)alkyl]$_2$amino, amino, (C_1-C_4)alkylamino, -C(O)NH_2, C(O)O(C_1-C_4)alkyl and pyrrolidinone;

R^3 and R^4 are each independently selected from hydrogen, (C_3-C_8)cycloalkyl, and (C_1-C_4)alkyl, said (C_3-C_8)cycloalkyl and (C_1-C_4)alkyl being optionally substituted by amino, (C_1-C_4)alkylamino, [(C_1-C_4)alkyl]$_2$amino or (C_3-C_8)cycloalkyl, or R^3 and R^4 form together with the N atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocycle wherein one C atom may be replaced by N or O and wherein said saturated heterocycle is optionally substituted by (C_1-C_4)alkyl, [(C_1-C_4)alkyl]$_2$amino, amino, (C_1-C_4)alkylamino, or –C(O)(C_1-C_4)alkyl, said –C(O)(C_1-C_4)alkyl being optionally substituted by methoxy or ethoxy,

Y is selected from CH_2, CH(OH), O, C=O and N, said N being substituted by H, (C_1-C_4)alkyl, C(O)(C_1-C_4)alkyl or (C_1-C_4)alkoxy(C_1-C_4)alkyl;

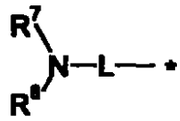
Z is selected from O, S, SO and SO_2;

m and p are both integers which are independently 1, 2 or 3, with the condition that m+p is equal to or less than 4 so that the ring formed by :

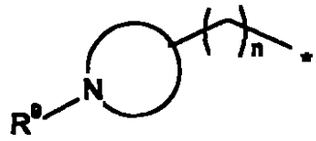


is a 4-, 5- or 6-membered ring;

and R is either a group of formula :



wherein * represents the attachment point to Z, L is a straight chain or branched (C_2-C_8)alkylene and R^7 and R^8 are each independently selected from hydrogen, (C_1-C_8)alkyl, (C_3-C_8)cycloalkyl, hydroxy(C_1-C_8)alkyl or R^7 and R^8 form together with the N atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocycle wherein one C atom is optionally replaced by N, O, S, SO or SO_2 and wherein said saturated heterocycle is optionally substituted by one or two groups independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkoxy(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, hydroxy, C(O)O(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl-NH_2, -C(O)NH_2, halo, amino, (C_1-C_4)alkylamino and [(C_1-C_4)alkyl]$_2$amino,
or R is a group of formula:



wherein * represents the attachment point to Z, the N-containing ring is a 4- to 7-membered saturated heterocycle, n is an integer equal to 0, 1 or 2, and R^9 represents a substituent selected from hydrogen, (C_1-C_4)alkyl, hydroxy$(C_1-C_6$ alkyl) and (C_3-C_6)cycloalkyl;

het^1 is selected from monocyclic or bicyclic heteroaromatic groups having 5 to 10 ring members, which contain 1, 2, 3 or 4 heteroatom(s) selected from nitrogen, oxygen and sulphur and het^2 is selected from monocyclic or bicyclic heteroaromatic groups having 5 to 10 ring members, which contain 1, 2, 3 or 4 heteroatom(s) selected from nitrogen, oxygen and sulphur.

2. A compound of formula (1) as defined in claim 1, wherein X is selected from $-CH_2-NR^1R^2$, $-C(O)NR^3R^4$, $-CH_2-het^1$ and het^1, het^1 being optionally substituted once or twice by (C_1-C_4)alkyl, wherein R^1, R^2, R^3, R^4 and het^1 are as previously defined in claim 1.

3. A compound of formula (1) as defined in claim 2, wherein X is $-CH_2-het^1$ or het^1, and het^1 is selected from a 5 or 6 membered monocyclic heteroaromatic group or a 9 membered bicyclic heteroaromatic group, each heteroaromatic group containing 1 to 3 nitrogen atoms, or 1 to 2 nitrogen atoms and 1 oxygen atom, or 1 nitrogen atom and 1 sulphur atom, and each heteroaromatic group being optionally substituted once or twice by (C_1-C_4)alkyl.

4. A compound of formula (1) as defined in claim 3, wherein X is thiazolyl, benzimidazolylmethyl-, pyridinyl, oxazolyl, imidazopyridinylmethyl-, pyrimidinyl, imidazolyl, imidazolylmethyl- or triazolylmethyl-, said thiazolyl, benzimidazolylmethyl-, pyridinyl, oxazolyl, imidazopyridinylmethyl-, pyrimidinyl, imidazolyl, imidazolylmethyl- and triazolylmethyl- each being optionally substituted with one methyl group.

5. A compound of formula (1) as defined in claim 1 or claim 2, wherein R^1 is hydrogen, methyl or ethyl.

6. A compound of formula (1) as defined in claim 1, claim 2 or claim 5, wherein R^2 is selected from the group consisting of

hydrogen,

(C_1-C_6)alkyl optionally substituted by one or two substituents independently selected from $-S-(C_1-C_4)$alkyl, $-O-(C_1-C_4)$alkyl, $-SO_2-(C_1-C_4)$alkyl, and phenyl, said phenyl being optionally substituted by one or two substituents independently selected from halo, hydroxy, cyano, (C_1-C_4)alkyl and (C_1-C_4)alkoxy,

(C_3-C_6)cycloalkyl,

het^2 optionally substituted by one or two substituents independently selected from halo, cyano, (C_1-C_4)alkyl and (C_1-C_4)alkoxy, wherein het^2 is defined as in claim 1,

$-SO_2-R^5$ wherein R^5 is selected from the group consisting of (C_1-C_4)alkyl, $[(C_1-C_4)alkyl]_2$amino, phenyl, and $-(C_1-C_4)$alkyl-phenyl, wherein said phenyl is optionally substituted by 1 substituent independently selected from halo and cyano and

$-C(O)-R^6$ wherein R^6 is selected from the group consisting of (C_1-C_4)alkyl, $((C_1-C_4)alkyl]_2$amino, amino, and $-(C_1-C_4)$alkyl-phenyl, said phenyl being optionally substituted by one or two substituents independently selected from halo, cyano, (C_1-C_4)alkyl and (C_1-C_4)alkoxy.

7. A compound of formula (1) as defined in claim 6, wherein R^2 is selected from the group consisting of
(C_1-C_3)alkyl optionally substituted by $-O-(C_1-C_3)$alkyl,
(C_3-C_6)cycloalkyl,
het^2, wherein het^2 is selected from the group consisting of 5 or 6 membered monocyclic heteroaromatic groups containing 1 to 2 nitrogen atoms or 1 nitrogen atom and 1 oxygen atom or 1 nitrogen atom and 1 sulphur atom, said het^2 being optionally substituted by (C_1-C_4)alkyl,
SO_2-R^6 wherein R^6 is (C_1-C_4)alkyl and
$C(O)-R^6$ wherein R^6 is (C_1-C_4)alkyl.

8. A compound of formula (1) as defined in claim 7, wherein R^2 is (C_1-C_3)alkyl optionally substituted by methoxy.

9. A compound of formula (1) as defined in claim 7, wherein R^2 is het^2, and het^2 is selected from the group consisting of 5 or 6 membered monocyclic heteroaromatic groups containing 1 or 2 nitrogen atoms.

10. A compound of formula (1) as defined in claim 9, wherein R^2 is a pyridazinyl group.

11. A compound of formula (1) as defined in claim 1 or claim 2, wherein R^1 and R^2 form together with the N atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocycle wherein one C atom may be replaced by N, O, S, SO or SO_2 and wherein said saturated heterocycle is optionally substituted by one or two groups independently selected from hydroxy, halo, =O, (C_1-C_4)alkyl, $-(C_1-C_4)$alkyl(C_3-C_6)cycloalkyl, (C_1-C_4)alkoxy, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy(C_1-C_4)alkyl, $-SO_2(C_1-C_4)$alkyl, $-C(O)(C_1-C_4)$alkyl, $[(C_1-C_4)alkyl]_2$amino, $-C(O)NH_2$, $C(O)O(C_1-C_4)$alkyl and pyrrolidinone.

12. A compound of formula (1) as defined in claim 11, wherein R^1 and R^2 form together with the N atom to which they are attached a morpholinyl group.

13. A compound of formula (1) as defined in claim 1 or claim 2, wherein R^3 and R^4 are each independently selected from hydrogen and (C_1-C_4)alkyl or R^3 and R^4 form together with the N atom to which they are attached a 4, 5 or 6 membered saturated heterocycle wherein one C atom may be replaced by N or O and wherein said saturated heterocycle is optionally substituted by (C_1-C_4)alkyl.

14. A compound of formula (1) as defined in claim 13, wherein R^3 and R^4 are selected independently from hydrogen, methyl and ethyl, or R^3 and R^4 form together with the N atom to which they are attached a pyrrolidinyl, piperidinyl, piperazinyl or azetidinyl ring, each pyrrolidinyl, piperidinyl, piperazinyl and azetidinyl ring being optionally methyl substituted.

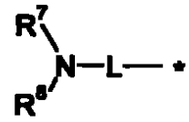
15. A compound of formula (1) as defined in any one of the preceding claims, wherein Y is selected from CH_2, CH(OH), O and C=O.

16. A compound of formula (1) as defined in claim 15, wherein Y is O.

17. A compound of formula (1) as defined in any one of the preceding claims, wherein Z is O.

18. A compound of formula (1) as defined in any one of the preceding claims, wherein m and p are both 2.

19. A compound of formula (1) as defined in any one of the preceding claims, wherein R is a group of formula :



wherein * represents the attachment point to Z, L is a (C_2-C_3)alkylene and R^7 and R^8 are each independently selected from hydrogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl or R^7 and R^8 form together with the N atom to which they are attached a 4-, 5-, 6- or 7-membered saturated heterocycle wherein one C atom is optionally replaced by N, O, S, SO or SO_2 and wherein said saturated heterocycle is optionally substituted by one or two groups independently selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkoxy(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, hydroxy, C(O)O(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl-NH_2, -C(O)NH_2 and halo.

20. A compound of formula (1) as defined in claim 19, wherein R^7 and R^8 form together with the N atom to which they are attached a morpholinyl or oxazepanyl group.

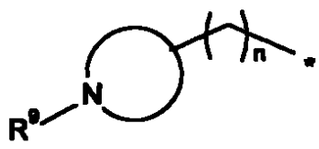
21. A compound of formula (1) as defined in claim 19, wherein R^7 and R^8 form together with the N atom to which they are attached a 4-, 5- or 6-membered saturated heterocycle, optionally substituted by one or two (C_1-C_4)alkyl groups.

22. A compound of formula (1) as defined in claim 21, wherein the saturated heterocycle is a pyrrolidinyl group, optionally substituted by one or two methyl groups.

23. A compound of formula (1) as defined in claim 19, wherein R^7 and R^8 are (C_1-C_3)alkyl.

24. A compound of formula (1) as defined in any one of claims 19 to 23, wherein L is propylene.

25. A compound of formula (1) as defined in any one of claims 1 to 18, wherein R is a group of formula :



wherein * represents the attachment point to Z, the N-containing ring is a 4- or 6-membered saturated heterocycle, n is an integer equal to 0 or 1, and R^8 represents a substituent selected from hydrogen, (C_1-C_4)alkyl and (C_3-C_6)cycloalkyl.

26. A compound of formula (1) as defined in claim 25, wherein R^8 is isopropyl or cyclobutyl.

27. A compound of formula (1) as defined in any one of the Examples herein.

28. A pharmaceutical composition including a compound of the formula (1) or a pharmaceutically acceptable salt and/or solvate thereof, as defined in any one of the preceding claims, together with a pharmaceutically acceptable excipient.

29. A compound of the formula (1) as defined in any one of claims 1 to 27 or a pharmaceutically acceptable salt and/or solvate thereof, for use as a medicament.

30. The use of a compound of the formula (1) as defined in any one of claims 1 to 27 or of a pharmaceutically acceptable salt and/or solvate thereof, for the manufacture of a medicament to treat a disease for which a H_3 ligand is indicated.

31. The use of a compound of the formula (1) according to claim 30, for the manufacture of a medicament for the treatment of sleep disorders, migraine, dyskinesia, stress-induced anxiety, psychotic disorders, epilepsy, Cognition deficiency diseases such as Alzheimer's disease or mild cognitive impairment, depression, mood disorders, schizophrenia, anxiety disorders, attention-deficit hyperactivity disorder (ADHD), psychotic disorders, obesity, dizziness, vertigo, epilepsy, motion sickness, inflammatory diseases, adult respiratory distress syndrome, acute respiratory distress syndrome, bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis, chronic sinusitis, allergy, allergy-induced airway responses, allergic rhinitis, viral rhinitis, non-allergic rhinitis, perennial and seasonal rhinitis, nasal congestion, allergic congestion, male sexual dysfunction or female sexual dysfunction.

32. A method of treatment of a mammal, including a human being, suffering from a disease for which a H_3 ligand is indicated, comprising administering to said mammal an effective amount of a compound of the formula (1) as defined in any one of claims 1 to 27 or a pharmaceutically acceptable salt and/or solvate thereof, or composition thereof.

33. A combination of a compound of formula (1) as defined in any one of claims 1 to 27, and another pharmacologically active agent.

34. A combination as claimed in claim 33, wherein the other pharmacologically active agent is a histamine H_1 receptor antagonist.

35. A compound of the formula (1) as defined in any one of claims 1 to 27 or a pharmaceutically acceptable salt and/or solvate thereof, for use as described in claim 30 or 31.

INTERNATIONAL SEARCH REPORT

PCT/IB2005/001114

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D309/06 C07D405/12 C07D309/08 C07D295/12 C07D405/06
C07D405/14 C07D295/14 C07D417/04 C07D417/06 A61K31/55
A61P25/06 C07D405/14 C07D405/06 C07D405/12 C07D405/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/06223 A (ABBOTT LAB) 24 January 2002 (2002-01-24) cited in the application Abstract; claims.	1-35
A	WO 02/12190 A (ORTHO MCNEIL PHARM INC) 14 February 2002 (2002-02-14) cited in the application Abstract; page 4, lines 14-15; pages 137-139, biological methods; claims.	1-35
A	WO 02/076925 A (BEAVERS LISA SELSAM ; SCHAUS JOHN MEHNERT (US); WATSON BRIAN MORGAN (U) 3 October 2002 (2002-10-03) cited in the application Abstract; claims; page 111, example 141.	1-35

-/--

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in 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
25 July 2005	03/08/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Weisbrod, T

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 269 363 A (CHEMINOVA AS) 1 June 1988 (1988-06-01) Abstract; claims; pages 26-27, examples 168-170.	1-35
A	DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002300332 Database Accession No. 5690069 (Citation No.). & Z. CHEM., vol. 20, no. 8, 1980, pages 298-299,	1-35
A	DE 30 24 836 A1 (A. NATTERMANN & CIE GMBH) 28 January 1982 (1982-01-28) Abstract; claims; page 4, paragraph 2; examples.	1-35

ZC4 225

INTERNATIONAL SEARCH REPORT

PCT/IB2005/001114

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 32 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

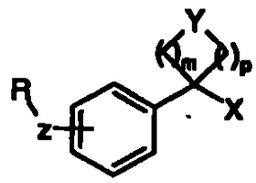
INTERNATIONAL SEARCH REPORT

PCT/IB2005/001114

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0206223 A	24-01-2002	AU 7338401 A	30-01-2002
		BR 0108088 A	06-04-2004
		CA 2415396 A1	24-01-2002
		EP 1301480 A1	16-04-2003
		JP 2004509076 T	25-03-2004
		MX PA02012851 A	05-09-2003
		WO 0206223 A1	24-01-2002
WO 0212190 A	14-02-2002	US 2002040024 A1	04-04-2002
		AU 8111901 A	18-02-2002
		AU 8112101 A	18-02-2002
		AU 8473301 A	18-02-2002
		BR 0113161 A	06-04-2004
		BR 0113162 A	06-04-2004
		CA 2418369 A1	14-02-2002
		CA 2419027 A1	14-02-2002
		CA 2419036 A1	14-02-2002
		CN 1468221 A	14-01-2004
		CN 1468227 A	14-01-2004
		CZ 20030685 A3	13-08-2003
		CZ 20030686 A3	13-08-2003
		EP 1311499 A2	21-05-2003
		EP 1311482 A2	21-05-2003
		EP 1313721 A2	28-05-2003
		HU 0302893 A2	29-12-2003
		HU 0302959 A2	29-12-2003
		JP 2004511438 T	15-04-2004
		JP 2004505960 T	26-02-2004
		MX PA03001267 A	30-07-2004
		PL 360373 A1	06-09-2004
		PL 360886 A1	20-09-2004
		WO 0212224 A2	14-02-2002
		WO 0212214 A2	14-02-2002
		WO 0212190 A2	14-02-2002
		US 2002037896 A1	28-03-2002
		US 2002065278 A1	30-05-2002
		ZA 200301853 A	21-06-2004
		ZA 200301854 A	21-06-2004
WO 02076925 A	03-10-2002	CA 2441080 A1	03-10-2002
		EP 1379493 A2	14-01-2004
		JP 2004532834 T	28-10-2004
		WO 02076925 A2	03-10-2002
EP 0269363 A	01-06-1988	DK 368687 A	22-05-1988
		AU 8278687 A	16-06-1988
		BR 8707539 A	21-02-1989
		WO 8803756 A1	02-06-1988
		EP 0269363 A2	01-06-1988
		JP 1501393 T	18-05-1989
		NO 883244 A	21-07-1988
DE 3024836 A1	28-01-1982	NONE	

DERIVADOS DE FENOL Y TIOFENOL 3- O 4-MONOSUSTITUIDOS ÚTILES COMO LIGANDOS DE H3

La presente invención se refiere a derivados de fenol y tiofenol 3- ó 4- monosustituidos de fórmula general:



(1)

en la que R, X, Y, Z, m y p tienen los significados que se indican a continuación,

y a procedimientos para la preparación de, a intermedios usados en la preparación de, a composiciones que contienen y a los usos de, tales derivados.

Los receptores de histamina H_3 se encuentran entre otros en las terminaciones presinápticas de los nervios periféricos, donde modulan la neurotransmisión autónoma y modulan diversas respuestas de órganos finales bajo el control del sistema nervioso autónomo. También son heterorreceptores, modulando la liberación de otros diversos neurotransmisores tales como dopamina, glutamato, noradrenalina, serotonina, GABA, acetilcolina, algunos péptidos y co-transmisores.

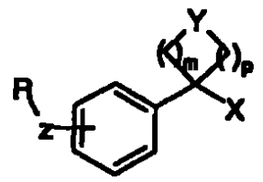
Recientemente, se han desarrollado diversos ligandos del receptor de la histamina H_3. En *Expert Opin. Ther. Patents* (2003) 13(6) se proporciona un análisis del avance actual en la investigación y las patentes sobre ligandos de H_3. En los documentos WO02/76925, WO00/06254, WO02/12190, 102/12214 y WO02/06223 pueden encontrarse ejemplos de ligandos del receptor de

histamina H_3.

Se cree que los ligandos del receptor de H_3 son adecuados para el tratamiento de diversas enfermedades incluyendo tanto trastornos del sistema nervioso central como trastornos inflamatorios. Son ejemplos de enfermedades en las que se cree que es útil el tratamiento con ligandos de H_3 la enfermedad inflamatoria del intestino, enfermedad de Crohn, colitis ulcerosa, trastornos del sueño, migraña, disquinesia, ansiedad inducida por estrés, trastornos psicóticos, epilepsia, enfermedades por deficiencia cognitiva tales como la enfermedad de Alzheimer o leve deterioro cognitivo, depresión, trastornos del estado emocional, esquizofrenia, trastornos de ansiedad, trastorno por déficit de atención con hiperactividad (ADHD), trastornos psicóticos, obesidad, mareos, epilepsia, enfermedad del movimiento, vértigo, enfermedades respiratorias tales como síndrome de insuficiencia respiratoria en adultos, síndrome de insuficiencia respiratoria aguda, bronquitis, bronquitis crónica, enfermedad pulmonar obstructiva crónica, fibrosis quística, asma, enfisema, rinitis, sinusitis crónica, alergia, respuestas de las vías respiratorias inducidas por alergia, rinitis alérgica, rinitis vírica, rinitis no alérgica, rinitis perenne y estacional, congestión nasal y congestión alérgica.

Aunque se conocen ligandos de H_3 todavía sigue existiendo la necesidad de proporcionar nuevos ligandos de H_3 que sean buenos candidatos a fármacos. En particular, los compuestos preferidos deben unirse fuertemente al receptor de la histamina H_3 al tiempo que muestran poca afinidad por otros receptores. Todos deben absorberse bien desde el tracto gastrointestinal, deben ser metabólicamente estables y tener propiedades farmacocinéticas favorables. No deben ser tóxicos y deben mostrar pocos efectos secundarios.

En este contexto, la presente invención se refiere a nuevos derivados de fenol y tiofenol sustituidos de fórmula general (1):



(1)

o a una sal farmacéuticamente aceptable y/o del mismo donde:

el sustituyente de fórmula -Z-R está en la posición meta o para del grupo fenilo;

X se selecciona entre -CN, $-CH_2OH$, $-CH_2$-O-alquilo (C_1-C_4), -C(O)OH, -C(O)Oalquilo (C_1-C_4), $-CH_2-NR^1R^2$, $-C(O)NR^3R^4$, $-CH_2$-O-het^2, $-CH_2-het^1$ y het^1, estando el grupo het^1 tanto en $-CH_2-het^1$ como en het^1 opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, ciano, alquilo (C_1-C_4), -S-alquilo (C_1-C_4) y alcoxi(C_1-C_4);

R^1 es hidrógeno o alquilo (C_1-C_4) opcionalmente sustituido con cicloalquilo (C_3-C_8);

R^2 se selecciona entre el grupo compuesto por:

hidrógeno,

alquilo (C_1-C_8)opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre cicloalquilo (C_3-C_8), hidroxi, -S-alquilo (C_1-C_4), -O-alquilo (C_1-C_4), $-SO_2$-alquilo (C_1-C_4), -SO-alquilo (C_1-C_4), halo, het^1, amino, alquil (C_1-C_4)amino [alquil (C_1-C_4)]$_2$amino y fenilo, estando dicho fenilo opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, hidroxi, ciano, alquilo (C_1-C_4) y alcoxi(C_1-C_4),

cicloalquilo (C_3-C_8),

het^2, opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, ciano, alquilo (C_1-C_4), NH_2 y alcoxi(C_1-C_4),

-SO_2-R^5 donde R^5 se selecciona entre el grupo compuesto por alquilo (C_1-C_4), amino, alquil (C_1-C_4)amino, [alquil (C_1-C_4)]$_2$amino, fenilo y -alquil (C_1-C_4)-fenilo, estando dicho fenilo opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, ciano, alquilo (C_1-C_4) y alcoxi(C_1-C_4), y

-C(O)-R^6 donde R^6 se selecciona entre el grupo compuesto por alquilo (C_1-C_4), amino, alquil (C_1-C_4)amino, [alquil (C_1-C_4)]$_2$amino, fenilo y -alquil (C_1-C_4)-fenilo, estando dicho fenilo opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, ciano, alquilo (C_1-C_4) y alcoxi(C_1-C_4);

o R^1 y R^2 forman conjuntamente con el átomo de N al que están unidos un heterociclo saturado de 3, 4, 5, 6 ó 7 miembros donde un átomo de C puede reemplazarse por N, O, S, SO o SO_2 y donde dicho heterociclo saturado está opcionalmente sustituido con uno o dos grupos seleccionados independientemente entre hidroxi, halo, =O, alquilo (C_1-C_4), -alquil (C_1-C_4)cicloalquilo (C_3-C_8), alcoxi(C_1-C_4), hidroxialquilo (C_1-C_4), alcoxi(C_1-C_4)alquilo (C_1-C_4), -SO_2alquilo (C_1-C_4), -C(O)alquilo (C_1-C_4), [alquil (C_1-C_4)]$_2$amino, amino, alquil (C_1-C_4)amino, -$C(O)NH_2$, C(O)Oalquilo (C_1-C_4) y pirrolidinona;

Cada uno de R^3 y R^4 se selecciona independientemente entre hidrógeno, cicloalquilo (C_3-C_8), y alquilo (C_1-C_4), estando dicho cicloalquilo (C_3-C_8) y alquilo (C_1-C_4) opcionalmente sustituido con amino, alquil (C_1-C_4)amino,

[alquil (C_1-C_4)]$_2$amino o cicloalquilo (C_3-C_6), o R^3 y R^4 forman junto con el átomo de N al que están unidos un heterociclo saturado de 4, 5, 6 ó 7 miembros donde un átomo de C puede reemplazarse por N u O y donde dicho heterociclo saturado está opcionalmente sustituido con alquilo (C_1-C_4), [alquil (C_1-C_4)]$_2$amino, amino, alquil (C_1-C_4)amino, o -C(O)alquilo (C_1-C_4), estando dicho -C(O)alquilo (C_1-C_4) opcionalmente sustituido con metoxi o etoxi,

Y se selecciona entre CH_2, CH(OH), O, C=O y N, estando dicho N sustituido con H, alquilo (C_1-C_4), C(O)alquilo (C_1-C_4) o alcoxi (C_1-C_4)alquilo (C_1-C_4);

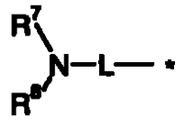
Z se selecciona entre O, S, SO y SO_2;

m y p son ambos números enteros que son independientemente 1, 2 ó 3, con la condición de que m+p sea igual a o menor que 4 de forma que el anillo formado por:



sea un anillo de 4, 5 ó 6 miembros;

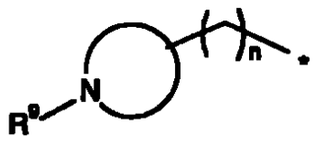
y R es un grupo de fórmula:



en la que * representa el punto de unión a Z, L es un alquileno (C_2-C_6) de cadena lineal o ramificada y cada uno de R^7 y R^8 se selecciona independientemente entre hidrógeno, alquilo (C_1-C_6), cicloalquilo (C_3-C_6), hidroxialquilo (C_1-C_6) o R^7 y R^8 forman junto con el átomo de N al que están unidos un heterociclo saturado de 4, 5, 6 ó 7 miembros donde un átomo de C

está opcionalmente reemplazado por N, O, S, SO o SO_2 y donde ducho heterociclo saturado está opcionalmente sustituido con uno o dos grupos seleccionados independientemente entre alquilo (C_1-C_4), alcoxi (C_1-C_4), alcoxi (C_1-C_4)-alquilo (C_1-C_4), hidroxialquilo (C_1-C_4), hidroxi, C(O)Oalquilo (C_1-C_4), -C(O)-alquil (C_1-C_4)-NH_2, -$C(O)NH_2$, halo, amino, alquil (C_1-C_4)amino y [alquil (C_1-C_4)]$_2$amino,

o R es un grupo de fórmula:



en la que * representa el punto de unión a Z, el anillo que contiene N es un heterociclo saturado de 4 a 7 miembros, n es un número entero igual a 0, 1 ó 2, y R^9 representa un sustituyente seleccionado entre hidrógeno, alquilo (C_1-C_4), hidroxi(alquilo C_1-C_6) y cicloalquilo (C_3-C_6);

het^1 se selecciona entre grupos heteroaromáticos monocíclicos o bicíclicos que tienen de 5 a 10 miembros en el anillo, que contienen 1, 2, 3 ó 4 heteroátomo(s) seleccionado(s) entre nitrógeno, oxígeno y azufre y het^2 se selecciona entre grupos heteroaromáticos monocíclicos o bicíclicos que tienen de 5 a 10 miembros en el anillo, que contienen 1, 2, 3 ó 4 heteroátomo(s) seleccionado(s) entre nitrógeno, oxígeno y azufre.

Se ha descubierto que estos compuestos son ligandos de H3 y por tanto son particularmente útiles para el tratamiento de enfermedades relacionadas con H3 tales como trastornos neurológicos o enfermedades, trastornos y afecciones inflamatorias, respiratorias y alérgicas.

En la descripción se usan las siguientes definiciones, a menos que se

especifique otra cosa.

"halo" indica un átomo de halógeno seleccionado entre el grupo compuesto por fluoro, cloro, bromo y yodo. "alquilo (C_1-C_x)" indica un grupo hidrocarburo de cadena lineal o ramificada saturado que tiene de 1 a x átomos de carbono e incluye por ejemplo (cuando x= 4) metilo, etilo, propilo, *i*-propilo, *n*-butilo, *i*-butilo, *sec*-butilo y *t*-butilo y además (cuando x=6) pentilo, *i*-pentilo, *n*-pentilo y hexilo. Esto también se aplica si el grupo alquilo lleva sustituyentes o es un sustituyente para otro grupo, por ejemplo en -S-alquilo (C_1-C_4), -O-alquilo (C_1-C_4), - SO_2-alquilo (C_1-C_4), -SO-alquilo (C_1-C_4), -CH_2-O-alquilo (C_1-C_4), -C(O)Oalquilo (C_1-C_4), alquil (C_1-C_4)amino, [alquil (C_1-C_4)]$_2$amino,-alquil (C_1-C_4)-fenilo, -alquil (C_1-C_4)cicloalquilo (C_3-C_6), hidroxialquilo (C_1-C_4), alcoxi (C_1-C_4) alquilo (C_1-C_4), -C(O)alquilo (C_1-C_4).

"Alcoxi(C_1-C_4)" indica grupos alcoxi de cadena lineal y ramificada e incluye, por ejemplo, metoxi, etoxi, *n*-propoxi, *i*-propoxi, *n*-butoxi, *i*-butoxi, *sec*-butoxi y *t*-butoxi.

"Alquileno (C_2-C_6)" indica un radical divalente derivado de un alcano de cadena lineal o ramificada que contiene de 2 a 6 átomos de carbono. Son ejemplos de radicales alquileno (C_2-C_6) metileno, etileno (1,2-etileno o 1,1-etileno), trimetileno (1,3-propileno), tetrametileno (1,4-butileno), pentametileno y hexametileno.

Los radicales "hidroxialquilo (C_1-C_4)" son radicales alquilo sustituidos con hidroxi. Pueden contener 1 o varios sustituyentes hidroxi, si no se indica otra cosa. Son ejemplos de radicales hidroxialquilo (C_1-C_4) adecuados hidroximetilo, 1-hidroxietilo o 2-hidroxietilo.

"Cicloalquilo (C_3-C_6)" indica un grupo carbocíclico monocíclico saturado

que tiene de 3 a 6 átomos de carbono e incluye por ejemplo ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo.

En el caso en el que los radicales alquilo (C_1-C_x) están sustituidos con halo, tal radical puede contener 1 o varios átomos de halógeno si no se indica otra cosa. Dicho halo es preferiblemente un fluoro, un cloro, un bromo o un yodo, en particular, fluoro o cloro. Por ejemplo, en un radical alquilo sustituido con fluoro, un grupo metilo puede estar presente en forma de grupo difluorometilo o trifluorometilo.

"Heterociclo saturado" indica un grupo monocíclico saturado que tiene de 4 a 7 miembros en el anillo, que contiene 1 átomo de nitrógeno y opcionalmente otro heteroátomo seleccionado entre nitrógeno, oxígeno y azufre. Son ejemplos de heterociclos saturados azetidinilo, pirrolidinilo, piperadinilo, morfolinilo, piperazinilo, oxazepanilo y azepanilo.

het^1 y het^2 son grupos heteroaromáticos monocíclicos o bicíclicos que tienen de 5 a 10 miembros en el anillo, que contienen 1, 2, 3 ó 4 heteroátomo(s) seleccionado(s) entre nitrógeno, oxígeno y azufre. En particular el grupo heteroaromático contiene (a) de 1 a 4 átomos de nitrógeno, (b) un átomo de oxígeno o un átomo de azufre o (c) 1 átomo de oxígeno o 1 átomo de azufre y 1 ó 2 átomos de nitrógeno. het^2 se une preferiblemente a C, lo que significa que el grupo está unido al átomo adyacente por un átomo de carbono del anillo. het^1 puede unirse a C o a N. El grupo heteroarilo puede estar no sustituido, monosustituido o disustituido, como indica la definición de X y R^2 anterior de fórmula general (1) de acuerdo con la presente invención. Los ejemplos de grupos heteroarilo incluyen, pero sin limitación, tiofenilo, furanilo, pirrolilo, pirazolilo, imidazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo,

triazolilo, oxadiazolilo, tiadiazolilo, tetrazolilo, piranilo, piridinilo, pirazinilo, pirimidinilo, piridazinilo, triazinilo, tiadiazinilo, isobenzofuranilo, benzofuranilo, chromenilo, indolizinilo, isoindolilo, indolilo, indazolilo, purinilo, quinolinilo, isoquinolilo, cinnolinilo, ftalazinilo, naftiridinilo, quinazolinilo, quinoxalinilo, benzoxazolilo, benzotiazolilo, bencimidazolilo, benzofuranilo, benzotiofenilo, pirrolopirazinilo, pirrolopiridinilo e imidazopiridinilo. Posteriormente se proporcionarán definiciones preferidas para het^1 y het^2.

En la fórmula general (1) de acuerdo con la presente invención, cuando un radical está mono- o poli-sustituido, dicho sustituyente(s) puede(n) estar en cualquier posición deseada, a menos que se indique otra cosa. Además, cuando un radical está polisustituido, dichos sustituyentes pueden ser iguales diferentes, a menos que se indique otra cosa.

De acuerdo con un aspecto preferido de la invención, X se selecciona entre -CN, $-CH_2OH$, -C(O)OH, $-CH_2-NR^1R^2$, $-C(O)NR^3R^4$, $-CH_2-het^1$ y het^1, estando het^1 tanto en $-CH_2-het^1$ como en het^1 opcionalmente sustituido una o dos veces con alquilo (C_1-C_4), más preferiblemente X se selecciona entre $-CH_2-NR^1R^2$, $-CONR^3R^4$, $-CH_2-het^1$ y het^1, estando het^1 tanto en $-CH_2-het^1$ como en het^1 opcionalmente sustituido una o dos veces con alquilo (C_1-C_4), donde R^1, R^2, R^3, R^4 y het^1 son como se han definido previamente.

het^1 se selecciona preferiblemente entre un grupo heteroaromático monocíclico de 5 ó 6 miembros, o un grupo heteroaromático bicíclico de 9 miembros, conteniendo cada grupo heteroaromático de 1 a 3 átomos de nitrógeno, o de 1 a 2 átomos de nitrógeno y 1 átomo de oxígeno, o 1 átomo de nitrógeno y 1 átomo de azufre, y estando cada grupo heteroaromático opcionalmente sustituido una o dos veces con alquilo (C_1-C_4), y

preferiblemente, opcionalmente sustituido una o dos veces con alquilo (C_1-C_2).

Más preferiblemente, X es tiazolilo, bencimidazolilmetil-, piridinilo, oxazolilo, imidazopiridinilmetil-, pirimidinilo, imidazolilo, imidazolilmetil- o triazolilmetil-, estando cada uno de dichos tiazolilo, bencimidazolilmetil-, piridinilo, oxazolilo, imidazopiridinilmetil-, pirimidinilo, imidazolilo, imidazolilmetil- y triazolilmetil- opcionalmente sustituido con un grupo metilo.

R^1 es preferiblemente hidrógeno, metilo o etilo.

R^2 se selecciona preferiblemente entre el grupo compuesto por

hidrógeno,

alquilo (C_1-C_6) opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre -S-alquilo (C_1-C_4), -O-alquilo (C_1-C_4), -SO_2-alquilo (C_1-C_4), y fenilo, estando dicho fenilo opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, hidroxi, ciano, alquilo (C_1-C_4) y alcoxi (C_1-C_4),

cicloalquilo (C_3-C_6),

het^2 opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, ciano, alquilo (C_1-C_4) y alcoxi (C_1-C_4), donde het^2 se define como anteriormente,

-SO_2-R^5 donde R^5 se selecciona entre el grupo compuesto por alquilo (C_1-C_4), [alquil (C_1-C_4)]$_2$amino, fenilo y -alquil (C_1-C_4)-fenilo, donde dicho fenilo está opcionalmente sustituido con 1 sustituyente independientemente seleccionado entre halo y ciano y

-C(O)-R^6 donde R^6 se selecciona entre el grupo compuesto por alquilo (C_1-C_4), [alquil (C_1-C_4)]$_2$amino, amino, y -alquil (C_1-C_4)-fenilo,

estando dicho fenilo opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, ciano, alquilo (C_1-C_4) y alcoxi (C_1-C_4).

Más preferiblemente R^2 se selecciona entre el grupo compuesto por

alquilo (C_1-C_3) opcionalmente sustituido con -O-alquilo (C_1-C_3), preferiblemente metoxi,

cicloalquilo (C_3-C_5),

het^2, donde het^2 se selecciona preferiblemente entre el grupo compuesto por sistemas anillo heteroaromático monocíclico de 5 ó 6 que contienen de 1 a 2 átomos de nitrógeno o 1 átomo de nitrógeno y 1 átomo de oxígeno o 1 átomo de nitrógeno y 1 átomo de azufre, estando dicho het^2 opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, ciano, alquilo (C_1-C_4) y alcoxi (C_1-C_4), preferiblemente alquilo (C_1-C_4),

SO_2-R^5 donde R^5 se selecciona entre el grupo compuesto por alquilo (C_1-C_4), [alquil (C_1-C_4)]$_2$amino, fenilo y -alquil (C_1-C_4)-fenilo, donde dicho fenilo está opcionalmente sustituido con 1 sustituyente seleccionado independientemente entre halo y ciano y donde R^5 es preferiblemente alquilo (C_1-C_4), C(O)-R^6 donde R^6 se selecciona entre el grupo compuesto por alquilo (C_1-C_4), [alquil (C_1-C_4)]$_2$amino, amino, y -alquil (C_1-C_4)-fenilo, estando dicho fenilo opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, ciano, alquilo (C_1-C_4) y alcoxi (C_1-C_4), y donde R6 es preferiblemente alquilo (C_1-C_4).

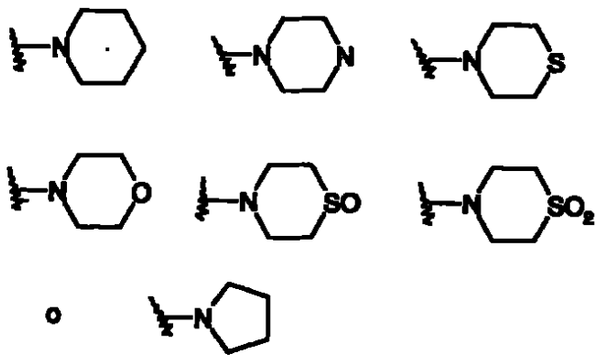
En otro aspecto de la invención, R^2 es preferiblemente alquilo (C_1-C_3)

opcionalmente sustituido con metoxi.

het^2 se selecciona preferiblemente entre el grupo compuesto por sistemas de anillo heteroaromático monocíclico de 5 ó 6 miembros que contienen 1 ó 2 átomos de nitrógeno.

En otro aspecto de la invención, R^2 es preferiblemente un grupo piridazinilo.

De acuerdo con otro aspecto preferido de la invención R^1 y R^2 forman junto con el átomo de N al que están unidos un heterociclo saturado de 4, 5, 6 ó 7 miembros donde un átomo de C puede reemplazarse por N, O, S, SO o SO_2 y donde dicho heterociclo saturado está opcionalmente sustituido con uno o dos grupos seleccionados independientemente entre hidroxi, halo, =O, alquilo (C_1-C_4), -alquil (C_1-C_4)cicloalquilo (C_3-C_6), alcoxi (C_1-C_4), hidroxialquilo (C_1-C_4), alcoxi (C_1-C_4)alquilo (C_1-C_4), -SO_2alquilo (C_1-C_4), -C(O)alquilo (C_1-C_4), [alquil (C_1-C_4)]$_2$amino, -$C(O)NH_2$, C(O)Oalquilo (C_1-C_4) y pirrolidinona, más preferiblemente R^1 y R^2 forman junto con el átomo de N al que están unidos un heterociclo saturado de 5 ó 6 miembros seleccionado entre



opcionalmente sustituido con uno o dos grupos seleccionados independientemente entre hidroxi, fluoro, hidroximetilo, metoximetilo,

SO_2alquilo (C_1-C_4), -C(O)alquilo (C_1-C_4), -$CONH_2$, y pirrolidinona.

Aún más preferiblemente, R^1 y R^2 forman junta con el átomo de N al que están unidos un grupo morfolinilo.

Preferiblemente cada uno de R^3 y R^4 se selecciona independientemente entre hidrógeno y alquilo (C_1-C_4) o R^3 y R^4 forman junto con el átomo de N al que están unidos un heterociclo saturado de 4, 5 ó 6 miembros donde un átomo de C puede reemplazarse por N u O y donde dicho heterociclo saturado está opcionalmente sustituido con alquilo (C_1-C_4).

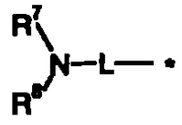
Más preferiblemente, R^3 y R^4 se seleccionan independientemente entre hidrógeno, metilo y etilo, o R^3 y R^4 forman junto con el átomo de N al que están unidos un anillo de pirrolidinilo, piperidinilo, piperazinilo o azetidinilo, (estando cada anillo pirrolidinilo, piperidinilo, piperazinilo y azetidinilo opcionalmente sustituido con metilo).

Preferiblemente, Y se selecciona entre CH_2, CH(OH), O y C=O, más preferiblemente Y es O.

Preferiblemente, Z es O

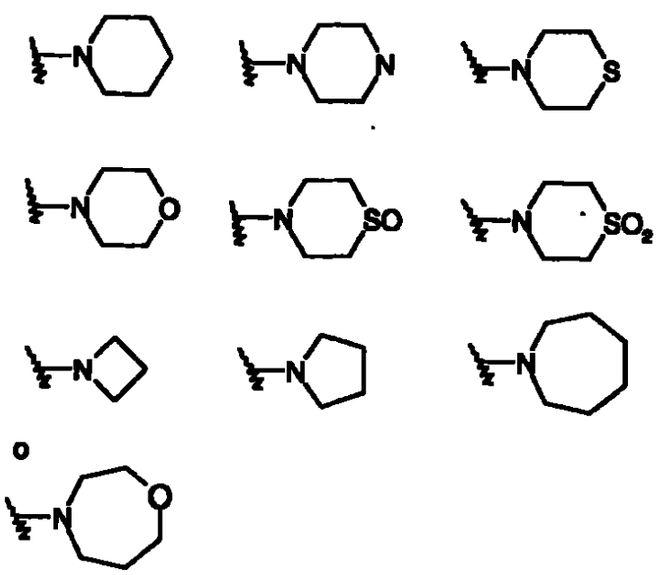
Preferiblemente m es igual a 1 ó 2 y p es igual a 2, más preferiblemente m y p son ambos 2.

En un aspecto preferido de la invención R es un grupo de fórmula:



en la que * representa el punto de unión a Z, L es un alquileno (C_2-C_5) y cada uno de R^7 y R^8 se selecciona independientemente entre hidrógeno, alquilo (C_1-C_6), cicloalquilo (C_3-C_6), hidroxialquilo (C_1-C_6) o R^7 y R^8 forman junto con el átomo de N al que están unidos un heterociclo saturado de 4, 5, 6 ó 7

miembros donde un átomo de C está opcionalmente sustituido con N, O, S, SO o SO_2 y donde dicho heterociclo saturado está opcionalmente sustituido con uno o dos grupos seleccionados independientemente entre alquilo (C_1-C_4), alcoxi (C_1-C_4), alcoxi (C_1-C_4)alquilo (C_1-C_4), hidroxialquilo (C_1-C_4), hidroxi, C(O)Oalquilo (C_1-C_4), -C(O)-alquil (C_1-C_4)-NH_2, -$C(O)NH_2$ y halo. Son ejemplos del heterociclo saturado de 4, 5, 6 ó 7 miembros:



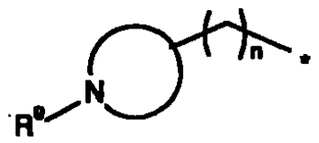
Aún más preferiblemente, R^7 y R^8 forman junto con el átomo de N al que están unidos un grupo morfolinilo u oxazepanilo.

En otro aspecto preferido, R^7 y R^8 forman junto con el átomo de N al que están unidos un heterociclo saturado de 4, 5 ó 6 miembros, opcionalmente sustituido con uno o dos alquilo (C_1-C_4), preferiblemente metilo. En otro aspecto más preferido, el heterociclo saturado es un grupo pirrolidinilo, opcionalmente sustituido con uno o dos grupos metilo.

Preferiblemente, L es propileno.

De acuerdo con otro aspecto preferido de la invención R es un grupo de

fórmula:



en la que * representa el punto de unión a Z, el anillo que contiene N es un heterocicio saturado de 4 ó 6 miembros, n es un número entero igual a 0 ó 1 y R^9 representa un sustituyente seleccionado entre hidrógeno, alquilo (C_1-C_4) y cicloalquilo (C_3-C_8).

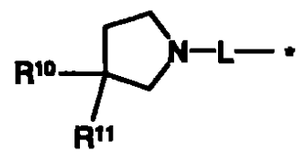
Preferiblemente, R^9 es isopropilo o ciclobutilo.

Cuando uno de los grupos en el compuesto de fórmula (1) está sustituido con halo, generalmente se prefiere fluoro o cloro, en particular fluoro.

Los compuestos particularmente preferidos de la invención incluyen aquellos en los que cada variable en la fórmula (1) se selecciona entre los grupos adecuados y/o preferidos para cada variable. Los compuestos aún más preferibles de la invención incluyen aquellos en los que cada variable en la fórmula (1) se selecciona entre los grupos más preferidos o aún más preferidos para cada variable.

De acuerdo con un aspecto particular de la invención, los siguientes compuestos se excluyen de la invención:

compuestos de fórmula (1), en la que Y es O, Z es O, R es un grupo de fórmula:



donde R^{10} es hidrógeno o alquilo (C_1-C_4), R^{11} es alcoxi (C_1-C_4), hidroxi o

N(alquil (C_1-C_4))$_2$ y X es -CN, - CH_2OH, -CH_2-O-alquilo (C_1-C_4), -C(O)OH, -C(O)Oalquilo (C_1-C_4), -$CONR^3R^4$ o $CH_2NR^1R^2$ donde R^1 es hidrógeno un grupo alquilo(C_1-C_4) y R^2 es hidrógeno, alquilo (C_1-C_4) (opcionalmente sustituido con fenilo) o -C(O)alquilo (C_1-C_4).

En otra realización de la presente invención, se proporciona un compuesto de fórmula (1) seleccionado entre:

3-(4-{4-[(dimetilamino)metil]tetrahidro-2*H*-piran-4-il}fenoxi)-*N*,*N*-dimetilpropan-1-amina

1-isopropil-4-{4-[4-(4-metil-1,3-tiazol-2-il)tetrahidro-2*H*-piran-4-il]fenoxi}piperidina

4-metil-2-{4-[4-(4-pirrolidin-1-ilbutoxi)fenil]tetrahidro-2*H*-piran-4-il}-1,3-tiazol

2-{4-[4-(4-pirrolidin-1-ilbutoxi)fenil]tetrahidro-2*H*-piran-4-il)-1,3-tiazol

4-(4-{3-[etil(metil)amino]propoxi}fenil)tetrahidro-2*H*-piran-4-carbonitrilo

4-[4-(4-pirrolidin-1-ilbutoxi)fenil]tetrahidro-2*H*-piran-4-carboxamida

1-({4-[4-(4-pirrolidin-1-ilbutoxi)fenil]tetrahidro-2*H*-piran-4-il}carbonil)pirrolidina

N-etil-*N'*,*N'*-dimetil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il]metil)etano-1,2-diamina

1-(4-[4-[4-(azetidin-1-ilcarbonil)tetrahidro-2*H*-piran-4-il]fenoxi}butil)pirrolidina

N,*N*-dimetil-4-[4-(4-pirrolidin-1-ilbutoxi)fenil]tetrahidro-2*H*-piran-4-carboxamida

N-metil-1-piridin-2-il-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il)metil)metanamina

1-ciclohexil-*N*-metil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)metanamina

N,*N*-dimetil-1-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}carbonil)azetidin-3-amina

N,N,N'-trimetil-*N'*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)etano-1,2-diamina

N,N-dimetil-1-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il)metil)azetidin-3-amina

N-(3-{4-[4-(aminometil)tetrahidro-2*H*-piran-4-il]fenoxi}propil)ciclobutanamina

3-{4-[4-(aminometil)tetrahidro-2*H*-piran-4-il]fenoxi}-*N*-etil-*N*-metilpropan-1-amina

N-ciclobutil-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxamida

N-ciclopentil-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxamida

N-(ciclopropilmetil)-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxamida

N-ciclohexil-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxamida

1-(4-{4-[(2-pirrolidin-1-iletil)tio]fenil}tetrahidro-2*H*-piran-4-il)metanamina

N,N-dimetil-1-(4-{4-[(2-pirrolidin-1-iletil)tio]fenil}tetrahidro-2*H*-piran-4-il)metanamina

1-[3-(4-(4-[(dimetilamino)metil]tetrahidro-2*H*-piran-4-il}fenoxi)propil]pirrolidin-3-ol

1-[4-(4-{3-[(2*R*,6*S*)-2,6-dimetilmorfolin-4-il]propoxi}fenil)tetrahidro-2*H*-piran-4-il]-*N,N*-dimetilmetanamina

1-[(4-{4-[(3-pirrolidin-1-ilpropil)tio]fenil}tetrahidro-2*H*-piran-4-il)carbonil]piperidina

1-[3-({4-[4-(pirrolidin-1-ilcarbonil)tetrahidro-2*H*-piran-4-il]fenil}tio)propil]pirrolidina

(4-{4-[(3-pirrolidin-1-ilpropil)tio]fenil}tetrahidro-2*H*-piran-4-il)metanol

N-etil-*N*-({4-[4-(3-tiomorfolin-4-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)acetamida

N,N-dimetil-1-[4-(4-[3-[(3*R*)-3-metilmorfolin-4-il]propoxi)fenil)tetrahidro-2*H*-piran-

4-il]metanamina

N-[(4-{4-[(3-pirrolidin-1-ilpropil)tio]fenil}tetrahidro-2*H*-piran-4-il)metil]acetamida

N-[(4-{4-[(3-pirrolidin-1-ilpropil)tio]fenil}tetrahidro-2*H*-piran-4-il)metil]etanamina

N-metil-*N*-[(4-{4-[(3-pirrolidin-1-ilpropil)tio]fenil}tetrahidro-2*H*-piran-4-il)metil]etanamina

N-etil-*N*-[(4-{4-[(3-pirrolidin-1-ilpropil)tio]fenil}tetrahidro-2*H*-piran-4-il)metil]acetamida

N-metil-*N*-({4-[4-(3-tiomorfolin-4-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)etanamina

N-etil-*N*-({4-[4-(3-tiomorfolin-4-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)etanamina

4-(3-{4-[4-(pirrolidin-1-ilcarbonil)tetrahidro-2*H*-piran-4-il]fenoxi}propil)tiomorfolina

N-etil-*N*-[(4-{4-[(3-pirrolidin-1-ilpropil)tio]fenil}tetrahidro-2*H*-piran-4-il)metil]etanamina

N-({4-[4-(3-tiomorfolin-4-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piridin-2-amina

4-[(4-{4-[(1-isopropil-piperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metoxi]piridina

4-[3-(4-{1-[(4-metilpiperazin-1-il)carbonil]ciclohexil}fenoxi)propil]morfolina

4-(3-{4-[1-(piperazin-1-ilcarbonil)ciclohexil]fenoxi}propil)morfolina

(4-{4-[(1-isopropilazetidin-3-il)metoxi]fenil}tetrahidro-2*H*-piran-4-il)metanol

4-[3-(4-{4-[(4-metilpiperazin-1-il)carbonil]tetrahidro-2*H*-piran-4-il}fenoxi)propil]morfolina

4-(3-{4-[4-(piperazin-1-ilcarbonil)tetrahidro-2*H*-piran-4-il]fenoxi}propil)morfolina

4-[(4-{4-[(1-isopropilazetidin-3-il)metoxi]fenil}tetrahidro-2*H*-piran-4-

il)metoxi]piridina

4-[(4-{4-[(1-isopropilazetidin-3-il)metoxi]fenil}tetrahidro-2*H*-piran-4-il)carbonil]morfolina

4-{4-[4-(1*H*-imidazol-1-ilmetil)tetrahidro-2*H*-piran-4-il]fenoxi}-1-isopropilpiperidina

4-[4-(1-metil-3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbonitrilo

4-(4-{3-[(3*R*)-3-hidroxipirrolidin-1-il]propoxi}fenil)tetrahidro-2*H*-piran-4-carbonitrilo

4-{4-[(1-etilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-carbonitrilo

4-{4-[(1-propilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-carbonitrilo

(3*R*)-*N*,*N*-dimetil-1-[3-(4-{4-[(metilamino)metil]tetrahidro-2*H*-piran-4-il}fenoxi)propil]pirrolidin-3-amina

N-{[4-(4-{3-[(3*R*)-3-(dimetilamino)pirrolidin-1-il]propoxi}fenil)tetrahidro-2*H*-piran-4-il]metil}-*N*-metilmetanosulfonamida

(3*R*)-1-{3-[4-(4-{[(2-metoxietil)(metil)amino]metil}tetrahidro-2*H*-piran-4-il)fenoxi]propil}-*N*,*N*-dimetilpirrolidin-3-amina

N-{[4-(4-{3-[(3*R*)-3-(dimetilamino)pirrolidin-1-il]propoxi}fenil)tetrahidro-2*H*-piran-4-il]metil}-*N*,*N*' *N*'-trimetilurea

(3*R*)-*N*,*N*-dimetil-1-(3-{4-[4-(1,3-tiazol-2-il)tetrahidro-2*H*-piran-4-il]fenoxi}propil)pirrolidin-3-amina

(3*R*)-*N*,*N*-dimetil-1-(3-{4-[4-(morfolin-4-ilcarbonil)tetrahidro-2*H*-piran-4-il]fenoxi}propil)pirrolidin-3-amina

N-{[4-(4-{3-[(3*R*)-3-(dimetilamino)pirrolidin-1-il]propoxi)fenil)tetrahidro-2*H*-piran-4-il]metil}-*N*-metilpirimidin-2-amina

(3*R*)-*N*,*N*-dimetil-1-(3-{4-[4-(morfolin-4-ilmetil)tetrahidro-2*H*-piran-4-

il]fenoxi}propil)pirrolidin-3-amina

1-isopropil-4-{4-[4-(piperidin-1-ilcarbonil)tetrahidro-2*H*-piran-4-il]fenoxi}piperidina

4-[(4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)carbonil]morfolina

N-isopropil-4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}-*N*-metiltetrahidro-2*H*-piran-4-carboxamida

*N**4*-{4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil}-piridin-3,4-diamina

N*2*-{4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil}-piridin-2,3-diamina

Compuestos particularmente preferidos de fórmula (1) son como se describen más adelante en este documento en la sección de Ejemplos. Cuando se obtiene la forma de sal en los Ejemplos, un compuesto de la presente invención incluye la base libre de la misma, por ejemplo:

{4-[4-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il}metilamina,

{4-[4-(3-Piperidin-1-ilpropoxi)fenil]tetrahidropiran-4-il)metilamina y

Dimetil-{4-[4-(3-piperidin-1-ilpropoxi)fenil]tetrahidro-piran-4-ilmetil)amina.

En otra realización de la invención, son compuestos particularmente preferidos:

{4-[4-(1-Isopropilpiperidin-4-iloxi)fenil]tetrahidropiran-4-ilmetil}dimetil-amina

Dimetil-{4-[4-(4-pirrolidin-1-ilbutoxi)fenil]tetrahidro-piran-4-ilmetil}amina

{4-[4-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il}metilamina

Dimetil-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]-tetrahidropiran-4-ilmetil}amina

{4-[4-(3-Piperidin-1-ilpropoxi)fenil]tetrahidropiran-4-il}metilamina

Dimetil-{4-[4-(3-piperidin-1-ilpropoxi)fenil]tetra-hidropiran-4-ilmetil}amina

1-Metil-4-{4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil}-piperazina

(*R*)-2-Metoximetil-1-{4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil)-pirrolidina

(*S*)-2-Metoximetil-1-{4-[4-(3-pirrolidin-1-ilpropoxi)-fenil]tetrahidropiran-4-ilmetil)pirrolidina

1-{4-[4-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil}piperidina

metil-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]-tetrahidropiran-4-ilmetil}amina

isopropil-metil-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]-tetrahidropiran-4-ilmetil}amina

1-{4-[4-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil}pirrolidina

4-{4-[4-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil}-morfolina

(2-metoxietil)-metil-{4-[4-(3-pirrolidin-1-ilpropoxi)-fenil]tetrahidropiran-4-ilmetil}amina

4-[4-(1-Isopropilpiperidin-4-iloxi)fenil]tetrahidropiran-4-carbonitrilo

Amida del ácido 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxílico

N-metil-1-{1-[4-(3-pirrolidin-1-ilpropoxi)fenil]-ciclohexil}metanamina

N-etil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)etanamina

N-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)etanamina

N-metil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]-tetrahidro-2*H*-piran-4-il}metil)etanamina

4-{4-[(1-ciclobutil-4-piperidinil)oxi]fenil}tetrahidro-2*H*-piran-4-carbonitrilo

4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-carboxamida

4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}-*N*,*N*-dimetiltetrahidro-2*H*-piran-4-carboxamida

4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}-*N*,*N*-dietiltetra-hidro-2*H*-piran-4-carboxamida

4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il]carbonil}pirrolidina

4-metil-2-[4-(4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il]-1,3-tiazol

2-[4-(4-(3-pirrolidin-1-ilpropoxi)fenil)tetrahidro-2*H*-piran-4-il]-1,3-tiazol

N-[(4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]-*N*-metilamina

N-[(4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]-*N*-etilamina

N-[[4-(4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il]metil}pirimidin-2-amina y

N-[[4-(4-(3-Pirrolidin-1-ilpropoxi)fenil)tetrahidro-2*H*-piran-4-il]metil}pirimidin-2-amina.

1-(4-{4-[(1-ciclopentilazetidin-3-il)metoxi]fenil}tetrahidro-2*H*-piran-4-il)-*N*,*N*-dimetilmetanamina

3-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)-3*H*-imidazo[4,5-b]piridina

2-[[metil({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)amino]metil}fenol

N-metil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)ciclopentanamina

2-[metil({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)amino]etanol

N-metil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)ciclopropanamina

1-(3-{4-[4-(aziridin-1-ilmetil)tetrahidro-2*H*-piran-4-il]fenoxi)propil)pirrolidina

N-({4-[4-(3-tiomorfolin-4-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)etanamina

1-(4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)-*N*,*N*-dimetilmetanamina

N,*N*-dimetil-1-(4-{4-[(3-pirrolidin-1-ilpropil)tio]fenil}tetrahidro-2*H*-piran-4-il)metanamina

N-metil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)ciclohexanamina

1-[3-({4-[4-(pirrolidin-1-ilmetil)tetrahidro-2*H*-piran-4-il]fenil}tio)propil]pirrolidina

1-({1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil}metil)piperidin-4-ol

1-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)-1*H*-bencimidazol

4-{4-[(1-ciclobutilpipendin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-carboxamida

N-metil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)hexan-1-amina

1-ciclopropil-*N*-(ciclopropilmetil)-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)metanamina

N-[2-(dimetilamino)etil]-*N*-etil-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxamida

N-metil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)butan-1-amina

4-{4-[4-(4,5-dimetil-1*H*-imidazol-2-il)tetrahidro-2*H*-piran-4-il]fenoxi}-1-isopropilpiperidina

3-[[metil({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)amino]metil]fenol

4-[(4-{4-[(1-ciclopentilazetidin-3-il)metoxi]fenil}tetrahidro-2*H*-piran-4-il)metil]morfolina

N-metil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)pentan-1-amina

4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}-*N*,*N*-dimetiltetrahidro-2*H*-piran-4-carboxamida

N,*N*-dimetil-1-(4-{4-[3-(1,4-oxazepan-4-il)propoxi]fenil}tetrahidro-2*H*-piran-4-il)metanamina

N,3,3-trimetil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)butan-1-amina

4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}-*N*-isopropil-tetrahidro-2*H*-piran-4-carboxamida

1-metil-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)-1,4-diazepan

1-ciclobutil-4-{4-[4-(1,3-tiazol-2-il)tetrahidro-2*H*-piran-4-il]fenoxi}piperidina

N-[(4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]piridin-2-amina

N-metil-1-{4-[4-(3-morfolin-4-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metanamina

1-[(4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)carbonil]-4-metilpiperazina

1-ciclopentil-*N*-metil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)metanamina

4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}-*N*-etiltetrahidro-2*H*-piran-4-carboxamida

N-[(4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]pirimidin-2-amina

N,*N*-dietil-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxamida

4-[(4-{4-[(1-ciclobutilazetidin-3-il)metoxi]fenil}tetrahidro-2*H*-piran-4-il)metil]morfolina

4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}-*N*-metiltetrahidro-2*H*-piran-4-carboxamida

1-ciclobutil-4-{4-[4-(4-metil-1,3-tiazol-2-il)tetrahidro-2*H*-piran-4-il]fenoxi}piperidina

4-[(4-{4-[(1-isopropilazetidin-3-il)metoxi]fenil}tetrahidro-2*H*-piran-4-il)metil]morfolina

1-isopropil-4-{4-[4-(1,3-tiazol-2-il)tetrahidro-2H-piran-4-il]fenoxi}piperidina

1-(4-{4-[(1-ciclobutilazetidin-3-il)metoxi]fenil}tetrahidro-2*H*-piran-4-il)metanamina

1-etil-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}carbonil)piperazina

N-etil-*N*-metil-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxamida

1-(4-{4-[(1-isopropilazetidin-3-il)metoxi]fenil}tetrahidro-2*H*-piran-4-il)metanamina

1-[(4-{4-[(1-isopropil-piperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]-4-metilpiperazina

1-(ciclopropilmetil)-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piperazina

N,*N*-dimetil-1-{4-[4-(3-morfolin-4-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il)metanamina

N-[2-(dimetilamino)etil]-*N*-metil-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-

piran-4-carboxamida

1-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}carbonil)piperazina

1-etil-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piperazina

4-[(4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)carbonil]morfolina

N-[(4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]piridin-3-amina

1-metil-4-({1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil}carbonil)piperazina

1-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)-1*H*-imidazol

N-[(4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]piridin-2-amina

1-isopropil-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piperazina

1-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)-1*H*-imidazo[4,5-c]piridina

N-({4-[4-(3-piperidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piridin-2-amina

1-propil-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}carbonil)piperazina

N-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piridazin-4-amina

N-etil-4-[4-[(1-isopropilpiperidin-4-il)oxi]fenil]-*N*-metiltetrahidro-2*H*-piran-4-carboxamida

1-metil-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-

il}carbonil)piperazina

1-propil-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piperazina

N-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piridin-2-amina

4-[4-[4-(azetidin-1-ilcarbonil)tetrahidro-2*H*-piran-4-il]fenoxi}-1-isopropilpiperidina

1-(2-metoxietil)-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piperazina

2-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}piridina

N-[(4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]piridazin-4-amina

N-[(4-{4-[(1-isopropilazetidin-3-il)metoxi]fenil}tetrahidro-2*H*-piran-4-il)metil]piridin-2-amina

4-[(4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]morfolina

1-metil-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}carbonil)-1,4-diazepan

4-(3-{4-[4-(morfolin-4-ilmetil)tetrahidro-2*H*-piran-4-il]fenoxi}propil)-1,4-oxazepan

1-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}carbonil)piperidina

1-metil-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]piperidin-4-carbonitrilo

1-(3-{4-[4-(pirrolidin-1-ilcarbonil)tetrahidro-2*H*-piran-4-il]fenoxi}propil)pirrolidina

2-(metiltio)-1-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)-1*H*-imidazol

4-[4-(3-pirrolidin-1-ilpropoxi)fenil]piperidin-4-carbonitrilo

N-[(4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]piridin-3-amina

6-metil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piridin-3-amina

N-[(4-{4-[(1-etilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]piridin-2-amina

N,*N*-dimetil-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxamida

4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)-4*H*-1,2,4-triazol

1-({1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil}metil)piperazina

1-isopropil-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]piperidin-4-carbonitrilo

5-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il]-1,3-oxazol

1-acetil-4-({1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil}metil)piperazina

4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metoxi)piridina

1-acetil-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piperazina

N-({4-[4-(4-pirrolidin-1-ilbutoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piridin-2-amina

1-[3-(4-{4-[(dimetilamino)metil]tetrahidro-2*H*-piran-4-il}fenoxi)propil]-*N*,*N*-dimetilazetidin-3-amina

1-(3-{4-[4-(azetidin-1-ilcarbonil)tetrahidro-2*H*-piran-4-il]fenoxi}propil)pirrolidina

N-[(4-{4-[(1-ciclobutilazetidin-3-il)metoxi]fenil}tetrahidro-2*H*-piran-4-il)metil]piridin-2-amina

N-[[4-(4-{3-[ciclobutil(metil)amino]propoxi}fenil)tetrahidro-2*H*-piran-4-il]metil}piridin-2-amina

N-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piridin-3-amina

4-(3-{4-[4-(morfolin-4-ilmetil)tetrahidro-2*H*-piran-4-il]fenoxi}propil)morfolina

N,*N*-dimetil-1-(4-{4-[3-(4-metil-1,4-diazepan-1-il)propoxi]fenil}tetrahidro-2*H*-piran-4-il)metanamina

1-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)-1*H*-imidazo[4,5-b]piridina

4-({4-[4-(3-azetidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)morfolina

2-{4-[4-(3-pirrolidin-1-ilopropoxi)fenil]tetrahidro-2*H*-piran-4-il}-1*H*-imidazol

4-(3-{4-[4-(piperazin-1-ilcarbonil)tetrahidro-2*H*-piran-4-il]fenoxi}propil)-1,4-oxazepan

4-[3-(4-{4-[(4-metilpiperazin-1-il)carbonil]tetrahidro-2*H*-piran-4-il}fenoxi)propil]-1,4-oxazepan

4-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}pirimidina

4-metil-1-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)-1*H*-imidazol

4-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}-1*H*-imidazol

4-[4-(4-{3-[etil(metil)amino]propoxi}fenil)tetrahidro-2*H*-piran-4-ilmetil]-morfolina

Otra realización de la invención es un intermedio como se describe en este documento.

Las sales farmacéuticamente aceptables de los compuestos de fórmula (I) incluyen las sales de adición de ácidos y bases de los mismos.

Las sales de adición de ácidos adecuadas se forman a partir de ácidos que forman sales no tóxicas. Los ejemplos incluyen las sales acetato, aspartato, benzoato, besilato, bicarbonato/carbonato, bisulfato/sulfato, borato, camsilato, citrato, edisilato, esilato, formiato, fumarato, gluceptato, gluconato, glucuronato, hexafluorofosfato, hibenzato, clorhidrato/cloruro, bromhidrato/bromuro, yodhidrato/yoduro, isetionato, lactato, malato, maleato,

malonato, mesilato, metilsulfato, naftilato, 2-napsilato, nicotinato, nitrato, orotato, oxalato, palmitato, pamoato, fosfato/hidrógenofosfato/dihidrógenofosfato, sacarato, estearato, succinato, tartrato, tosilato y trifluoroacetato.

Las sales básicas adecuadas se forman a partir de bases que forman sales no tóxicas. Los ejemplos incluyen las sales de aluminio, arginina, benzatina, calcio, colina, dietilamina, diolamina, glicina, lisina, magnesio, meglumina, olamina, potasio, sodio, trometamina y cinc.

También pueden formarse hemisales de ácidos y bases, por ejemplo, sales hemisulfato y hemicálcicas.

Para un análisis sobre sales adecuadas, véase "Handbook of Pharmaceutical Salts: Properties, Selection and Use" de Stahl y Wermuth, (Wiley-VCH, Weinheim, Alemania, 2002).

Las sales farmacéuticamente aceptables de compuestos de fórmula (1) pueden prepararse por uno o más de tres procedimientos:

(i) haciendo reaccionar el compuesto de fórmula (1) con el ácido o base deseado;

(ii) retirando un grupo protector lábil a ácidos o a bases de un precursor adecuado del compuesto de fórmula (1) o abriendo el anillo de un precursor cíclico adecuado, por ejemplo, una lactona o lactama, usando el ácido o base deseado; o

(iii) convirtiendo una sal del compuesto de fórmula (1) en otra mediante reacción con un ácido o base apropiado o mediante una columna de intercambio iónico adecuada.

Las tres reacciones se realizan típicamente en solución. La sal resultante

puede precipitarse y recogerse por filtración o puede recuperarse por evaporación del disolvente. El grado de ionización en la sal resultante puede variar de completamente ionizada a casi no ionizada.

Los compuestos de la invención pueden existir tanto en formas solvatadas como no solvatadas. El término "solvato" se usa en este documento para describir un complejo molecular que comprende el compuesto de la invención y una cantidad estequiométrica de una o más moléculas de disolvente farmacéuticamente aceptables, por ejemplo, etanol. El término "hidrato" se emplea cuando dicho disolvente es agua.

Dentro del alcance de la invención se incluyen complejos tales como clatratos, complejos de inclusión fármaco-huésped en los que, al contrario que en los solvatos mencionados anteriormente, el fármaco y el huésped están presentes en cantidades estequiométricas o no estequiométricas. También se incluyen los complejos de fármacos que contienen dos o más componentes orgánicos y/o inorgánicos que pueden estar en cantidades estequiométricas o no estequiométricas. Los complejos resultantes pueden estar ionizados, parcialmente ionizados o no ionizados. Para un análisis de tales complejos véase J Pharm Sci, 64 (8), 1269-1288 de Haleblian (agosto de 1975).

En lo sucesivo, todas las referencias a compuestos de fórmula (I) incluyen referencia a sales, solvatos y clatratos de los mismos y a solvatos y complejos de sales de los mismos.

Los compuestos de la invención incluyen compuesto de fórmula (I) como se han definido anteriormente en este documento, incluyendo todos los polimorfos y hábitos cristalinos de los mismos, profármacos e isómeros de los mismos (incluyendo isómeros ópticos, geométricos y tautoméricos) como se

definen más adelante en este documento y compuestos de fórmula (I) marcados isotópicamente.

Como se indica, los llamados "pro-fármacos" de los compuestos de fórmula (I) también están dentro de alcance de la invención. Por tanto, ciertos derivados de compuestos de fórmula (I) que tienen poca o ninguna actividad farmacológica por si mismos pueden, cuando se administran en o sobre el cuerpo, convertirse en compuestos de fórmula (I) que tienen la actividad deseada por ejemplo, por escisión hidrolítica. Tales derivados se denominan "profármacos". Puede encontrarse información adicional sobre el uso de profármacos en "Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T Higuchi y W Stella) y "Bioreversible Carriers in Drug Design", Pergamon Press, 1987 (ed. E B Roche, American Pharmaceutical Association).

Los profármacos de acuerdo con la invención pueden producirse, por ejemplo, reemplazando las funcionalidades apropiadas presentes en los compuestos de fórmula (I) con ciertos restos conocidos para los especialistas en la técnica como "pro-restos" como se describe, por ejemplo, en "Design of Prodrugs" H Bundgaard (Elsevier, 1985).

Algunos ejemplos de profármacos de acuerdo con la invención incluyen:

(i) cuando el compuesto de fórmula (I) contiene una funcionalidad ácido carboxílico (-C(O)OH), un éster del mismo, por ejemplo, un compuesto en el que el hidrógeno de la funcionalidad ácido carboxílico del compuesto de fórmula (1) se reemplaza por alquilo (C_1-C_8);

(ii) cuando el compuesto de fórmula (I) contiene una funcionalidad alcohol (-OH), un éter del mismo, por ejemplo, un compuesto en el que el

hidrógeno de la funcionalidad alcohol del compuesto de fórmula (1) se reemplaza por alcanoiloximetilo (C_1-C_6); y

(iii) cuando el compuesto de fórmula (I) contiene una funcionalidad amino primaria o secundaria (-NH_2 o NHR donde R ≠ H), una amida del mismo, por ejemplo, un compuesto en el que, según sea el caso, uno o ambos hidrógenos de la funcionalidad amino del compuesto de fórmula (1) se reemplaza(n) por alcanoílo (C_1-C_{10}).

En las referencias mencionadas anteriormente pueden encontrarse más ejemplos de grupos de reemplazamiento de acuerdo con los ejemplos anteriores y ejemplos de otros tipos de profármacos.

Además, ciertos compuestos de fórmula (1) pueden actuar por sí mismos como profármacos de otros compuestos de fórmula (1).

Dentro del alcance de la invención también se incluyen metabolitos de compuestos de fórmula (1), es decir, compuestos formados *in vivo* tras la administración del fármaco. Algunos ejemplos de metabolitos de acuerdo con la invención incluyen:

(i) cuando el compuesto de fórmula (1) contiene un grupo metilo, un derivado hidroximetilo del mismo (-CH_3 → -CH_2OH);

(ii) cuando el compuesto de fórmula (1) contiene un grupo alcoxi, un derivado hidroxi del mismo (-OR → -OH);

(iii) cuando el compuesto de fórmula (1) contiene un grupo amino terciario, un derivado amino secundario del mismo (-NR^aR^b → -NHR^b o -NHR^b);

(iv) cuando el compuesto de fórmula (1) contiene un grupo amino secundario, un derivado primario del mismo (-NHR^a → -NH_2);

(v) cuando el compuesto de fórmula (1) contiene un resto fenilo, un

derivado fenol del mismo (-Ph → -PhOH); y

(vi) cuando el compuesto de fórmula (1) contiene un grupo amida, un derivado ácido carboxílico del mismo (-CONR^{c}R^d → -COOH);

Los compuestos de fórmula (1) que contienen uno o más átomos de carbono asimétricos pueden existir en forma de dos o más estereoisómeros. Cuando los isómeros estructurales pueden intercambiarse mediante una barrera de baja energía, puede producirse isomería tautomérica ("tautomería"). Éste puede tomar la forma de la tautomería de protón en compuestos de fórmula (1) que contienen, por ejemplo, un grupo imino, ceto u oxima, o la denominada tautomería de valencia en compuestos que contienen un resto aromático. De esto se entiende que un único compuesto puede mostrar más de un tipo de isomería.

Dentro del alcance de la presente invención se incluyen todos los estereoisómeros, isómeros geométricos y formas tautoméricas de los compuestos de fórmula (1), incluyendo compuestos que muestran más de un tipo de isomería, y mezclas de uno o más de los mismos. También se incluyen sales de adición de ácidos o bases en las que el contraión es ópticamente activo, por ejemplo, *d*-lactato o *l*-lisina o racémico, por ejemplo *dl*-tartrato o *dl*-arginina.

Las técnicas convencionales para la preparación/aislamiento de enantiómeros individuales incluyen síntesis quiral a partir de un precursor adecuado ópticamente puro o resolución del racemato (o el racemato de una sal o derivado) usando, por ejemplo, cromatografía líquida de alta presión quiral (HPLC).

Como alternativa, el racemato (o precursor racémico) se puede hacer

reaccionar con un compuesto adecuado ópticamente adecuado, por ejemplo, un alcohol o, en el caso de que el compuesto de fórmula (1) contenga un resto ácido o básico, un ácido o base tal como ácido tartárico o 1-feniletilamina. La mezcla diastereomérica resultante puede separarse por cromatografía y/o cristalización fraccionada y uno o ambos de los diastereoisómeros puede convertirse en el(los) correspondiente(s) enantiómero(s) puro(s) por medios bien conocidos para un especialista.

Los compuestos quirales de la invención (y precursores quirales de los mismos) pueden obtenerse en forma enantioméricamente enriquecida usando cromatografía, típicamente HPLC, en una resina asimétrica con una fase móvil que comprende un hidrocarburo, típicamente heptano o hexano, que contiene del 0 al 50% en volumen de isopropanol, típicamente del 2% al 20% y del 0 al 5% en volumen de una alquilamina, típicamente dietilamina al 0,1%. La concentración del eluato proporciona la mezcla enriquecida.

Los conglomerados estereoisoméricos pueden separarse por técnicas convencionales conocidas para los especialistas en la técnica -véase, por ejemplo, "Stereochemistry of Organic Compounds" de E. L. Eliel (Wiley, Nueva York, 1994).

La presente invención incluye todos los compuestos isotópicamente marcados farmacéuticamente aceptables de fórmula (1) en los que uno o más átomos se reemplazan con átomos que tienen el mismo número atómico pero una masa atómica o número másico diferente de la masa atómica o número másico que predomina en la naturaleza.

Los ejemplos de isótopos adecuados para inclusión en los compuestos de la invención incluyen isótopos de hidrógeno, tales como ^{2}H y ^{3}H, carbono,

tales como ^{11}C, ^{13}C y ^{14}C, cloro tales como ^{36}Cl, flúor, tal como ^{18}F, yodo, tales como ^{123}I y ^{125}I, nitrógeno, tales como ^{13}N y ^{15}N, oxígeno, tales como ^{15}O, ^{17}O y ^{18}O, fósforo, tal como ^{32}P y azufre, tal como ^{35}S.

Ciertos compuestos isotópicamente marcados de fórmula (1), por ejemplo, los que incorporan un isótopo radiactivo, son útiles en estudios de distribución de fármaco y/o sustrato en tejidos. Los isótopos radiactivos tritio, es decir, ^{3}H, y carbono 14, es decir, ^{14}C, son particularmente útiles para este propósito en vista de su facilidad de incorporación y de los fáciles medios de detección.

La sustitución con isótopos más pesados tales como deuterio, es decir, ^{2}H puede proporcionar ciertas ventajas terapéuticas resultantes de una mayor estabilidad metabólica, por ejemplo, aumento de la semivida *in vivo* o reducción de los requerimientos de dosificación y por lo tanto se pueden preferir en algunas circunstancias.

La sustitución con isótopos que emiten positrones, tales como ^{11}C, ^{18}F, ^{15}O y ^{13}N puede ser útil en estudios de Tomografía de Emisión de Positrones (PET) para examinar la ocupación de receptores del sustrato.

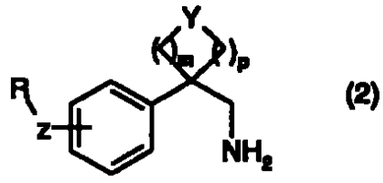
Los compuestos isotópicamente marcados de fórmula (1) pueden prepararse generalmente por técnicas convencionales conocidas para los especialistas en la técnica o por procedimientos análogos a los descritos en los Ejemplos y Preparaciones adjuntas usando reactivos apropiados isotópicamente marcados en lugar del reactivo no marcado empleado previamente.

Los solvatos farmacéuticamente aceptables de acuerdo con la invención incluyen aquellos en los que el disolvente de cristalización puede estar

isotópicamente sustituido, por ejemplo, D_2O, d_6-acetona, d_6-DMSO.

Los derivados de fenol y tiofenol de fórmula (1) puede prepararse usando procedimientos convencionales tales como mediante los siguientes procedimientos ilustrativos en los que R, X, Y, Z, m, p, R^1, R^2, R^3, R^4, R^5, R^6, R^7 R^8 y R^9 son como se han definido previamente a menos que se indique otra cosa.

Los compuestos de fórmula (1), donde X es $-CH_2NR^1R^2$, pueden prepararse a partir de compuestos de fórmula (2)



(2)

usando técnicas convencionales para la interconversión de grupos funcionales conocida para los especialistas en la técnica, por ejemplo, como las que se describe en *Comprehensive Organic Transformations*, R.C. Larock, 1ª Edición, 1989 VCH Publishers Inc.

Estas técnicas incluyen:

1) Alquilación reductora con aldehídos o cetonas con un agente reductor (por ejemplo ácido fórmico o $NaHB(OAc)_3$) en un disolvente adecuado (por ejemplo diclorometano, tetrahidrofurano), opcionalmente con la adición de ácido acético, a una temperatura entre temperatura ambiente (aproximadamente 20ºC) y temperatura de reflujo;

2) Alquilaciones con haluros de alquilo y una base (por ejemplo carbonato potásico, *terc*-butóxico potásico) en un disolvente adecuado (por ejemplo acetonitrilo, tetrahidrofurano) a una temperatura entre temperatura ambiente (aproximadamente 20ºC) y temperatura de reflujo;

3) Sulfonilación con un cloruro de sulfonilo y una base (por ejemplo trietilamina, *N*-etildiisopropilamina) en un disolvente adecuado (por ejemplo diclorometano) a una temperatura entre la temperatura ambiente y la temperatura de reflujo;

4) Heteroarilación con un compuesto de ácido sulfónico haloheteroaromático o heteroaromático y una base (por ejemplo carbonato potásico) en un disolvente adecuado (por ejemplo acetonitrilo) a una temperatura entre temperatura ambiente (aproximadamente 20°C) y temperatura de reflujo. Como alternativa, esta reacción puede realizarse con radiación de microondas, alternativamente usando *N*-etildiisopropilamina como base, opcionalmente en un disolvente adecuado (por ejemplo *N*-metil-pirrolidinona, acetonitrilo).

5) Formación de urea con un cloruro de dialquilcarbamoílo o una sal cianato, opcionalmente en presencia de una base (por ejemplo trietilamina) o un ácido (por ejemplo ácido acético) en un disolvente adecuado (por ejemplo diclorometano o agua) a una temperatura entre la temperatura ambiente y la temperatura de reflujo;

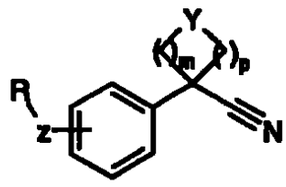
6) Formación de sulfonil urea con un cloruro de dialquilsulfamoílo y una base (por ejemplo trietilamina) en un disolvente adecuado (por ejemplo diclorometano) a una temperatura entre la temperatura ambiente y la temperatura de reflujo;

7) Acilación con un ácido activado (por ejemplo un cloruro o anhídrido de acilo) y una base (por ejemplo, trietilamina) en un disolvente adecuado (por ejemplo diclorometano) a una temperatura entre la temperatura ambiente y la temperatura de reflujo.

8) Por acoplamiento cruzado catalizado con paladio con un compuesto haloheteroaromático, usando una fuente de paladio adecuada (por ejemplo tris(dibencilidenacetona)paladio (0)), opcionalmente en presencia de un ligando de quelación (por ejemplo BINAP) y en presencia de una base adecuada (por ejemplo *terc*-butóxico sódico) en un disolvente (por ejemplo tolueno), a una temperatura entre la temperatura ambiente y la temperatura de reflujo.

Estas transformaciones pueden realizarse secuencialmente para preparar compuestos en los que R^1 y R^2 son como se han definido anteriormente.

Los compuestos de fórmula (2) pueden prepararse mediante la reducción de los correspondientes derivados ciano de fórmula (3):

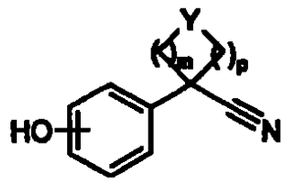


(3)

con un agente de reducción adecuado (por ejemplo $LiAlH_4$ o gas hidrógeno en presencia de un catalizador tal como PtO_2) en un disolvente adecuado (por ejemplo Et_2O/diclorometano, tetrahidrofurano o isopropanol) a una temperatura entre la temperatura ambiente y la temperatura de reflujo.

Los compuestos de fórmula (3) anteriores corresponden en realidad a compuestos de fórmula (1) en la que X es un grupo CN.

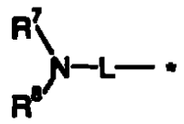
Los compuestos de fórmula (3) en la que Z es O pueden prepararse por alquilación de los correspondientes derivados hidroxi de fórmula (4):



(4)

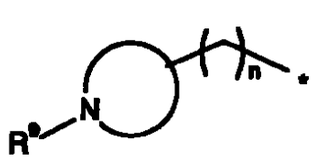
con un derivado de fórmula R-R^{LG} donde R^{LG} es un grupo saliente tal como halo, mesilato o tosilato, en presencia de una base (por ejemplo carbonato potásico) y opcionalmente en presencia de un aditivo (por ejemplo yoduro potásico) en un disolvente adecuado (por ejemplo dimetilformamida) a una temperatura entre la temperatura ambiente y la temperatura de reflujo.

Cuando R es un grupo de fórmula:



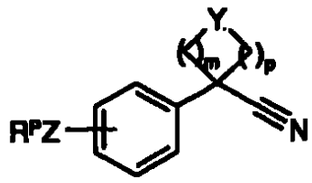
como se ha definido previamente, entonces el derivado de fórmula R-R^{LG} puede prepararse por alquilación del correspondiente derivado amino de fórmula NHR^7R^8 con un derivado de fórmula R^{LG}-L-R^{LG} y una base (por ejemplo NaOH, Na_2CO_3, K_2CO_3, Cs_2CO_3), opcionalmente en presencia de un aditivo (por ejemplo yoduro potásico) en un disolvente adecuado (por ejemplo *N,N*-dimetilformamida, acetonitrilo, acetona/H_2O) a una temperatura entre la temperatura ambiente y la temperatura de reflujo. El derivado amino de fórmula NHR^7R^8 está disponible en el mercado o puede fabricarse usando procedimientos conocidos para el especialista en la técnica.

Cuando R es un grupo de fórmula:



como se ha definido previamente, entonces el derivado de fórmula R-R^{LG} está disponible en el mercado o puede prepararse usando procedimientos de la bibliografía bien conocidos para el especialista en la técnica.

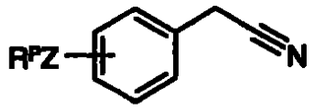
Los compuestos de fórmula (4) pueden prepararse por desprotección de los correspondientes derivados de fórmula (5) en la que Z es O:



(5)

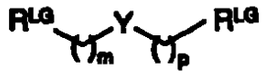
en la que R^P es un grupo protector (por ejemplo metilo, desprotegido con BBr_3 en diclorometano a una temperatura entre 0ºC y la temperatura ambiente).

Los compuestos de fórmula (5) están disponibles en el mercado o pueden prepararse por alquilación doble de los compuestos de fórmula (6):



(6)

en la que R^P es como se ha definido previamente, con los compuestos de fórmula (7):



(7)

en la que R^{LG} es como se ha definido previamente y una base (por ejemplo NaH), opcionalmente en presencia de un aditivo (por ejemplo yoduro potásico) en un disolvente adecuado (por ejemplo *N*,*N*-dimetilformamida, *N*-metil pirrolidinona) a una temperatura entre la temperatura ambiente y la temperatura de reflujo.

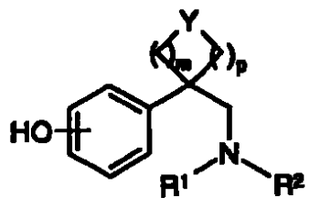
Los compuestos de fórmula (6) y (7) están disponibles en el mercado o pueden fabricarse usando procedimientos de la bibliografía bien conocidos para el especialista en la técnica.

Los compuestos de fórmula (3), en la que Z representa S pueden prepararse a partir de compuestos de fórmula (5) en la que Z representa S y R^P es Me mediante transposición de Pummerer, seguido de la alquilación del intermedio resultante con un derivado de fórmula R-R^{LG}. La reacción se consigue mediante el tratamiento del compuesto de fórmula (5) con un oxidante adecuado (por ejemplo m-CPBA) en un disolvente adecuado (por ejemplo diclorometano) a 0ºC proporcionando el sulfuro correspondiente. El tratamiento de este intermedio con anhídrido trifluoroacético en presencia de una base adecuada (por ejemplo 2,6-lutidina) en un disolvente adecuado (por ejemplo acetonitrilo) a aproximadamente -15ºC, seguido de la reacción con R-R^{LG}-, en presencia de una base (por ejemplo trietilamina, carbonato potásico) en un disolvente adecuado (por ejemplo *N*,*N*-dimetilformamida) a una temperatura entre 0ºC y la temperatura ambiente proporciona el compuesto de fórmula (3).

Como alternativa, los compuestos de fórmula (3) en la que Z es O pueden prepararse por alquilación de los compuestos de fórmula (4) con el derivado de alcohol de fórmula ROH, que está disponible en el mercado o se fabrica usando procedimientos de la bibliografía bien conocidos para el especialista en la técnica, usando reactivos de Mitsunobu tales como PPh_3 y DIAD en un disolvente adecuado (por ejemplo THF) a una temperatura entre 0ºC y temperatura de reflujo.

Los especialistas en la técnica apreciarán que, para obtener compuestos de fórmula (1) de una forma alternativa o más conveniente, las etapas

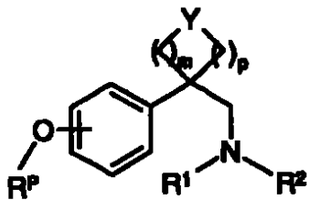
individuales de procedimiento mencionadas en esta sección pueden realizarse en distinto orden. Por ejemplo, pueden prepararse compuestos de fórmula (1) en la que Z es O y X es $-CH_2NR^1R^2$ pueden prepararse por alquilación de los compuestos de fórmula (8):



(8)

con un derivado de fórmula $R\text{-}R^{LG}$ o ROH como se ha definido previamente, usando condiciones análogas a las descritas para la preparación de compuestos de fórmula (3).

Los compuestos de fórmula (8) pueden prepararse por desprotección de compuestos de fórmula (9):

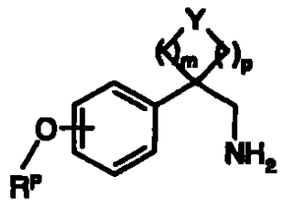


(9)

en la que R^P es como se ha definido previamente,

usando condiciones apropiadas para el grupo protector y la naturaleza de R^1 y R^2 (por ejemplo usando NaSMe en dimetilformamida a 130ºC donde R^P es metilo y R^1 y R^2 son alquilo (C_1-C_4).

Los compuestos de fórmula (9) pueden prepararse a partir de los correspondientes derivados amino de fórmula (10)

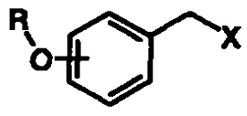


(10)

usando condiciones análogas a las descritas para la preparación de compuestos de fórmula (1) a partir de compuestos de fórmula (2).

Los compuestos de fórmula (10) pueden prepararse a partir de compuestos de fórmula (5) en la que Z es O usando condiciones de reducción análogas a las descritas para la preparación de compuestos de fórmula (2) a partir de compuestos de fórmula (3).

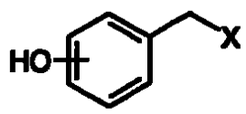
Un ejemplo adicional de la realización de las etapas de procedimiento individuales descritas en esta sección en un orden diferente para obtener compuestos de fórmula (1) de una forma alternativa o más conveniente, es la preparación de compuestos de fórmula (1) en la que Z es O por alquilación doble de compuestos de fórmula (11):



(11)

con los compuestos de fórmula (7) como se ha definido previamente, usando condiciones análogas descritas para la preparación de compuestos de fórmula (5) a partir de compuestos de fórmula (6).

Los compuestos de fórmula (11) pueden prepararse a partir de los correspondientes derivados hidroxi de fórmula (12):

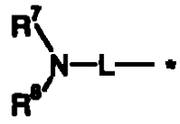


(12)

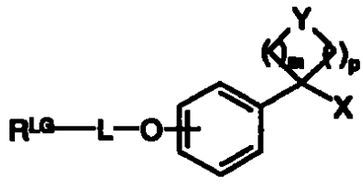
usando condiciones análogas descritas para la preparación de compuestos de fórmula (3) a partir de compuestos de fórmula (4).

Los compuestos de fórmula (12) están en el mercado o se fabrican usando procedimientos de la bibliografía bien conocidos para el especialista en la técnica.

Un ejemplo de realización de las etapas de procedimiento individuales descrito en esta sección en un orden diferente para obtener compuestos de fórmula (1) en la que Z es O y R es un grupo de fórmula:



es la preparación de estos compuestos mediante la reacción de los compuestos de fórmula (13):



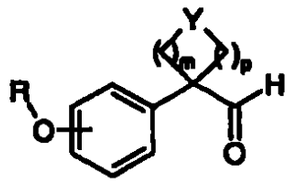
(13)

donde R^{LG} es como se ha definido previamente, con los derivados amino de fórmula NHR^7R^8 usando condiciones análogas a las descritas previamente para la preparación de $R\text{-}R^{LG}$.

Como alternativa, puede conseguirse la misma transformación calentando los compuestos de fórmula (13) con los derivados amino de fórmula NHR^7R^8 y una base (por ejemplo diisopropiletilamina) en un disolvente

adecuado (por ejemplo *N*-metilpirrolidinona) a 150-200°C durante 5-10 minutos usando una estufa por microondas.

Como alternativa, los compuestos de fórmula (1) en la que Z es O, X es -$CH_2NR^1R^2$ y R^1 y R^2 son hidrógeno o un alquilo (C_1-C_4) opcionalmente sustituido o junto con el átomo de N al que están unidos forman un heterociclo saturado de 4, 5 ó 6 miembros opcionalmente sustituido donde un átomo de C puede reemplazarse por N, O, S, SO o SO_2, pueden prepararse por aminación reductora de los compuestos de fórmula (14):



(14)

con el derivado amino de fórmula HNR^1R^2 y un agente reductor (por ejemplo $NaHB(OAc)_3$), opcionalmente en presencia de un ácido de Lewis (por ejemplo $Ti(O^iPr)_4$) en un disolvente adecuado (por ejemplo EtOH) a una temperatura entre 0°C y la temperatura de reflujo.

Los compuestos de fórmula (14) pueden prepararse por reducción de los compuestos de fórmula (3) en la que Z es O con un agente reductor (por ejemplo hidruro de diisobutilaluminio) en un disolvente adecuado (por ejemplo tolueno) a una temperatura entre -78°C y la temperatura ambiente (aproximadamente 20°C).

Como alternativa, los compuestos de fórmula (14) pueden prepararse por oxidación de los compuestos de fórmula (1) en la que Z es O y X es –CH_2OH, usando un oxidante (por ejemplo clorocromato de piridinio) en un disolvente adecuado (por ejemplo diclorometano) a una temperatura entre 0°C y la temperatura de reflujo.

Los compuestos de fórmula (1) en la que X es $-CH_2OH$, pueden prepararse por reducción de los compuestos de fórmula (1) en la que X es -C(O)Oalquilo (C_1-C_4), con un agente reductor (por ejemplo $LiAlH_4$) en un disolvente adecuado (por ejemplo tetrahidrofurano) a una temperatura entre -78ºC y la temperatura de reflujo.

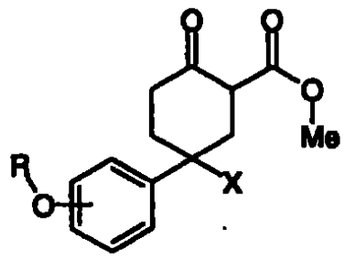
Los compuestos de fórmula (1) en la que X es -C(O)Oalquilo (C_1-C_4), pueden prepararse por esterificación de los compuestos de fórmula (1) en la que X es COOH, usando los procedimientos convencionales bien conocidos para el especialista en la técnica. Por ejemplo, la esterificación puede conseguirse usando un reactivo capaz de activar un ácido carboxílico (por ejemplo cloruro de tionilo) y HOalquilo (C_1-C_4), opcionalmente en presencia de un disolvente adicional (por ejemplo diclorometano) a una temperatura entre 0ºC y la temperatura de reflujo.

Los compuestos de fórmula (1) en la que X es C(O)OH, pueden prepararse por hidrólisis de los compuestos de fórmula (3) como se ha definido previamente con un ácido mineral (por ejemplo HCl acuoso concentrado), opcionalmente en presencia de un co-disolvente adecuado (por ejemplo dioxano) a una temperatura entre 0ºC y la temperatura de reflujo.

Los compuestos de fórmula (1) en la que m y p son ambos iguales a 2, Z es O e Y es CH(OH), pueden prepararse por reducción de los compuestos de fórmula (1) en la que m y p son ambos iguales a 2 e Y es C=O, con un agente reductor (por ejemplo $LiAlH_4$) en un disolvente adecuado (por ejemplo Et_2O) a una temperatura entre 0ºC y la temperatura de reflujo.

Los compuestos de fórmula (1) en la que m y p son ambos iguales a 2, Z es O e Y es C=O, pueden prepararse mediante el tratamiento de los

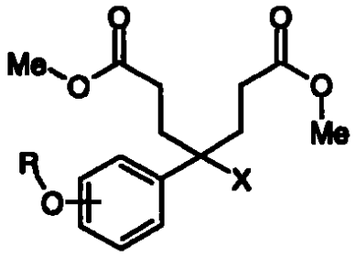
compuestos de fórmula (15):



(15)

con cloruro sódico en un disolvente adecuado (por ejemplo dimetilsulfóxido/agua) a una temperatura entre 100ºC y la temperatura de reflujo.

Los compuestos de fórmula (15) pueden prepararse mediante el tratamiento de los compuestos de fórmula (16):



(16)

con una base (por ejemplo NaH) en un disolvente adecuado (por ejemplo 1,2-dimetoxietano) a una temperatura entre la temperatura ambiente y la temperatura de reflujo.

Los compuestos de fórmula (16) pueden prepararse por alquilación de los compuestos de fórmula (11) como se ha definido previamente con acrilato de metilo y una base (por ejemplo hidróxido benciltrimetilamónico) en un disolvente adecuado (por ejemplo metanol/acetonitrilo) a una temperatura entre la temperatura ambiente y la temperatura de reflujo.

Los compuestos de fórmula (1) en la que X es $-CONH_2$, pueden

prepararse mediante el tratamiento de los compuestos de fórmula (3) como se ha definido previamente con ácido polifosfórico o complejo de trifluoruro de boro-ácido acético a una temperatura entre la temperatura ambiente y 100°C.

Los compuestos de fórmula (1) en la que X es -$CONR^3R^4$, pueden prepararse por reacción de los compuestos de fórmula (1) en la que X es COOH, secuencialmente con un reactivo que puede activar un ácido carboxílico (por ejemplo cloruro de tionilo) y después con el derivado amino de fórmula HNR^3R^4, en un disolvente adecuado (por ejemplo diclorometano) a una temperatura entre 0°C y la temperatura de reflujo. Como alternativa el ácido puede tratarse con la amina de fórmula HNR^3R^4, en presencia de un agente de acoplamiento (por ejemplo TBTU, hexafluorofosfato de O-benzotriazol-1-il-*N,N,N',N'*-tetrametiluronio, clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida), opcionalmente en presencia de un aditivo adecuado (por ejemplo 1-hidroxibenzotriazol) y una base (por ejemplo trietilamina) en un disolvente adecuado (por ejemplo diclorometano, *N,N*-dimetilformamida) a temperatura ambiente.

Los compuestos de fórmula (1) en la que X es $CH_2NR^1R^2$ pueden prepararse por reducción de compuestos de fórmula (1) en la que X es -$CONR^3R^4$ y NR^1R^2 es igual a NR^3R^4, con un agente reductor (por ejemplo hidruro de litio y aluminio) en un disolvente adecuado (por ejemplo tetrahidrofurano, éter) a una temperatura entre la temperatura ambiente y 50°C.

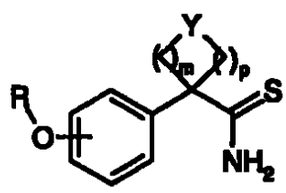
Los compuestos de fórmula (1) en la que X es -CH_2-O-alquilo (C_1-C_4) pueden prepararse por alquilación de los compuestos de fórmula (1) en la que X es -CH_2-OH, con un derivado de fórmula R^{LG}alquilo (C_1-C_4), donde R^{LG} es como se ha definido previamente y una base (por ejemplo NaH) en un

disolvente adecuado (por ejemplo dimetilformamida) a una temperatura entre la temperatura ambiente y la temperatura de reflujo.

Los compuestos de fórmula (1) en la que X es $-CH_2-O-het^2$ pueden prepararse por alquilación de los compuestos de fórmula (1) en la que X es $-CH_2-OH$, con un derivado de fórmula $R^{LG}Het^2$, por acoplamiento cruzado catalizado con paladio con un compuesto haloheteroaromático, usando una fuente de paladio adecuada (por ejemplo tris(dibencilidenacetona)paladio (0)), opcionalmente en presencia de un ligando de quelación (por ejemplo BINAP) y en presencia de una base adecuada (por ejemplo *terc*-butóxido sódico) en un disolvente (por ejemplo tolueno) a una temperatura entre la temperatura ambiente y la temperatura de reflujo.

Los compuestos de fórmula (1) en la que X es het^1, pueden prepararse a partir de compuestos de fórmula (1) en la que X es COOH o como alternativa a partir de compuestos de fórmula (3) o (14) usando procedimientos conocidos para los especialistas en la técnica, tales como los descritos en textos heterocíclicos generales tales como *Heterociclic Chemistry*, J.A. Joule y K. Mills, 4ª Edición, Blackwell publishing, 2000 o Comprehensive Heterociclic chemistry I y II, Pergamon Press.

Por ejemplo, los compuestos de fórmula (1) en la que X es 2-tiazolilo opcionalmente sustituido y Z es O pueden prepararse tratando los compuestos de fórmula (17):



(17)

con un reactivo adecuado (por ejemplo dimetil acetal de bromoacetaldehído, cloroacetona) y HCl en un disolvente adecuado (por ejemplo EtOH) a reflujo.

Los compuestos de fórmula (17) pueden prepararse haciendo reaccionar compuestos de fórmula (3) en la que Z es O con ditilditiofosfato y agua a 60ºC.

Los compuestos de fórmula (1) en la que X es $-CH_2-het^1$ y donde dicho het^1 se une por N, pueden prepararse a partir de compuestos de fórmula (1) en la que X es $-CH_2-NH_2$ usando procedimientos conocidos para los especialistas en la técnica, tales como los descritos en textos heterocíclicos generales tales como *Heterociclic Chemistry*, J.A. Joule y K. Mills, 4ª Edición, Blackwell publishing, 2000 o Comprehensive Heterociclic chemistry I y II, Pergamon Press.

Los compuestos de fórmula (1) en la que X es $-CH_2-het^1$ y donde dicho het^1 se une por C, pueden prepararse a partir de compuestos de fórmula (1) en la que X es -COOH por un procedimiento de dos etapas de homologación de CH_2 usando la síntesis de Arndt-Eistert *(Advanced Organic Chemistry, J.* March, 4ª edición, Wiley-Interscience publication, 1992) seguido de técnicas convencionales para la construcción de heterocicios a partir de un ácido carboxílico conocido para los especialistas en la técnica.

Los compuestos de fórmula (1) y sus precursores que contienen un grupo sulfuro pueden oxidarse para dar los correspondientes sulfóxidos o sulfonas usando técnicas convencionales bien conocidas para los especialistas en la técnica, por ejemplo como se describe en *Comprehensive Organic Transformations*, R.C. Larock, 1ª Edición, 1989 VCH Publishers Inc.

Los especialistas en la técnica apreciarán que ciertos compuestos de

fórmula (1) pueden convertirse en compuestos alternativos de fórmula (1) usando transformaciones químicas convencionales. Los ejemplos de éstos incluyen la acilación y sulfonación de funciones amina (por ejemplo, véanse los ejemplos 166, 229, 230), reacciones reductoras de aminación (por ejemplo, véanse los ejemplos 167, 168), alquilación (por ejemplo, véase el ejemplo 228) o hidrogenación de átomos de halo (por ejemplo, véanse los ejemplos 202, 203).

Los especialistas en la técnica apreciarán que, al realizar los procedimientos descritos anteriormente, puede ser necesario proteger los grupos funcionales de los compuestos intermedios mediante grupos protectores.

Estos grupos funcionales incluyen hidroxilo, amino y ácido carboxílico. Los grupos protectores adecuados para hidroxilo incluyen trialquilsililo y diarilalquilsililo (por ejemplo, *terc*-butildimetilsililo, *terc*-butildifenilsililo o trimetilsililo), alquilo (por ejemplo, metilo o metoxietilo) y tetrahidropiranilo. Los grupos protectores adecuados para amino incluyen *terc*-butiloxicarbonilo, 9-fluorenilmetoxicarbonilo o benciloxicarbonilo. Los grupos protectores adecuados para el ácido carboxílico incluyen ésteres alquílicos (C_1-C_4) o bencílicos.

La protección y desprotección de grupos funcionales puede tener lugar antes o después de cualquiera de las etapas de reacción descritas anteriormente en este documento.

La introducción y retirada de grupos protectores se describe completamente en *Protective Groups in Organic Chemistry*, editado por J.W.F. McOmie, Plenum Press (1973), *Protective Groups in Organic Synthesis*, 2ª

edición, T.W. Greene & P.G.M. Wutz, Wiley-Interscience Publication, 1991) y *Protecting Groups*, P.J. Kocienski, Thieme, 1994.

Además, los compuestos de fórmula (1) así como los intermedios para su preparación, pueden purificarse de acuerdo con diversos procedimientos bien conocidos tales como recristalización y cromatografía.

Los compuestos de fórmula (1), sus sales y/o formas derivadas farmacéuticamente aceptables, son compuestos valiosos farmacéuticamente activos, que son adecuados para la terapia y profilaxis de diversos trastornos en los que está implicado el receptor de histamina H_3 o en los que el agonismo o antagonismo de este receptor puede inducir un beneficio.

Los compuestos de la invención destinados para uso farmacéutico pueden administrarse en forma de productos cristalinos o amorfos. Pueden obtenerse, por ejemplo, en forma de lechos cortos sólidos, polvos o películas por procedimientos tales como precipitación, cristalización, liofilización, secado por pulverización o secado por evaporación. Para este propósito se puede usar secado por microondas o radiofrecuencia.

Pueden administrarse solos o en combinación con uno o más de otros compuestos de la invención o en combinación con uno o más de otros fármacos (o en forma de cualquier combinación de los mismos). Generalmente, se administrarán en forma de formulación junto con uno o más excipientes farmacéuticamente aceptables. El término "excipiente" se usa en este documento para describir cualquier ingrediente distinto del(los) compuesto(s) de la invención. La elección de excipiente dependerá en gran medida de factores tales como el modo particular de administración, el efecto del excipiente en solubilidad y estabilidad y de la naturaleza de la forma de

dosificación.

De acuerdo con otro aspecto de la invención, se proporciona una composición farmacéutica que incluye un compuesto de fórmula (1) o una sal y/o solvato farmacéuticamente aceptable del mismo, como se define en una cualquiera de las reivindicaciones precedentes, junto con un excipiente farmacéuticamente aceptable.

Las composiciones farmacéuticas adecuadas para la administración de compuestos de la presente invención y los procedimientos para su preparación serán fácilmente evidentes para los especialistas en la técnica. Tales composiciones y procedimientos para su preparación pueden encontrarse, por ejemplo en Remington's Pharmaceutical Sciences, 19ª Edición (Mack Publishing Company, 1995).

Los compuestos de la invención pueden administrarse por vía oral. La administración oral puede implicar tragar, de forma que el compuesto entra en el tracto gastrointestinal, o puede emplearse administración bucal o sublingual mediante la cual el compuesto entra directamente en el torrente circulatorio desde la boca.

Las formulaciones adecuadas para la administración oral incluyen formulaciones sólidas tales como comprimidos, cápsulas que contienen particulados, líquidos o polvos, grageas (incluyendo rellenas de líquido), gomas de mascar, multi- y nano-particulados, geles, solución sólido, liposoma, películas, óvulos, pulverizadores y formulaciones líquidas.

Las formulaciones líquidas incluyen suspensiones, soluciones, jarabes y elixires. Tales formulaciones pueden emplearse como cargas en cápsulas duras o blandas y comprenden típicamente un vehículo, por ejemplo agua,

etanol, polietilenglicol, propilenglicol, metilcelulosa o un aceite adecuado y uno o más agentes emulsionantes y/o agentes de suspensión. Las formulaciones líquidas también pueden prepararse mediante la reconstitución de un sólido, por ejemplo, a partir de un sello.

Los compuestos de la invención también pueden usarse en formas de dosificación de rápida disolución y de rápida disgregación tales como las descritas en Expert Opinion in Therapeutic Patents, 11 (6), 981-986 de Liang y Chen (2001).

Para formas de dosificación en comprimidos, dependiendo de la dosis, el fármaco puede prepararse con el 1% en peso al 80% en peso de la forma de dosificación, más típicamente del 5% en peso al 60% en peso de la dosificación. Además del fármaco, los comprimidos contienen generalmente un disgregante. Los ejemplos de disgregantes incluyen almidón glicolato sódico, carboximetilcelulosa sódica, carboximetilcelulosa cálcica, croscarmelosa sódica, crospovidona, polivinilpirrolidona, metilcelulosa, celulosa microcristalina, hidroxipropilceluosa sustituida con alquilo inferior, almidón, almidón pregelatinizado y alginato sódico. Generalmente, el disgregante comprenderá del 1% en peso al 25% en peso, preferiblemente del 5% en peso al 20% en peso de la forma de dosificación.

Los aglutinantes se usan generalmente para impartir calidades cohesivas a una formulación en comprimido. Los aglutinantes adecuados incluyen celulosa microcristalina, gelatina, azúcares, polietilenglicol, gomas naturales y sintéticas, polivinilpirrolidona, almidón pregelatinizado, hidroxipropilcelulosa e hidroxipropilmetilcelulosa. Los comprimidos también pueden contener diluyentes tales como lactosa (monohidrato, monohidrato

secado con pulverizador, anhidro y similares), manitol, xilitol, dextrosa, sacarosa, celulosa microcristalina, almidón y fosfato cálcico dibásico dihidrato.

Los comprimidos también pueden contener tensioactivos, tales como lauril sulfato sódico y polisorbato 80 y deslizantes tales como dióxido de silicio y talco. Cuando están presentes, los agentes tensioactivos pueden comprender del 0,2% en peso al 5% en peso y los deslizantes pueden comprender del 0,2% en peso al 1% en peso del comprimido.

Los comprimidos también contienen generalmente lubricantes tales como estearato de magnesio, estearato de calcio, estearato de cinc, estearil fumarato sódico y mezclas de estearato de magnesio con lauril sulfato sódico. Los lubricantes comprenden generalmente del 0,25% en peso al 10%, preferiblemente del 0,5% en peso al 3% en peso del comprimido.

Otros posibles ingredientes incluyen anti-oxidantes, colorantes, agentes aromatizantes, conservantes y agentes que enmascaran el sabor.

Los comprimidos ilustrativos contienen hasta aproximadamente el 80% del fármaco, de aproximadamente el 10% en peso a aproximadamente el 90% en peso de aglutinante, de aproximadamente el 0% en peso a aproximadamente el 85% en peso de diluyente, de aproximadamente el 2% en peso a aproximadamente el 10% en peso de disgregante y de aproximadamente el 0,25% en peso a aproximadamente el 10% en peso de lubricante.

Las mezclas de comprimido pueden comprimirse directamente o con un rodillo para formar comprimidos. Las mezclas de comprimidos o porciones de mezclas pueden, alternativamente, granularse en húmedo, en seco o por fusión, cuajarse en estado fundido o extruirse antes de la formación de

comprimidos. La formulación final puede comprender una o más capas y puede estar recubierta o no recubierta; pueden estar incluso encapsulada.

La formulación de comprimidos se analiza en Pharmaceutical Dosage Forms: Tablets, Vol. 1, de H. Lieberman y L. Lachman, (Marcel Dekker, Nueva York, 1980).

Las películas orales consumibles para uso humano o veterinario son típicamente formas de dosificación en películas finas flexibles solubles o hinchables en agua que pueden ser de disolución rápida o mucoadhesivas y comprenden típicamente un compuesto de fórmula (1), un polímero que forma una película, un aglutinante, un disolvente, un humectante, un plastificante, un estabilizante o emulsionante, un agente que modifica la viscosidad y un disolvente. Algunos componentes de la formulación pueden realizar más de una función.

El compuesto de fórmula (1) puede ser soluble o insoluble en agua. Un compuesto soluble en agua comprende típicamente del 1% en peso al 80% en peso, más típicamente del 20% en peso al 50% en peso de los solutos. Los compuestos menos solubles pueden comprender una mayor proporción de composición, típicamente hasta el 88% en peso de los solutos. Como alternativa, el compuesto de fórmula (1) puede estar en forma de perlas multiparticuladas.

El polímero que forma una película puede seleccionarse entre polisacáridos naturales, proteínas o hidrocoloides sintéticos y está típicamente presente en el intervalo del 0,01 al 99% en peso, más típicamente en el intervalo del 30 al 80% en peso.

Otros posibles ingredientes incluyen anti-oxidantes, colorantes,

aromatizantes y potenciadores del sabor, conservantes, agentes de estimulación salivar, agentes refrescantes, co-disolventes (incluyendo aceites), emolientes, agentes para carga, agentes anti-espumantes, tensioactivos y agentes que enmascaran el sabor.

Las películas de acuerdo con la invención se preparan típicamente por secado con evaporación de películas acuosas finas recubiertas en un soporte o papel desprendible. Esto puede realizarse en una estufa o embudo de secado, típicamente un secador recubridor combinado o por liofilización o al vacío.

Las formulaciones sólidas para administración oral pueden formularse para ser de liberación inmediata y/o modificada. Las formulaciones de liberación modificada incluyen liberación retardad, sostenida, por pulsos, controlada, dirigida y programada.

Las formulaciones de liberación modificada adecuadas para los propósitos de la invención se describen en la Patente de Estados Unidos Nº 6.106.864. Los detalles de tecnologías de liberación modificada adecuadas tales como dispersiones de alta energía, partículas osmóticas y recubiertas se encuentran en Verma *y col.*, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). El uso de goma de mascar para conseguir una liberación controlada se describe en el documento WO 00/35298.

Los compuestos de la invención también pueden administrarse directamente en el flujo sanguíneo, en el músculo o en un órgano interno. Los medios adecuados para la administración parenteral incluyen intravenosa, intraarterial, intraperitoneal, intratecal, intraventricular, intrauretral, intrasternal, intracraneal, intramuscular y subcutánea. Los dispositivos adecuados para la administración parenteral incluyen agujas (incluyendo microagujas), inyectores

sin agujas y técnicas de infusión.

Las formulaciones parenterales son típicamente soluciones acuosas que pueden contener excipientes tales como sales, carbohidratos y agentes de tamponación (preferiblemente a un pH de 3 a 9) pero, para algunas aplicaciones, pueden formularse de forma más adecuada como solución estéril no acuosa o como forma seca para usarse junto con un vehículo adecuado tal como agua estéril sin pirógenos.

La preparación de formulaciones parenterales en condiciones estériles, por ejemplo, por liofilización, pueden conseguirse fácilmente usando técnicas farmacéuticas convencionales que conocen bien los especialistas en la técnica.

La solubilidad de los compuestos de fórmula (1) usados en la preparación de soluciones parenterales se puede aumentar mediante el uso de técnicas de formulación apropiadas, tales como la incorporación de agentes que mejoran la solubilidad.

Las formulaciones para administración parenteral pueden formularse para ser de liberación inmediata y/o modificada. Las formulaciones de liberación modificada incluyen liberación retrasada, sostenida, por pulsos, controlada, dirigida y programada. De esta forma, los compuestos de la invención pueden formularse en forma de sólido, semi-sólido o líquido tixotrópico para la administración en forma de depósito implantado que proporciona una liberación modificada del compuesto activo. Los ejemplos de tales formulaciones incluyen stents recubiertos de fármaco y microesferas de ácido poli(*dl*-láctico-coglicólico) (PGLA).

Los compuestos de la invención también se pueden administrar de forma tópica en la piel o mucosa, es decir, por vía dérmica o transdérmica. Las

formulaciones típicas para este propósito incluyen geles, hidrogeles, lociones, soluciones, cremas, pomadas, polvos, apósitos, espumas, películas, parches para la piel, obleas, implantes, esponjas, fibras, vendajes y microemulsiones. También se pueden usar liposomas. Los vehículos típicos incluyen alcohol, agua, aceite mineral, petrolato líquido, petrolato blanco, glicerina, polietilenglicol y propilenglicol. Pueden incorporarse agentes que mejoran la penetración - véase, por ejemplo, J Pharm Sci, 88 (10), 955-958 de Finnin y Morgan (Octubre 1999).

Otros medios de administración tópica incluyen la administración por electroporación, iontoforesis, fonoforesis, sonoforesis e inyección con microagujas o sin agujas (por ejemplo, Powderject™, Bioject™, etc.)

Las formulaciones para administración tópica pueden formularse para ser de liberación inmediata y/o modificada. Las formulaciones de liberación modificada incluyen liberación retrasada, sostenida, por pulsos, controlada, dirigida y programada.

Los compuestos de la invención también se pueden administrar por vía intranasal o por inhalación, típicamente en forma de polvo seco (sólo o en forma de mezcla por ejemplo, en una mezcla seca con lactosa o en forma de partícula de componentes mezclados, por ejemplo, mezclado con fosfolípidos, tal como fosfatidilcolina) con un inhalador de polvo seco o en forma de aerosol nebulizador con un recipiente presurizado, bomba, nebulizador, atomizador (preferiblemente un atomizador que usa electrohidrodinámica para producir una niebla fina) o nebulizador, con o sin el uso de un propelente adecuad , tal como 1,1,1,2-tetrafluoroetano o 1,1,1,2,3,3,3-heptafluoropropano. Para el uso intranasal, el polvo puede comprender un agente bioadhesivo, por ejemplo,

quitosano o ciclodextrina. .

El recipiente presurizado, bomba, nebulizador, atomizador o nebulizador contiene una solución o suspensión de los compuestos de la invención que comprende, por ejemplo, etanol, etanol acuoso o un agente alternativo adecuado para dispersar, solubilizar o extender la liberación del componente activo, un propulsor en forma de disolvente y un tensioactivo opcional, tal como trioleato de sorbitán, ácido oleico o un ácido oligoláctico.

Antes de usar en una formulación de polvo seco o suspensión, el fármaco producto se microniza a un tamaño adecuado para la administración por inhalación (típicamente menos de 5 micrómetros). Esto se puede conseguir mediante cualquier procedimiento de molienda adecuado, tal como por trituración por chorro en espiral, trituración por chorro en lecho fluido, procesado con fluido supercrítico para formar nanopartículas, homogeneización a alta presión o secado con nebulizador.

Las cápsulas (fabricadas, por ejemplo, a partir de gelatina o hidroxipropilmetilcelulosa), ampollas y cartuchos para usar en un inhalador o insuflador pueden formularse para contener una mezcla en polvo del compuesto de la invención, una base en polvo adecuada tal como lactosa o almidón y un modificador de la actuación, tal como *l*-leucina, manitol o estearato de magnesio. La lactosa puede ser anhidra o en forma de monohidrato, preferiblemente la última. Otros excipientes adecuados incluyen dextrano, glucosa, maltosa, sorbitol, xilitol, fructosa, sacarosa y trehalosa.

Una formulación en solución adecuada para usar en un atomizador usando electrohidrodinámica para producir una niebla fina puede contener de 1 µg a 20 mg del compuesto de la invención por actuación y el volumen de la

actuación puede variar de 1 µl a 100 µl. Una formulación típica puede comprender un compuesto de fórmula (1), propilenglicol, agua estéril, etanol y cloruro sódico. Otros disolventes alternativos que pueden usarse en lugar de propilenglicol incluyen glicerol y polietilenglicol.

Pueden añadirse aromatizantes adecuados, tales como mentol y levomentol o edulcorantes tales como sacarina o sacarina sódica a aquellas formulaciones de la invención que se van a administrar por inhalación o por vía intranasal.

Las formulaciones para administración inhalada/intranasal pueden formularse para ser de liberación inmediata y/o modificada usando, por ejemplo, PGLA. Las formulaciones de liberación modificada incluyen liberación retrasada, sostenida, por pulsos, controlada, dirigida y programada.

En el caso de inhaladores de polvo seco y aerosoles, la unidad de dosificación se determina por medio de una válvula que suministra una cantidad medida. Las unidades de acuerdo con la invención se preparan típicamente para administrar una cantidad medida o "puff" que contiene de 1 µg a 400 µg del compuesto de fórmula (1). La dosis total diaria estará típicamente en el intervalo de 1 µg a 20 mg que puede administrarse en una única dosis o, más habitualmente, en dosis divididas a lo largo del día.

Los compuestos de la invención pueden administrarse por vía rectal o vaginal, por ejemplo, en forma de supositorio, pesario o enema. La manteca de coco es una base de supositorio convencional, pero pueden usarse diversas alternativas según sea apropiado.

Las formulaciones para administración rectal/vaginal pueden formularse para ser de liberación inmediata y/o modificada. Las formulaciones de

liberación modificada incluyen liberación retrasada, sostenida, por pulsos, controlada, dirigida y programada.

Los compuestos de la invención también pueden administrarse directamente en el ojo u oído, típicamente en forma de gotas de una suspensión o solución micronizada en solución salina isotónica estéril con pH ajustado. Otras formulaciones adecuadas para administración ocular y aural incluyen lociones, implantes biodegradables (por ejemplo, esponjas de gel absorbible, colágeno) y no biodegradables (por ejemplo silicona), obleas, lentillas y sistemas particulados o vesiculares, tales como niosomas o liposomas. Puede incorporarse un polímero tal como ácido poliacrílico reticulado, poli(alcohol vinílico), ácido hialurónico, un polímero de celulosa, por ejemplo, hidroxipropilmetilcelulosa, hidroxietilcelulosa o metilcelulosa o un polímero heteropolisacárido, por ejemplo, goma de gelano, junto con un conservante tal como cloruro de benzalconio. Tales formulaciones también pueden administrarse por iontoforesis.

Las formulaciones para administración ocular/aural pueden formularse para ser de liberación inmediata y/o modificada. Las formulaciones de liberación modificada incluyen liberación retrasada, sostenida, por pulsos, controlada, dirigida y programada.

Los compuestos de la invención pueden combinarse con entidades macromoleculares solubles, tales como ciclodextrina y derivados adecuados de la misma o polímeros que contiene polietilenglicol, para mejorar su solubilidad, velocidad de disolución, enmascarado del sabor, biodisponibilidad y/o estabilidad para usar en cualquiera de los modos de administración mencionados anteriormente.

Los complejos de fármaco-ciclodextrina, por ejemplo, son útiles generalmente para la mayoría de las formas de dosificación y vías de administración. Pueden usarse complejos de inclusión y no inclusión. Como alternativa a la formación directa de complejo con el fármaco, la ciclodextrina puede usarse como aditivo auxiliar, es decir, como un vehículo, diluyente o solubilizante. Las más utilizadas habitualmente para estos propósitos son alfa-, beta- y gamma-ciclodextrinas, ejemplos de las cuales se pueden encontrar en las Solicitudes Internacionales de Patentes Nº WO/9111172, WO 94/02518 y WO 98/55148.

Siempre que sea deseable administrar una combinación de compuestos activos, por ejemplo, con el propósito de tratar una enfermedad o afección particular, está dentro del alcance de la presente invención que se pueden combinar convenientemente dos o más composiciones farmacéuticas, al menos una de las cuales contiene un compuesto de acuerdo con la invención, en forma de kit adecuado para la coadministración de las composiciones.

De esta forma, el kit de la invención comprende dos o más composiciones farmacéuticas distintas, al menos una de las cuales contiene un compuesto de fórmula (1) de acuerdo con la invención y medios para mantener separadas dichas composiciones, tal como un recipiente, un bote dividido un paquete dividido con papel de aluminio. Un ejemplo de tal kit es el envase tipo blíster familiar que se usa para el envasado de comprimidos, cápsulas y similares.

EL kit de la invención es particularmente adecuado para administrar distintas formas de dosificación, por ejemplo parenteral, para administrar las distintas composiciones en distintos intervalos de dosificación o para valorar las

distintas composiciones entre sí. Para mejorar la aceptación, el kit contiene típicamente instrucciones para la administración y puede proporcionarse con el denominado recordatorio.

Para la administración a pacientes humanos, la dosis total diaria de los compuestos de la invención está típicamente en el intervalo de 0,001 mg a 2000 mg dependiendo, por supuesto, de la vía de administración. Por ejemplo, la administración oral puede requerir una dosis total diaria de 1 mg a 2000 mg mientras que una dosis diaria intravenosa puede requerir solamente de 0,01 mg a 100 mg. La dosis total diaria administrada en una única dosis o en dosis divididas puede, a discreción del médico, estar fuera del intervalo típico que se proporciona en este documento.

Estas dosificaciones están basadas en un sujeto humano medio con un peso de aproximadamente 60 kg a 70 kg. El médico será capaz de determinar fácilmente dosis para sujetos cuyos pesos están fuera de este intervalo, tales como niños y ancianos.

Para evitar dudas, las referencias en este documento a "tratamiento" incluyen referencias a tratamiento curativo, paliativo y profiláctico.

De acuerdo con otra realización de la presente invención, los compuestos de fórmula (1) o sales farmacéuticamente aceptables, formas derivadas o composiciones de los mismos, pueden usarse también como combinación con uno o más agentes terapéuticos adicionales para co-administrarse a un paciente para obtener algún resultado terapéutico deseado. El segundo y los demás agentes terapéuticos adicionales también pueden ser un compuesto de fórmula (1), o una sal farmacéuticamente aceptable, formas derivadas o composiciones de la misma, o uno o más ligandos del receptor H_3

conocidos en la técnica. Más típicamente, el segundo y los demás agentes terapéuticos se seleccionarán entre una clase distinta de agentes terapéuticos.

Como se usa en este documento, los términos "co-administración", "co-administrado" y "en combinación con", en referencia a los compuestos de fórmula (1) y uno o más agentes terapéuticos, significa, se refiere e incluye los siguientes:

- administración simultánea de tal combinación de compuesto o compuestos de fórmula (1) y agentes terapéuticos a un paciente en necesidad de tratamiento, cuando tales componentes se formulan juntos en un única forma de dosificación que libera dichos componentes sustancialmente al mismo tiempo en dicho paciente,
- administración sustancialmente simultánea de tal combinación de compuesto o compuestos de fórmula (1) y agentes terapéuticos a un paciente en necesidad de tratamiento, cuando tales componentes se formulan por separado en formas de dosificación distintas que el paciente toma sustancialmente al mismo tiempo, tras lo cual dichos componentes se liberan sustancialmente al mismo tiempo en el paciente,
- administración secuencial de tal combinación de compuesto compuestos de fórmula (1) y agentes terapéuticos a un paciente en necesidad de tratamiento, cuando tales componentes se formulan por separado en formas de dosificación distintas que el paciente toma en momentos consecutivos con un intervalo de tiempo significativo entre cada administración, tras lo cual dichos componentes se liberan en momentos sustancialmente distintos en el paciente,

- administración secuencial de tal combinación de compuesto o compuestos de fórmula (1) y agentes terapéuticos a un paciente en necesidad de tratamiento, cuando tales componentes se formulan juntos en un única forma de dosificación que libera dichos componentes de una forma controlada tras lo cual se administran de forma concurrente, consecutiva y/o solapada al mismo tiempo y/o en distintos momentos por dicho paciente,

donde cada parte puede administrarse por la misma o distinta ruta.

Los ejemplos adecuados de otros agentes terapéuticos que pueden usarse en combinación con los compuestos de fórmula (1) o sales farmacéuticamente aceptables, formas derivadas o composiciones de la misma incluyen, pero sin limitación:

- Antagonistas del receptor de histamina H_1, pór ejemplo loratidina, desloratidina, fexofenadina y cetirizina
- Antagonistas del receptor de histamina H_4
- Antagonistas del receptor de histamina H_2
- Antagonistas del leucotrieno, incluyendo antagonistas de LTB_4, LTC_4, LTD_4 y LTE_4 en particular Montelukast
- Inhibidores de fosfodiesterasa tales como inhibidores de PDE4 o PDE5
- Inhibidores de la recaptación de neurotransmisores, por ejemplo fluoxetina, sertralina, paroxetina, ziprasidona
- Inhibidores de 5-lipoxigenasa (5-LO) o antagonistas de la proteína de activación de la 5-lipoxigenasa (FLAP),
- Agentes agonistas vasoconstrictores y simpatomiméticos del adrenorreceptor α_1 y α_2 para uso descongestivo

- Antagonistas del receptor muscarínico M3 o agentes anticolinérgicos
- Agonistas del adrenoceptor-β_2
- Teofilina
- Cromoglicato sódico
- Inhibidores de COX-1 (NSAID) e inhibidores selectivos de COX-2
- Glucocorticosteroides orales o inhalados
- Anticuerpos monoclonales activos frente a entidades inflamatorias endógenas
- Agentes anti factor de necrosis tumoral α (anti-TNF-α)
- Inhibidores de adhesión molecular incluyendo antagonistas VLA-4
- Antagonistas del receptor de quinina B_1 y B_2
- Agentes inmunosupresores
- Inhibidores de metaloproteasas de matriz (MMP)
- Antagonistas del receptor de taquiquinina NK_1, NK_2 y NK_3
- Inhibidores de elastasa
- Agonistas del receptor de adenosina A2a
- Inhibidores de la uroquinasa
- Compuestos que actúan en los receptores de dopamina, por ejemplo agonistas D2
- Moduladores de la ruta $NF_k\beta$, por ejemplo inhibidores IKK
- Agentes que pueden clasificarse como mucolíticos o anti-tusivos
- Antibióticos
- Moduladores de las rutas de señalización de citoquina tales como inhibidores de quinasa p38 MAP, quinasa syk o quinasa JAK
- inhibidores de HDAC (histona desacetilasa) e

- inhibidores de quinasa PI3

De acuerdo con la presente invención, se prefiere la combinación de los compuestos de fórmula (1) con:

- Antagonistas del receptor de histamina H_1, por ejemplo loratidina, desloratidina, fexofenadina y cetirizina
- Antagonistas del receptor de histamina H_4
- Antagonistas del receptor de histamina H_2
- Antagonistas del leucotrieno (LTRA) incluyendo antagonistas de LTB_4, LTC_4, LTD_4 y LTE_4 en particular Montelukast
- Inhibidores de fosfodiesterasa PDE4
- Inhibidores de la recaptación de neurotransmisores, por ejemplo fluoxetina, sertralina, paroxetina, ziprasidona

Los compuestos de fórmula (1) tienen la capacidad de interactuar con el receptor H_3 y por lo tanto tienen un amplio intervalo de aplicaciones terapéuticas, como se describe adicionalmente a continuación, dado el papel esencial que juega el receptor H_3 en la fisiología de todos los mamíferos. De acuerdo con esta invención, los ligandos H_3 incluyen antagonistas, agonistas y agonistas inversos del receptor H_3. Para las afecciones preferidas a tratar de acuerdo con la invención, se cree que los antagonistas de H_3 son los más adecuados.

En otro aspecto de la invención se proporciona un compuesto de la fórmula (1) como se define en este documento, o una sal y/o solvato farmacéuticamente aceptable del mismo, para usar como medicamento.

Un aspecto adicional de la invención se refiere a los compuestos de fórmula (1), o sales farmacéuticamente aceptables, formas derivadas o

composiciones de los mismos, para usar en el tratamiento de enfermedades, trastornos y afecciones en las que está implicado el receptor H_3. Más específicamente, la presente invención también se refiere a los compuestos de fórmula (1), o sales farmacéuticamente aceptables, formas derivadas o composiciones de los mismos, para usar en el tratamiento de enfermedades, trastornos y afecciones seleccionados entre el grupo compuesto por:

- Enfermedades del sistema nervioso central: trastornos del sueño, migraña, disquinesia, ansiedad inducida por estrés, trastornos psicóticos, epilepsia, enfermedades con deficiencias cognitivas tales como la enfermedad de Alzheimer o el impedimento cognitivo leve, depresión, trastornos del estado anímico, esquizofrenia, trastornos de ansiedad, trastorno de hiperactividad por déficit de atención (ADHD), trastornos psicóticos, obesidad, mareos, vértigo, epilepsia, mareo en movimiento,
- Enfermedades inflamatorias
- Enfermedades respiratorias (síndrome de insuficiencia respiratoria en adultos, síndrome de insuficiencia respiratoria aguda, bronquitis, bronquitis crónica, enfermedad pulmonar obstructiva crónica, fibrosis quística, asma, enfisema, rinitis, sinusitis crónica), alergia, respuestas de las vías respiratorias inducidas por alergia, rinitis alérgica, rinitis vírica, rinitis no alérgica, rinitis perenne y estacional, congestión nasal y congestión alérgica.
- Disfunción sexual femenina incluyendo trastorno del deseo sexual hipoactivo, trastorno de la excitación sexual, trastorno orgásmico y trastorno de dolor sexual

- Disfunción sexual masculina incluyendo trastornos del deseo en hombres, disfunción eréctil masculina, trastornos orgásmicos masculinos tales como eyaculación precoz
- Disfunciones cardiacas tales como isquemia miocárdica y arritmia
- Enfermedades del tracto gastrointestinal tales como enfermedad inflamatoria intestinal, enfermedad de Crohn, colitis ulcerosa
- Cáncer
- Hipotensión
- Dolor y
- Afecciones de vejiga superactiva.

Los compuestos de fórmula (1) de la invención son particularmente adecuados para tratar alergia, respuestas de las vías respiratorias inducidas por alergia, rinitis alérgica, rinitis vírica, rinitis no alérgica, rinitis perenne y estacional, congestión nasal y congestión alérgica.

Otro aspecto de la invención también se refiere al uso de los compuestos de fórmula (1), o sales farmacéuticamente aceptables, formas derivadas o composiciones de los mismos, para la fabricación de un fármaco como ligando H_3. En particular, la presente invención se refiere al uso de compuestos de fórmula (1), o sales farmacéuticamente aceptables, formas derivadas o composiciones de los mismos, para la fabricación de un fármaco para el tratamiento de enfermedades y/o afecciones mediadas por H_3, en particular las enfermedades y/o afecciones enumeradas anteriormente.

Otro aspecto de la invención se refiere al uso de un compuesto de fórmula (1) o una sal farmacéuticamente aceptable, forma derivada o composición del mismo, para la fabricación de un medicamento para el

tratamiento de disfunción sexual femenina, incluyendo trastornos de deseo sexual hipoactivo, trastorno de la excitación sexual, trastorno orgásmico y trastorno de dolor sexual o para el tratamiento de la disfunción sexual masculina incluyendo trastornos del deseo masculino, disfunción eréctil masculina o trastornos orgásmicos masculinos tales como eyaculación precoz.

Como consecuencia, la presente invención proporciona un procedimiento particularmente interesante para tratar un mamífero, incluyendo un ser humano, con una cantidad eficaz de un compuesto de fórmula (1), o una sal farmacéuticamente aceptable, forma derivada o composición del mismo. Más precisamente, la presente invención proporciona un procedimiento particularmente interesante para el tratamiento de enfermedades y/o afecciones mediadas por H3 en un mamífero, incluyendo un ser humano, en particular las enfermedades y/o afecciones enumeradas anteriormente, que comprende administrar a dicho mamífero una cantidad eficaz de un compuesto de fórmula (1), sus sales farmacéuticamente aceptables y/o formas derivadas.

EJEMPLOS

Los siguientes ejemplos ilustran la preparación de derivados fenol y tiofenol de fórmula (1)

glosario

APCI	ionización química a presión atmosférica
Arbocel®	agente de filtrado
BINAP	2,2'-Bis(difenilfosfino)-1,1'-binaftilo
BOC	*terc*-butoxicarbonilo
a	ancho
CDI	carbonildiimidazol

δ	desplazamiento químico
d	doblete
Δ	calor
DCM	diclorometano
DIAD	azodicarboxilato de diisopropilo
DMF	*N*,*N*-dimetilformamida
DMSO	dimetilsulfóxido
EDCI	véase WSCDI
IEN$^+$	barrido positivo en ionización por electronebulización
IEN$^-$	barrido negativo en ionización por electronebulización
h	horas
HBTU	hexafluorofosfato de O-(1*H*-benzotriazol-1-il)-*N*,*N*,*N*',*N*'-tetrametiluronio
HOAT	1-hidroxi-7-azabenzotriazol
HOBT	1-hidroxibenzotriazol
HPLC	cromatografía líquida a alta presión
base de Hunig	diisopropiletilamina
m/z	relación masa carga
min	minutos
EM	espectro de masa
NH_3	solución acuosa de amoniaco 0,88
NMM	*N*-metil-morfolina
RMN	resonancia magnética nuclear
c	cuadruplete
s	singlete

STAB	triacetoxiborohidruro sódico
t	triplete
TBME	éter de *terc*-butil metilo
TBTU	tetrafluoroborato de 2-(1*H*-benzotriazol-1-il)-1,1,3,3-tetrametiluronio
Tf	trifluorometanosulfonilo
TFA	ácido trifluoroacético
THF	tetrahidrofurano
TLC	cromatografía de capa fina
TosMIC	isocianuro de tosilmetilo
WSCDI	clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida

Intermedio 1: 4-(4-metoxifenil)-tetrahidro-2*H*-piran-4-carbonitrilo

Se añadió lentamente 4-metoxifenilacetonitrilo (10 g, 67,9 mmol) en DMF (50 ml) a una suspensión de NaH (5,04 g, 150 mmol) en DMF (50 ml) a 0ºC en una atmósfera de N_2. La reacción se dejó calentar a temperatura ambiente y se agitó durante 30 minutos. La reacción se enfrió a 0ºC y se añadió gota a gota bis(2-cloroetil)éter (10,7 g, 74,7 mmol) en DMF (100 ml) durante 80 minutos. La reacción se dejó calentar a temperatura ambiente y se agitó durante 1 hora. La reacción se inactivó con agua (200 ml) y se extrajo con acetato de etilo (3x300 ml). Los extractos orgánicos combinados se lavaron con agua (2x200 ml), salmuera (200 ml), se secaron sobre $MgSO_4$, se filtraron, se lavaron con acetato de etilo y se concentraron *al vacío* dando el compuesto del título (17,2 g, 100%).

Intermedio 2: 4-(4-Hidroxi-fenil)-tetrahidro-piran-4-carbonitrilo

Se añadió tribromuro de boro (1 M en DCM, 262 ml) a una solución de 4-

(4-metoxifenil)-tetrahidro-2*H*-piran-4-carbonitrilo (14,7 g, 67,9 mmol) en DCM (294 ml) a 0ºC en una atmósfera de N_2 manteniendo la temperatura por debajo de 5ºC. La reacción se dejó calentar a temperatura ambiente y se agitó durante 48 horas. La mezcla se enfrió a -10-0ºC con acetona en hielo seco y se inactivó con bicarbonato sódico acuoso saturado (294 ml). La mezcla se dejó calentar a temperatura ambiente y se agitó durante 1 hora. La mezcla se separó y la fase acuosa se extrajo con DCM (3x250 ml). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron, se lavaron con DCM y se concentraron *al vacío* dando el compuesto del título (10,8 g, 78%).

Intermedio 3: 4-(4-Dimetilaminometil-tetrahidro-piran-4-il)-fenol

Etapa 1:

A una suspensión agitada de $LiAlH_4$ (79 g, 2,08 mol, 5 eq) en THF (900 ml) a una temperatura de 0 a 5ºC en una atmósfera de nitrógeno se le añadió 4-(4-metoxifenil)-tetrahidro-2*H*-piran-4-carbonitrilo (90 g, 0,414 mol) en THF (900 ml) durante 25 minutos manteniendo la temperatura entre 5 y 10ºC. La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó hasta completarse. Se añadió gota a gota hidróxido sódico (2 N, 850 ml), los sólidos resultantes se filtraron y se lavaron con THF (2x800 ml), los extractos orgánicos se concentraron *al vacío* a 40ºC. El residuo se disolvió en EtOAc (300 ml) y se secó sobre $MgSO_4$, se filtró y se concentró *al vacío* a 40ºC proporcionando {[4-(4-metoxifenil)-tetrahidro-2*H*-piran-4-il]metil}amina en forma de un aceite amarillo claro (92 g, cuantitativo).

Etapa 2

A una solución de {[4-(4-metoxifenil)-tetrahidro-2*H*-piran-4-il]metil}amina (60 g, 0,271 mol) en H_2O (444 ml) y AcOH (213 ml) se le añadió formaldehído

(solución al 37% p/p en H_2O, 408 ml) y la mezcla se enfrió entre 0 y 5 °C. Se añadió triacetoxiborohidruro sódico (345 g, 1,626 mol, 6 eq) en porciones manteniendo la temperatura por debajo de 12°C. La mezcla se agitó a temperatura ambiente hasta completarse. Se añadió lentamente hidróxido sódico (2 M, 1000 ml) y la mezcla se extrajo con DCM (4x250 ml). Los extractos orgánicos se secaron sobre $MgSO_4$, se filtraron y se concentraron *al vacío* a 30°C proporcionando {[4-(4-metoxifenil)-tetrahidro-2*H*-piran-4-il]metil}dimetilamina en forma de un aceite amarillo (53,5 g, 80%).

Etapa 3:

A una suspensión de tiometóxido sódico (49,2 g, 0,702 mol, 5 eq) en DMF (140 ml) se le añadió ([4-(4-metoxifenil)-tetrahidro-2*H*-piran-4-il]metil)dimetilamina (35 g, 0,140 mol) y la mezcla resultante se calentó a 130°C. Una vez completada, se dejó enfriar a temperatura ambiente y se añadió NH_4Cl acuoso saturado (525 ml). La mezcla resultante se extrajo con EtOAc (3x500 ml), se secó sobre $MgSO_4$, se filtró y se concentró *al vacío* a 35°C proporcionando 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (Intermedio 3) en forma de un sólido amarillo (35,7 g, 108%) que contiene DMF y EtOAc residual.

Intermedio 4: 3-{4-[(dimetilamino)metil]tetrahidro-piran-4-il}fenol

Etapa 1:

Se añadió lentamente 3-metoxifenilacetonitrilo (10 g, 67,9 mmol) en DMF (50 ml) a una suspensión de NaH (5,04 g, 150 mmol) en DMF (50 ml) a 0°C en una atmósfera de N_2. La reacción se dejó calentar a temperatura ambiente y se agitó durante 30 minutos. La reacción se enfrió a 0°C y se añadió gota a gota bis(2-cloroetil)éter (10,7 g, 74,7 mmol) en DMF (100 ml) durante 80 minutos. .

La reacción se dejó calentar a temperatura ambiente y se agitó durante 1 hora. La reacción se inactivó con agua (500 ml) y se extrajo con acetato de etilo (3x100 ml). Los extractos orgánicos combinados se lavaron con salmuera (3x50 ml), se secaron sobre $MgSO_4$, se filtraron, se lavaron con acetato de etilo y se concentraron *al vacío*. La mezcla en bruto se purificó por cromatografía en columna, eluyendo con heptano aumentando la polaridad a heptano:acetato de etilo (90:10), dando 4-(3-metoxifenil)tetrahidro-piran-4-carbonitrilo (4,1 g, 28%).

Etapa 2:

A una suspensión agitada de $LiAlH_4$ (3,7 g, 96,7 mmol) en éter dietílico (100 ml) se enfrió a 0°C se le añadió gota a gota una solución de 4-(3-metoxifenil)-tetrahidro-piran-4-carbonitrilo (4,2 g, 19,3 mmol) en éter dietílico (100 ml). Después de agitarse a temperatura ambiente durante 30 minutos, la mezcla de reacción se calentó a reflujo durante 15 minutos más. La mezcla se enfrió a 10°C y se añadieron sucesivamente gota a gota agua, hidróxido sódico (15% p/v en agua, 0,48 ml) y agua. Después de agitarse durante 15 minutos a temperatura ambiente, la mezcla se filtró sobre tierra de diatomeas y se concentró. El residuo se purificó con cromatografía ultrarrápida (DCM/MeOH: 95/5) proporcionando [4-(3-metoxifenil)tetrahidro-piran-4-il]metilamina (4 g, 94%).

Etapa 3:

Una mezcla de [4-(3-metoxifenil)tetrahidro-piran-4-il]metilamina (0,51 g, 2,3 mmol), ácido acético (0,535 ml, 9,2 mmol), triacetoxiborohidruro sódico (0,974 g, 4,6 mmol), solución al 37% de formaldehído en agua (0,55 ml) y DCM (40 ml) se agitó durante 72 horas a temperatura ambiente. La fase orgánica se lavó dos veces con agua. Se añadió NaOH concentrado a la fase acuosa (pH

12) y la mezcla se extrajo dos veces con diclorometano. Los extractos orgánicos se secaron sobre Na_2SO_4, se filtraron y se concentraron al vacío proporcionando *N*-[[4-(3-metoxifenil)tetrahidro-piran-4-il]metil]-*N*,*N*-dimetilamina en forma de un aceite (0,35 g, 61%).

Etapa 4:

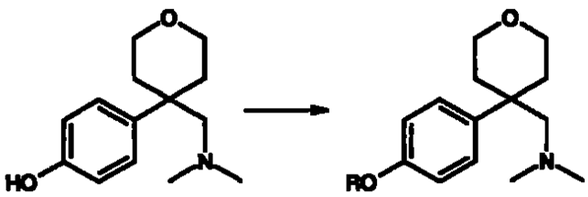
A una suspensión de tiometóxido sódico (0,42 g, 6 mmol) en DMF (1,2 ml) se le añadió *N*-[[4-(3-metoxifenil)tetrahidro-piran-4-il]metil]-*N*,*N*-dimetilamina (0,3 g, 1,2 mmol) y la mezcla resultante se calentó a 65ºC durante 7 horas, se dejó enfriar a temperatura ambiente y se inactivó con NH_4Cl acuoso saturado (6 ml). La mezcla se extrajo con DCM, se secó sobre Na_2SO_4, se filtró y se concentró al vacío proporcionando 0,25 g de producto en bruto. Una mezcla del producto en bruto y HBr (3 ml) se calentó a reflujo durante 1 horas. Después de enfriarse, se añadió agua para inactivar la reacción y la mezcla se basificó con $NaHCO_3$ y se extrajo con DCM. Los extractos orgánicos se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo se purificó por cromatografía ultrarrápida (DCM / MeOH (NH_3 al 10%)) proporcionando 3-[4-[(dimetilamino)metil]tetrahidro-piran-4-il]fenol (0,100 g, 35,5%).

Procedimiento general A para la síntesis de cloruros (R-R^{LG} donde R^{LG} es cloruro):

Se cargó amina (1 eq.) en un matraz de reacción seguido de acetona (3 vol o 20 vol), solución de NaOH 5 M (1,2 eq.) y 1-bromo-3-cloropropano (1,5 eq. o 3 eq.). La reacción se agitó durante una noche a temperatura ambiente. Las fases se separaron y la fase de acetona se concentró al vacío. La fase acuosa se acidificó con una solución de HCl 2 M un pH 1 (~10 vol). El concentrado se diluyó con TBME (30 vol) y se lavó con agua (15 vol). La fase

acuosa se extrajo con TBME (2 x 15 ml). La fase combinada de TBME se lavó con una solución de HCl 2 M (15 ml) y se combinó con la primera fase ácida. Las fases ácidas combinadas se lavaron con TBME (15 vol) y se basificaron un pH 14 con una solución de NaOH 4 M (~40 ml). La fase acuosa se extrajo *con* TBME (3 x 30 ml). Las fases orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron, se lavaron con TBME (5 vol) y se concentraron al vacío dando el cloruro requerido.

Procedimiento General B:



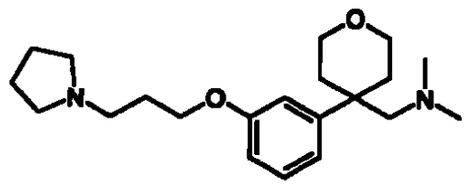
Se calentaron 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (500 mg, 2,13 mmol), cloruro (378 mg, 2,13 mmol), DMF (10 ml), agua (17 ml) y K_2CO_3 (1,18 g, 8,52 mmol) a 130°C. Se enfrió a temperatura ambiente, se le añadió agua (40 ml), se extrajo con EtOAc (3x25 ml) y los extractos orgánicos combinados se lavaron con agua (2x25 ml). Los extractos orgánicos se secaron sobre $MgSO_4$, se filtraron y se concentraron al vacío a 35°C. La purificación del material en bruto por cromatografía sobre sílice, eluyente (MeOH al 4%, NH_3 al 1% en DCM) proporcionó el compuesto del título.

Intermedio 5: 1-(3-Cloro-propil)-pirrolidina

Se agitó pirrolidina (10 g, 0,14 mol), acetona (28 ml), una solución de NaOH 5 M (21 ml) y 1-bromo-3-cloropropano (24,4 g, 0,15 mol) en una atmósfera de N_2 durante 8 horas. La fase orgánica se separó y se concentró *al vacío.* El producto en bruto se purificó por destilación al vacío (p.f. 90°C/30

mbar) dando el compuesto del título (11,7 g, 57%) en forma de un aceite incoloro.

Ejemplo 1: Dimetil-[4-[3-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-piran-4-ilmetil]amina



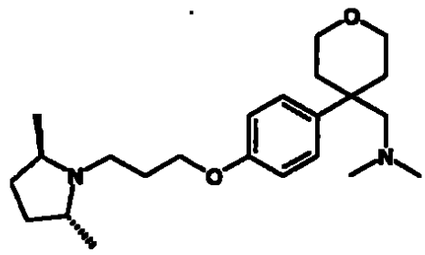
La alquilación de 3-[4-(dimetilamino)metiltetrahidro-2*H*-piran-4-il]fenol (0,1 g, 0,425 mmol) con 1-(3-cloropropil)pirrolidina (0,125 g, 0,85 mmol) de acuerdo con el procedimiento general B dio el compuesto deseado después de la purificación por cromatografía ultrarrápida (0,030 g, 20%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,27-7,18 (m, 1H), 6,92-6,84(m, 2H), 6,75 (dd, 1H), 4,05 (t, 2H), 3,8-3,7 (m, 2H), 3,55 (t, 2H), 2,65 (t, 2H), 2,6-2,5 (m, 4H), 2,4(s, 2H), 2,15-1,85 (m, 6H), 2,0 (s, 6H), 1,85-1,75 (m, 4H).

Intermedio 6: 1-(3-Cloro-propil)-2(*R*),5(*R*)-trans-dimetil-pirrolidina

Se hicieron reaccionar de forma conjunta 2(*R*),5(*R*)-trans-dimetil-pirrolidina (0,75 g, 7,56 mmol), acetona (15 ml, 20 vol), solución de NaOH 5 M (1,8 ml, 1,2 eq.) y 1-bromo-3-cloropropano (3,57 g, 22,7 mmol, 3 eq.) de acuerdo con el procedimiento general A dando el compuesto del título (0,5 g, 38%) en forma de un aceite amarillo.

Ejemplo 2: (4-[4-[3-(2,5-dimetilpirrolidin-1-il)propoxi]fenil]tetrahidro-piran-4-ilmetil)dimetilamina

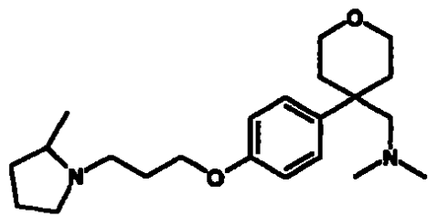


Se hicieron reaccionar de forma conjunta 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (330 mg, 1,43 mmol), 1-(3-cloro-propil)-2,5-trans-dimetil-pirrolidina (221 mg, 1,26 mmol), DMF (7,6 ml) y K_2CO_3 (790 mg, 5,72 mmol) de acuerdo con el procedimiento general B. El material aislado se sometió a cromatografía sobre sílice, eluyente 95:4:1 (DCM, MeOH, NH_3) dando el compuesto del título en forma de un aceite amarillo (180 mg, 34%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,87 (d, 2H), 4,08-3,95 (m, 2H), 3,79-3,70 (m, 2H), 3,59-3,49 (m, 2H), 3,11-3,00 (m, 2H), 2,77 (m, 1H), 2,54 (m, 1H), 2,40 (s, 2H), 2,14-1,81 (m, 8H), 1,96 (s, 6H), 1,44-1,31 (m, 2H), 0,97 (d, 6H).

Intermedio 7: 1-(3-Cloro-propil)-2-metil-pirrolidina

Se hicieron reaccionar de forma conjunta 2-metilpirrolidina (0,9 g, 10,6 mmol), acetona (18 ml, 20 vol), una solución de NaOH 5 M (2,50 ml) y 1-bromo-3-cloropropano (5 g, 31,8 mmol, 3 eq) de acuerdo con el procedimiento general A dando el compuesto del título (1 g, 59%) en forma de un aceite amarillo pálido.

Ejemplo 3: Dimetil-(4-{4-[3-(2-metil-pirrolidin-1-il)-propoxi]-fenil}-tetrahidro-piran-4-ilmetil)-amina



Se hicieron reaccionar de forma conjunta 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (500 mg, 2,13 mmol), 1-(3-cloro-propil)-2-metil-pirrolidina (344 mg, 2,13 mmol), DMF (10 ml) y K_2CO_3 (1,18 g, 8,52 mmol) de acuerdo con el procedimiento general B. El material aislado se sometió a cromatografía sobre sílice, eluyente 95:4:1 (DCM, MeOH, NH_3) dando el compuesto del título en forma de un aceite amarillo (120 mg, 16%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,87 (d, 2H), 4,08-3,96 (m, 2H), 3,75 (dt, 2H), 3,55 (td, 2H), 3,18 (td, 1H), 2,98 (m, 1H), 2,40 (s, 2H), 2,29 (m, 1H), 2,20 (m, 1H), 2,16-1,62 (m, 10H), 1,96 (s, 6H), 1,42 (m, 1H), 1,09 (d, 3H).

Intermedio 8: 1-(3-Cloro-propil)-2,6-*cis*-dimetil-piperidina

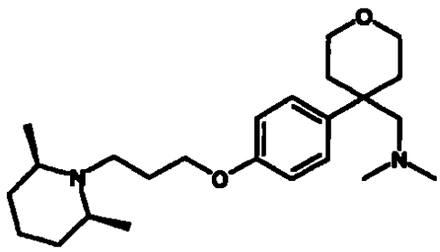
Etapa 1:

Se hizo reaccionar de forma conjunta 2,6-cis-dimetil-piperidina (1,0 g, 8,83 mmol), K_2CO_3 (1,52 g, 1,25 eq.) y 3-bromopropanol (6,14 g, 44,2 mmol, 4 vol) a 100°C durante 2 horas. La reacción se dejó enfriar a temperatura ambiente, se diluyó con DCM (20 ml) y se inactivó con una solución de HCl 2 M (20 ml). La fase acuosa se extrajo con DCM (2 x 20 ml) y se basificó a pH 14 con una solución de NaOH 2 M (~15 ml). La fase acuosa se extrajo con DCM (3 x 20 ml). Las fases de DCM combinada se secaron sobre $MgSO_4$, se filtraron, se lavaron con DCM y se concentraron *al vacío* dando 1-(propan-1'-ol)-2,6-cis-dimetil-piperidina (1,22 g, 81%) en forma de un aceite amarillo pálido.

Etapa 2:

Se disolvió 1-(propan-1'-ol)-2,6-cis-dimetil-piperidina (1,22 g, 7,12 mmol) en DCM (24 ml) y se enfrió a 0-5ºC en una atmósfera de N_2. Se añadió gota a gota cloruro de tionilo (1,04 ml, 14,25 mmol). La reacción se dejó calentar a temperatura ambiente y se agitó durante 30 minutos. La reacción se inactivó con una solución de HCl 2 M (25 ml). La fase acuosa se extrajo con DCM (25 ml) y se basificó a pH 14 con una solución de NaOH 5 M (~25 ml). La fase acuosa se extrajo con TBME (3 x 25 ml). Las fases orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron, se lavaron con TBME y se concentraron *al vacío* dando el compuesto del título (1,28 g, 93%) en forma de un aceite amarillo.

Ejemplo 4: (4-[4-[3-(2,6-Dimetilpiperidin-1-il)propoxi]fenil]tetra-hidro-piran-4-ilmetil)dimetil-amina



Se hizo reaccionar de forma conjunta 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (500 mg, 2,13 mmol), 1-(3-cloro-propil)-2,6-cis-dimetil-piperidina (410 mg, 2,13 mmol), DMF (10 ml) y K_2CO_3 (1,18 g, 8,52 mmol) de acuerdo con el procedimiento general B. El material aislado se sometió a cromatografía sobre sílice, eluyente 95:4:1 (DCM, MeOH, NH_3) dando el compuesto del título en forma de un aceite amarillo (280 mg, 33,9%).

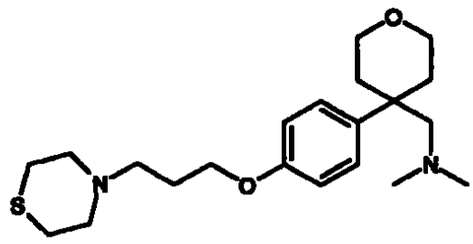
^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,85 (d, 2H), 3,93 (t, 2H), 3,75 (dt, 2H), 3,55 (td, 2H), 2,95 (t, 2H), 2,51-2,36 (m, 2H), 2,40 (s, 2H), 2,14-2,04 (m, 2H), 1,96 (s, 6H), 1,93-1,82 (m, 4H), 1,74-1,51 (m, 3H), 1,41-1,21 (m, 3H), 1,13

(d, 6H).

Intermedio 9: 4-(3-Cloro-propil)-tiomorfolina

Se hizo reaccionar de forma conjunta tiomorfolina (5 g, 49 mmol), acetona (15 ml, 3 vol), una solución de NaOH 5 M (11,8 ml) y 1-bromo-3-cloropropano (11,6 g, 73,5 mmol, 1,5 eq.) de acuerdo con el procedimiento general A dando el compuesto del título (8,5 g, 96%) en forma de un aceite amarillo pálido.

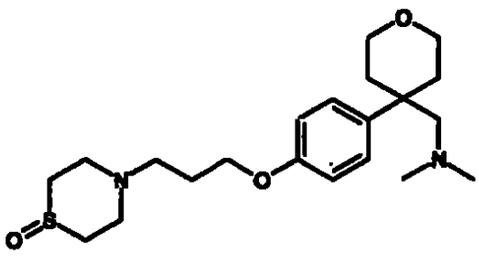
Ejemplo 5: Dimetil-{4-[4(3-tiomorfolin-4-ilpropoxi)fenil]tetra-hidro-piran-4-ilmetil}amina



Se hizo reaccionar de forma conjunta 4-(4-Dimetilaminometil-tetrahidro-piran-4-il)-fenol (1000 mg, 4,25 mmol), 4-(3-cloro-propil)-tiomorfolina (764 mg, 2,13 mmol), DMF (20 ml), y K_2CO_3 (2,34 g, 17 mmol) de acuerdo con el procedimiento general B. El material aislado se sometió a cromatografía sobre sílice, eluyente DCM:MeOH:NH_3 (95:5:1) dando el compuesto del título (320 mg, 20%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,86 (d, 2H), 3,99 (t, 2H), 3,75 (dt, 2H), 3,55 (td, 2H), 2,79-2,64 (m, 8H), 2,55 (t, 2H), 2,40 (s, 2H), 2,16-2,04 (m, 2H), 2,01-1,82 (m, 4H), 1,97 (s, 6H).

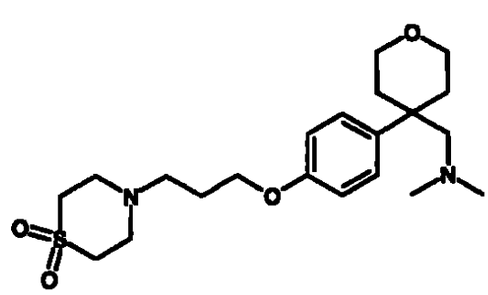
Ejemplo 6: Dimetil-(4{4-[3-(1-oxotiomorfolin-4-il)propoxi]fenil}-tetrahidropiran-4-ilmetil)amina



Dimetil-(4-[4-(3-tiomorfolin-4-ilpropoxi)fenil]tetrahidro-piran-4-ilmetil)amina (300 mg, 0,792 mmol) y TFA (0,99 ml) se enfrió entre 0 y 5 °C y se añadió ácido trifluoro-peracético (4 M, 0,77 ml) [solución 4 M preparada por adición de H_2O_2 al 27,5% (0,94 ml) a TFA (1,56 ml)] y la reacción se agitó durante seis horas a una temperatura entre 0 y 5°C. La mezcla se diluyó con DCM (6 ml), se basificó con NaOH (2 M, 8 ml) y se extrajo con DCM (2x20 ml). Los extractos de DCM se secaron sobre $MgSO_4$, se filtraron y se concentraron *al vacío* a 35°C. La purificación por cromatografía sobre sílice, eluyente DCM:MeOH:NH_3 (96:4:1) proporcionó el compuesto del título (200 mg, 61%) en forma de un sólido blanco.

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,21 (d, 2H), 6,86 (d, 2H), 4,01 (t, 2H), 3,75 (dt, 2H), 3,55 (td, 2H), 3,15-3,02 (m, 2H), 2,93-2,79 (m, 4H), 2,72 (dt, 2H), 2,64 (t, 2H), 2,40 (s, 2H), 2,16-1,82 (m, 6H), 1,97 (s, 6H).

Ejemplo 7: (4[4[3-(1,1-Dioxo-tiomorfolin-4-il)propoxi]fenil]tetra-hidro-piran-4-ilmetil)dimetil-amina



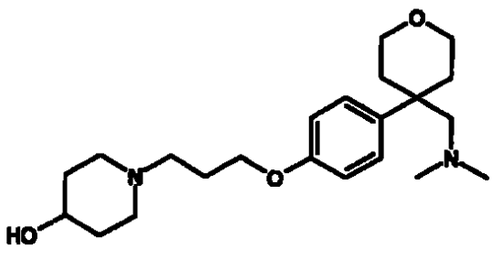
Dimetil-(4-[4-(3-tiomorfolin-4-ilpropoxi)fenil]tetrahidro-piran-4-

ilmetil)amina (300 mg, 0,792 mmol) y TFA (0,99 ml) se enfrió a una temperatura de entre 0 y 5ºC y se añadió ácido trifluoro-peracético (4 M, 0,77 ml) y la reacción se dejó calentar a temperatura ambiente durante una noche. La mezcla se diluyó con DCM (6 ml), se basificó con NaOH (2 M, 8 ml) y se extrajo con DCM (2x20 ml). Los extractos de DCM se secaron sobre $MgSO_4$, se filtraron y se concentraron *al vacío* a 35ºC. La purificación por cromatografía sobre sílice, eluyente DCM:MeOH:NH_3 (96:4:1) proporcionó el compuesto del título (151 mg, 46%) en forma de un sólido blanco. ^{1}H RMN (400 MHz, $CDCl_3$) 87,22 (d, 2H), 6,85 (d, 2H), 4,01 (t, 2H), 3,75 (dt, 2H), 3,55 (td, 2H), 3,10-2,97 (m, 8H), 2,72 (t, 2H), 2,40 (s, 2H), 2,14-1,82 (m, 6H), 1,97 (s, 6H).

Intermedio 10: 1-(3-Cloro-propil)-piperidin-4-ol

Se hizo reaccionar de forma conjunta 4-hidroxipiperidina (3 g, 30 mmol), acetona (60 ml, 20 vol), una solución de NaOH 5 M (7,2 ml) y 1-bromo-3-cloropropano (14,2 g, 90 mmol, 3 eq.) de acuerdo con el procedimiento general A dando el compuesto del título (1,5 g, 28%) en forma de un aceite amarillo pálido.

Ejemplo 8: 1-{3-[4-(4-Dimetilaminometil-tetrahidro-piran-4-il)-fenoxi]-propil}-piperidin-4-ol



Se hizo reaccionar de forma conjunta 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (500 mg, 2,13 mmol), 1-(3-cloro-propil)-piperidin-4-ol (378 mg, 2,13 mmol), DMF (10 ml) y K_2CO_3 (1,18 g, 8,52 mmol) de acuerdo con el

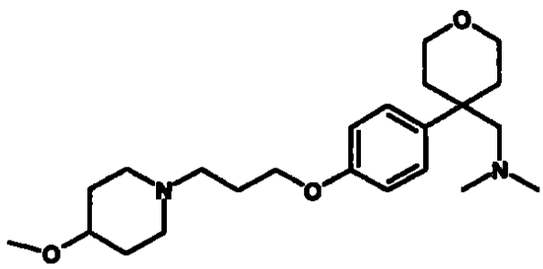
procedimiento general B. El material aislado se disolvió en EtOAc (30 ml), se lavó con NaOH (2 M, 2x20 ml) y agua (25 ml), se secó sobre $MgSO_4$ se filtró y se concentró *al vacío* a 35ºC dando el compuesto del título (411 mg, 51%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,86 (d, 2H), 4,00 (t, 2H), 3,80-3,65 (m, 3H), 3,55 (td, 2H), 2,85-2,73 (m, 2H), 2,52 (t, 2H), 2,40 (s, 2H), 2,22-1,82 (m, 10H), 1,97 (s, 6H), 1,66-1,54 (m, 2H), 1,52 (s a, 1H).

Intermedio 11: 1-(3-Cloro-propil)-4-metoxi-piperidina

Se hizo reaccionar de forma conjunta 4-metoxi-piperidina (1,5 g, 13 mmol), acetona (30 ml, 20 vol), una solución de NaOH 5 M (3,13 ml) y 1-bromo-3-cloropropano (6,14 g, 39 mmol, 3 eq.) de acuerdo con el procedimiento general A dando el compuesto del título (1,5 g, 60%) en forma de un aceite amarillo pálido.

Ejemplo 9: (4[4-[3-(4-Metoxi-piperidin-1-il)-propoxi]-fenil)-tetrahidro-piran-4-ilmetil)-dimetil-amina



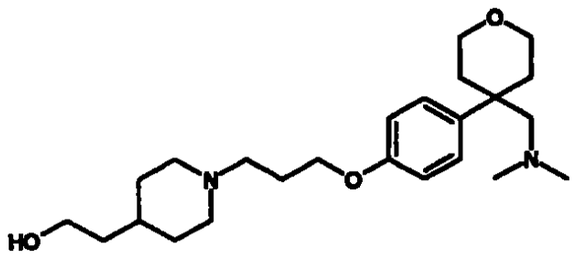
Se hizo reaccionar de forma conjunta 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (500 mg, 2,13 mmol), 1-(3-cloro-propil)-4-metoxi-piperidina (410 mg, 2,13 mmol), DMF (10 ml) y K_2CO_3 (1,18 g, 8,52 mmol) de acuerdo con el procedimiento general B. El material aislado se sometió a cromatografía sobre sílice, eluyente 95:4:1 (DCM: MeOH: NH_3) dando el compuesto del título en forma de un aceite amarillo (415 mg, 50%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,86 (d, 2H), 4,00 (t, 2H), 3,75 (dt, 2H), 3,55 (td, 2H), 3,34 (s, 3H), 3,22 (m, 1H), 2,83-2,71 (m, 2H), 2,51 (t, 2H), 2,40 (s, 2H), 2,23-1,81 (m, 10H), 1,97 (s, 6H), 1,67-1,53 (m, 2H).

Intermedio 12: 2-[1-(3-Cloro-propil)-piperidin-4-il]-etanol

Se hizo reaccionar de forma conjunta 4-piperidina etanol (0,9 g, 7,5 mmol), acetona (18 ml, 20 vol), una solución de NaOH 5 M (1,8 ml) y 1-bromo-3-cloropropano (3,54 g, 22,5 mmol, 3 eq.) de acuerdo con el procedimiento general A dando el compuesto del título (0,6 g, 37%) en forma de un aceite naranja.

Ejemplo 10: 2-(1-{3-[4-(4-Dimetilaminometiltetrahidropiran-4-il)fenoxi]propil}piperidin-4-il)etanol



Se hizo reaccionar de forma conjunta 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (288 mg, 1,22 mmol), 2-[1-(3-cloro-propil)-piperidin-4-il]-etanol (252 mg, 1,22 mmol), DMF (8 ml) y K_2CO_3 (674 mg, 4,88 mmol) de acuerdo con el procedimiento general B. La purificación por cromatografía sobre sílice, eluyente DCM:MeOH:NH_3 (96:4:1) proporcionó el compuesto del título (180 mg, 36%) en forma de un sólido blanquecino.

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,86 (d, 2H), 3,99 (t, 2H), 3,75 (dt, 2H), 3,70 (t, 2H), 3,55 (td, 2H), 2,98-2,88 (m, 2H), 2,49 (t, 2H), 2,40 (s, 2H), 2,14-1,82 (m, 6H), 1,97 (s, 6H), 1,75-1,15 (m, 10H).

Intermedio 13: 1-(3-Cloro-propil)-4-(2-metoxi-etil)-piperidina

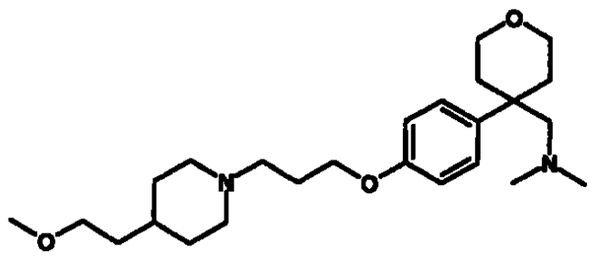
Etapa 1:

Se añadió *N*-Boc-4-(2-hidroxi-etil)-piperidina (5 g, 21,8 mmol) en THF (25 ml) a una suspensión de NaH (1,47 g, 43,7 mmol) en THF (75 ml) a 0ºC en una atmósfera de N_2. La reacción se agitó durante 1 hora a 0ºC y se añadió MeI lentamente (2,72 ml, 43,7 mmol). La reacción se dejó calentar a temperatura ambiente y se agitó durante una noche. La reacción se inactivó con agua (100 ml) y se extrajo con DCM (3 x 100 ml). Las fases de DCM combinadas se secaron sobre $MgSO_4$, se filtraron, se lavaron con DCM y se concentraron *al vacío*. La reacción en bruto (7,5 g) se trató con una solución de HCl 3 M en EtOH (150 ml) durante 12 horas. La reacción se concentró *al vacío* y formó un azeótropo con tolueno (2 x 150 ml) dando clorhidrato de 4-(2-metoxi-etil)-piperidina (3,5 g, 89%) en forma de un sólido amarillo pálido.

Etapa 2:

Se hizo reaccionar de forma conjunta clorhidrato de 4-(2-metoxi-etil)-piperidina (1,5 g, 8,4 mmol), acetona (30 ml, 20 vol), una solución de NaOH 5 M (6,03 ml, 3,6 eq.) y 1-bromo-3-cloropropano (3,96 g, 25,1 mmol, 3 eq.) de acuerdo con el procedimiento general A dando el compuesto del título (1,6 g, 88%) en forma de un aceite amarillo pálido.

Ejemplo 11: [4-(4{3-[4(2-Metoxi-etil)-piperidin-1-il]-propoxi}-fenil)-tetrahidro-piran-4-ilmetil]-dimetil-amina



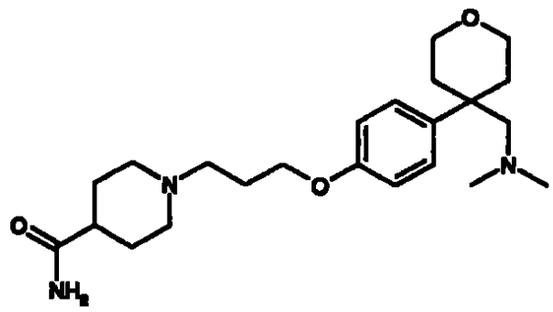
Se hizo reaccionar de forma conjunta 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (500 mg, 2,13 mmol), 1-(3-cloro-propil)-4-(2-metoxi-etil)-piperidina (466 mg, 2,13 mmol), DMF (10 ml) y K_2CO_3 (1,18 g, 8,52 mmol) de acuerdo con el procedimiento general B. La purificación por cromatografía sobre sílice, eluyente DCM:MeOH:NH_3 (96:4:1) proporcionó el compuesto del título (409 mg, 46%) en forma de un aceite amarillo.

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,86 (d, 2H), 3,99 (t, 2H), 3,75 (dt, 2H), 3,55 (td, 2H), 3,41 (t, 2H), 3,33 (s, 3H), 2,97-2,86 (m, 2H), 2,49 (t, 2H), 2,40 (s, 2H), 2,15-1,78 (m, 8H), 1,97 (s, 6H), 1,74-1,17 (m, 7H).

Intermedio 14: Amida del ácido 1-(3-cloro-propil)-piperidin-4-carboxílico

Se hizo reacciona de forma conjunta amida del ácido piperidin-4-carboxílico (0,5 g, 3,90 mmol), acetona (1,5 ml, 3 vol), una solución de NaOH 5 M (1,20 ml, 1,2 eq.) y 1-bromo-3-cloropropano (0,50 ml, 5,04 mmol, 1 eq.) de acuerdo con el procedimiento general A dando el compuesto del título (0,16 g, 20%) en forma de un aceite amarillo pálido.

Ejemplo 12: Amida del ácido 1-{3-[4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenoxi]-propil}-piperidin-4-carboxílico



Se hizo reaccionar de forma conjunta 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (500 mg, 2,13 mmol), amida del ácido 1-(3-cloro-propil)-piperidin-4-carboxílico (436 mg, 2,13 mmol), DMF (10 ml) y K_2CO_3 (1,18 g, 8,52

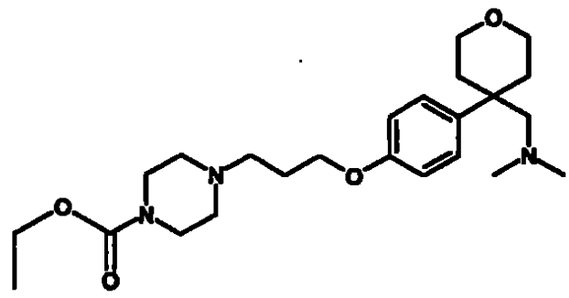
mmol) de acuerdo con el procedimiento general B. El material aislado se sometió a cromatografía sobre sílice, eluyente 95:4:1 (DCM: MeOH: NH_3) dando el compuesto del título en forma de un sólido blanco (175 mg, 20%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,21 (d, 2H), 6,86 (d, 2H), 5,44 (s a, 1H), 5,25 (s a, 1H), 4,00 (t, 2H), 3,75 (dt, 2H), 3,55 (td, 2H), 3,03-2,93 (m, 2H), 2,51 (t, 2H), 2,40 (s, 2H), 2,22-1,66 (m, 13H), 1,97 (s, 6H).

Intermedio 15: Éster etílico del ácido 4-(3-cloro-propil)-piperazin-1-carboxílico

Se hizo reaccionar de forma conjunta éster etílico del ácido piperazin-1-carboxílico (3,0 g, 18,9 mmol), K_2CO_3 (2,8 g, 1,1 eq.), DMF (30 ml, 10 vol) y 1-bromo-3-cloropropano (1,8 ml, 18,9 mmol, 1 eq.) a temperatura ambiente durante una noche. La reacción se inactivó con agua (100 ml) y se extrajo con DCM (3 x 50 ml). Los extractos de DCM combinados se secaron sobre $MgSO_4$, se filtraron, se lavaron con DCM y se concentraron *al vacío* dando el compuesto del título (3,1 g, 70%) en forma de un aceite amarillo pálido.

Ejemplo 13: Éster etílico del ácido {3-[4-(4-dimetilaminometiltetrahidropiran-4-il)fenoxi]-propil}piperazin-1-carboxílico



Se hizo reaccionar de forma conjunta 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (500 mg, 2,13 mmol), éster etílico del ácido 4-(3-cloro-propil)-piperazin-1-carboxílico (499 mg, 2,13 mmol), DMF (10 ml) y K_2CO_3 (1,18 g,

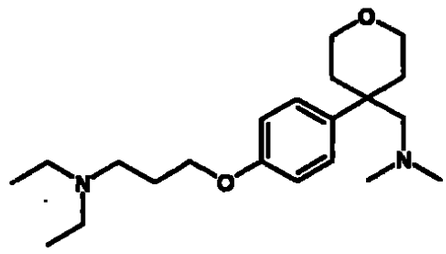
8,52 mmol) de acuerdo con el procedimiento general B. La purificación por cromatografía sobre sílice, eluyente (MeOH al 10% en DCM) dando el compuesto del título (276 mg, 26%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,21 (d, 2H), 6,86 (d, 2H), 4,14 (q, 2H), 4,01 (t, 2H), 3,75 (dt, 2H), 3,60-3,42 (m, 6H), 2,54 (t, 2H), 2,47-2,36 (m, 4H), 2,40 (s, 2H), 2,16-1,82 (m, 6H), 1,97 (s, 6H), 1,26 (t, 3H).

Intermedio 16 : (3-Cloro-propil)-dietil-amina

Se hizo reaccionar de forma conjunta dietil-amina (7,27 ml, 70 mmol), acetona (15 ml, 3 vol), una solución de NaOH 5 M (16,8 ml, 1,2 eq.) y 1-bromo-3-cloropropano (16,5 g, .105 mmol, 1,5 eq.) de acuerdo con el procedimiento general A dando el compuesto del título (6,2 g, 59%) en forma de un aceite incoloro.

Ejemplo 14: {3-[4-(4-Dimetilaminometiltetrahidropiran-4-il)fenoxi]-propil}dietil-amina



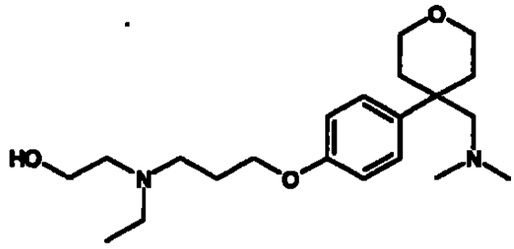
Se hizo reaccionar de forma conjunta 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (500 mg, 2,13 mmol), (3-cloro-propil)-dietil-amina (319 mg, 2,13 mmol), DMF (10 ml) y K_2CO_3 (1,18 g, 8,52 mmol) de acuerdo con el procedimiento general B. La purificación por cromatografía sobre sílice, eluyente (EtOH al 3%:NH_3 al 1% en DCM) dio el compuesto del título en forma de un aceite transparente amarillo (160 mg, 22%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,86 (d, 2H), 4,00 (t, 2H), 3,75 (dt, 2H), 3,55 (td, 2H), 2,61 (t, 2H), 2,54 (q, 4H), 2,40 (s, 2H), 2,15-1,82 (m, 6H), 1,97 (s, 6H), 1,02 (t, 6H).

Intermedio 17: 2-[(3-Cloro-propil)-etil-amino]-etanol

Se hizo reaccionar de forma conjunta 2-etilamino etanol (6,2 g, 70 mmol), acetona (18 ml, 3 vol), una solución de NaOH 5 M (16,8 ml, 1,2 eq.) y 1-bromo-3-cloropropano (16,5 g, 105 mmol, 1,5 eq.) de acuerdo con el procedimiento general A dando el compuesto del título (4,5 g, 39%) en forma de un aceite incoloro.

Ejemplo 15: 2-({3-[4-(4-Dimetilaminometiltetrahidropiran-4-il)fenoxi]propil}etilamino)etanol



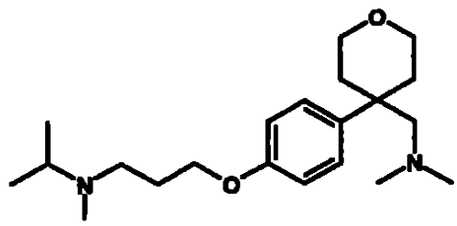
Se hizo reaccionar de forma conjunta 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (500 mg, 2,13 mmol), 2-[(3-cloro-propil)-etilamino]-etanol (353 mg, 2,13 mmol), DMF (10 ml) y K_2CO_3 (1,18 g, 8,52 mmol) de acuerdo con el procedimiento general B. El material aislado se sometió a cromatografía sobre sílice, eluyente 95:4:1 (DCM: MeOH: NH_3) dando el compuesto del título en forma de un sólido blanco (150 mg, 19%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,21 (d, 2H), 6,86 (d, 2H), 4,00 (t, 2H), 3,75 (dt, 2H), 3,60-3,49 (m, 4H), 2,68 (t, 2H), 2,62 (t, 2H), 2,59 (q, 2H), 2,40 (s, 2H), 2,14-1,82 (m, 6H), 1,97 (s, 6H), 1,62 (s a, 1H), 1,03 (t, 3H).

Intermedio 18: (3-Cloro-propil)-isopropil-metil-amina

Se hizo reaccionar de forma conjunta isopropilmetilamina (4 g, 56 mmol), acetona (12 ml, 3 vol), una solución de NaOH 5 M (13,44 ml, 1,2 eq.) y 1-bromo-3-cloropropano (13,22 g, 84 mmol, 1,5 eq.) de acuerdo con el procedimiento general A dando el compuesto del título (4,8 g, 66%) en forma de un aceite incoloro.

Ejemplo 16: {3-[4-(4-Dimetilaminometiltetrahidropiran-4-il)fenoxi]-propil}isopropilmetilamina



Se hizo reaccionar de forma conjunta 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (500 mg, 2,13 mmol), (3-cloro-propil)-isopropil-metil-amina (318 mg, 2,13 mmol), DMF (10 ml) y K_2CO_3 (1,18 g, 8,52 mmol) de acuerdo con el procedimiento general B. La purificación por cromatografía sobre sílice, eluyente DCM:MeOH:NH_3 (96:3:1) proporcionó el compuesto del título (200 mg, 43%) en forma de un sólido blanco.

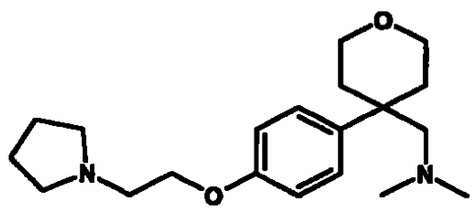
^{1}H RMN (400 MHz, $CDCl_3$) 87,20 (d, 2H), 6,87 (d, 2H), 4,00 (t, 2H), 3,75 (dt, 2H), 3,55 (td, 2H), 2,83 (sep, 1H), 2,55 (t, 2H), 2,40 (s, 2H), 2,22 (s, 3H), 2,14-2,05 (m, 2H), 1,96 (s, 6H), 2,00-1,82 (m, 4H), 1,00 (d, 6H).

Intermedio 19: 1-(2-cloro-etil)-pirrolidina

Se hizo reaccionar de forma conjunta pirrolidina (10,4 g, 0,15 mol), acetona (200 ml), una solución de NaOH 5 M (35 ml) y 1-bromo-2-cloroetano (62,9 g, 0,44 mol) de acuerdo con el procedimiento general A. La mezcla en

bruto se purificó por cromatografía en columna eluyendo con acetato de etilo dando el compuesto del título (2,0 g, 10%) en forma de un aceite amarillo pálido.

Ejemplo 17: Dimetil-[4-[4(2-pirrolidin-1-iletoxi)fenil]tetrahidro-piran-4-ilmetil]amina



Se calentó 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (389 mg, 1,65 mmol), 1-(2-cloro-etil)-pirrolidina (210 mg, 1,57 mmol), DMF (4,5 ml) y K_2CO_3 (885 g, 6,40 mmol) a 130ºC durante 30 minutos. La mezcla se enfrió a temperatura ambiente; se añadió agua (9 ml) y la mezcla se extrajo con EtOAc (3 x 4,5 ml). La fase orgánica se lavó con salmuera (10 ml), una solución de NaOH (2 M, 10 ml) y agua (10 ml). La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró *al vacío* a 35ºC y el residuo se sometió a cromatografía sobre sílice eluyendo con DCM:MeOH:NH_3 (98:1:1) dando el compuesto del título en forma de un sólido blanco (150 mg, 27%).

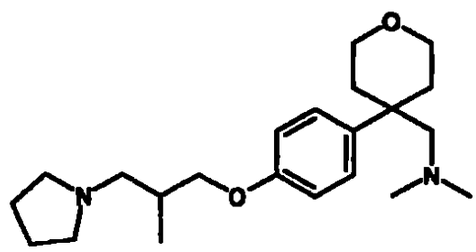
^{1}H RMN (400 MHz, $CDCl_3$) δ 7,21 (d, 2H), 6,89 (d, 2H), 4,10 (t, 2H), 3,75 (dt, 2H), 3,55 (td, 2H), 2,89 (t, 2H), 2,67-2,58 (m, 4H), 2,40 (s, 2H), 2,13-2,05 (m, 2H), 1,97 (s, 6H), 1,88 (ddd, 2H), 1,84-1,77 (m, 4H).

Intermedio 20: 1-(3-Cloro-2-metil-propil)-pirrolidina

Se hizo reaccionar de forma conjunta pirrolidina (3,0 g, 42 mmol), acetona (60 ml), una solución de NaOH 5 M (10 ml) y 1-bromo-3-cloro-2-metil-propano (21,7 g, 0,13 mol) de acuerdo con el procedimiento general A dando el

compuesto del título (3,9 g, 58%) en forma de un aceite amarillo pálido.

Ejemplo 18: Dimetil-[4-[4-(2-metil-3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil]-amina



Se hizo reaccionar de forma conjunta 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (0,91 g, 3,87 mmol), 1-(3-cloro-2-metil-propil)-pirrolidina (500 mg, 3,10 mmol), DMF (5 ml) y K_2CO_3 (2,14 g, 15,50 mmol) de acuerdo con el procedimiento general B. La fase orgánica se lavó con NaOH 2 N (3 x 20 ml), agua (*2 x* 20 ml), se secó sobre $MgSO_4$, se filtró y se concentró *al vacío* a 35°C. El material en bruto se sometió a cromatografía sobre sílice eluyendo con DCM:MeOH:NH_3 (97:2:1) proporcionando el compuesto del título (464 mg, 42%) en forma de un aceite amarillo pálido.

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,88 (d, 2H), 4,00 (dd, 1H), 3,80-3,70 (m, 3H), 3,55 (td, 2H), 2,59-2,43 (m, 5H), 2,40 (s, 2H), 2,33 (dd, 1H), 2,21-2,04 (m, 3H), 1,97 (s, 6H), 1,88 (ddd, 2H), 1,82-1,70 (m, 4H), 1,08 (d, 3H).

Intermedio 21: Éster 1-isopropil-piperidin-4-ilo del ácido metanosulfónico

Etapa 1:

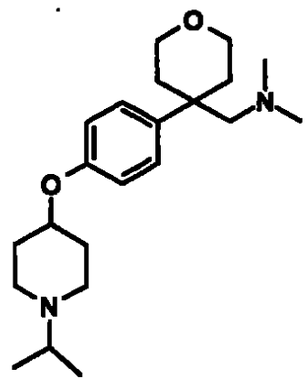
Se calentó a reflujo 4-hidroxipiperidina (2,13 g, 21,1 mmol), K_2CO_3 (5,83 g, 2 eq.), 2-bromopropano (11,2 g, 91 mmol, 4,3 eq.) y MeOH (21,3 ml) durante una noche. La reacción se dejó enfriar a temperatura ambiente y se inactivó con una solución de HCl 2 M (40 ml) y se extrajo con TBME (40 ml). La fase acuosa se basificó a pH 14 con una solución de NaOH 2 M y se extrajo con

DCM (9 x 50 ml). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron, se lavaron con DCM y se concentraron *al vacío* dando 1-isopropil-4-hidroxipiperidina (2,41 g, 80%) en forma de un aceite amarillo pálido.

Etapa 2:

1-Isopropil-4-hidroxipiperidina (1 g, 6,98 mmol), DCM (10 ml) y trietilamina (1,08 ml, 7,68 mmol) se enfriaron a 0-5°C y se añadió gota a gota cloruro de mesilo (0,54 ml, 6,98 mmol) en una atmósfera de N_2. La reacción se dejó calentar a temperatura ambiente y se agitó durante 1 hora. La reacción se inactivó con $NaHCO_3$ saturado (20 ml) y la fase acuosa se extrajo con DCM (2 x 5 ml). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron, se lavaron con DCM y se concentraron *al vacío* dando el compuesto del título (1,55 g, 100%) en forma de un aceite amarillo pálido.

Ejemplo 19: {4-[4-(1-Isopropilpiperidin-4-iloxi)fenil]tetrahidropiran-4-ilmetil}-dimetil-amina



Se añadió 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (532 mg, 2,26 mmol) en DMF (2 ml) a una solución de NaH (100 mg, 2,5 mmol) en DMF (2 ml) a temperatura ambiente en una atmósfera de N_2. La reacción se agitó

durante 1 hora y se añadió lentamente una solución de éster 1-isopropil-piperidin-4-ilo del ácido metanosulfónico (400 mg, 1,81 mmol) en DMF (1,3 ml). La reacción se calentó a 75ºC y se agitó durante 6 horas. La reacción se dejó enfriar a temperatura ambiente y se diluyó con TBME (20 ml), agua (10 ml) y una solución de NaOH 5 M (10 ml). La fase orgánica se lavó con NaOH 2,5 M (2 x 20 ml), salmuera (2 x 20 ml), se secó sobre $MgSO_4$, se filtró y se concentró *al vacío*. La reacción en bruto se purificó por cromatografía en columna, eluyendo con DCM:MeOH:NH_3 (98:1:1) dando el compuesto del título en forma de un sólido cristalino blanco (113 mg, 17%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,87 (d, 2H), 4,27 (m, 1H), 3,75 (dt, 2H), 3,55 (td, 2H), 2,85-2,68 (m, 3H), 2,45-2,32 (m, 2H), 2,40 (s, 2H), 2,14-1,94 (m, 4H), 1,96 (s, 6H), 1,93-1,75 (m, 4H), 1,06 (d, 6H).

Intermedio 22: Éster 1-ciclopentil-piperidin-4-ilo del ácido metanosulfónico

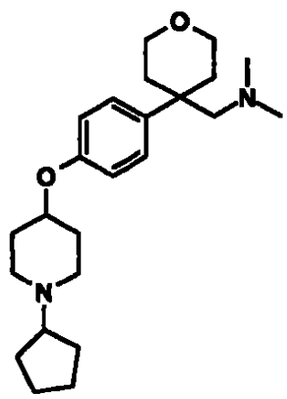
Etapa 1:

Se calentó a reflujo 4-hidroxipiperidina (2,08 g, 21,2 mmol), K_2CO_3 (5,86 g, 2 eq.), bromuro de ciclopentilo (11,51 g, 77,6 mmol, 3,7 eq.) y MeOH (20,8 ml) durante una noche. La reacción se dejó enfriar a temperatura ambiente y se inactivó con una solución de HCl 2 M (40 ml) y se extrajo con TBME (40 ml). La fase acuosa se basificó a pH 14 con a una solución de NaOH 2 M y se extrajo con DCM (4 x 50 ml). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron, se lavaron con DCM y se concentraron *al vacío* dando 1-ciclopentil-4-hidroxipiperidina (2,55 g, 71%) en forma de un aceite amarillo pálido.

Etapa 2:

Se enfrió 1-ciclopentil-4-hidroxipiperidina (1 g, 5,91 mmol), DCM (10 ml) y trietilamina (0,91 ml, 6,5 mmol) a 0-5°C y se añadió gota a gota cloruro de mesilo (0,46 ml, 5,91 mmol) en una atmósfera de N_2. La reacción se dejó calentar a temperatura ambiente y se agitó durante 1 hora. La reacción se inactivó con $NaHCO_3$ saturado (20 ml) y la fase acuosa se extrajo con DCM (2 x 5 ml). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron, se lavaron con DCM y se concentraron *al vacío* dando el compuesto del título (1,38 g, 95%) en forma de un aceite amarillo pálido.

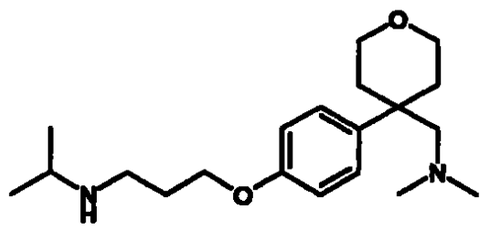
Ejemplo 20: {4-[4-(1-Ciclopentilpiperidin-4-iloxi)fenil]tetrahidropiran-4-ilmetil}dimetilamina



Se añadió 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (487 mg, 2,07 mmol) en DMF (2 ml) a una solución de NaH (100 mg, 2,5 mmol) en DMF (2 ml) a temperatura ambiente en una atmósfera de N_2. La reacción se agitó durante 1 hora y se le añadió lentamente una solución de éster 1-ciclopentil-piperidin-4-ilo del ácido metanosulfónico (409 mg, 1,65 mmol) en DMF (1,5 ml). La reacción se calentó a 75°C y se agitó durante 6 horas. La reacción se dejó enfriar a temperatura ambiente y se diluyó con TBME (20 ml), agua (10 ml) y una solución de NaOH 5 M (10 ml). La fase orgánica se lavó con NaOH 2,5 M

(2 x 20 ml), salmuera (2 x 20 ml), se secó sobre $MgSO_4$, se filtró y se concentró *al vacío*. La reacción en bruto se purificó por cromatografía en columna, eluyendo con DCM:MeOH:NH_3 (98:1:1) dando el compuesto del título en forma de un sólido blanco (78 mg, 12%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,87 (d, 2H), 4,28 (m, 1H), 3,75 (dt, 2H), 3,55 (td, 2H), 2,89-2,76 (m, 2H), 2,52 (p, 1H), 2,40 (s, 2H), 2,37-2,25 (m, 2H), 2,14-1,94 (m, 4H), 1,96 (s, 6H), 1,93-1,77 (m, 6H), 1,76-1,34 (m, 6H).

Ejemplo 21: {3-[4-(4-Dimetilaminometil-tetrahidro-piran-4-il)-fenoxi]-propil}-isopropilamina

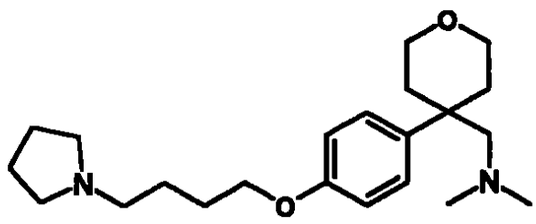


Se hizo reaccionar de forma conjunta 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (730 mg, 3,10 mmol), 3-cloro-1-bromopropano (980 mg, 6,20 mmol), DMF (10 ml) y K_2CO_3 (1,72 g, 12,40 mmol) de acuerdo con el procedimiento general B. La purificación por cromatografía sobre sílice, eluyente DCM:MeOH (20: 1) proporcionó una mezcla de bromo y cloro fenoxi éter (250 mg) que se usó en la siguiente etapa. La mezcla (250 mg) se calentó a reflujo con isopropilamina (34°C) (10 ml, 40 vol) durante 7 días. La reacción se concentró *al vacío* y se dividió entre NaOH 2 M (10 ml) y DCM (10 ml). La fase acuosa se extrajo con DCM (3 x 10 ml). Las fases de DCM combinadas se secaron sobre $MgSO_4$, se filtraron, se lavaron con DCM y se concentraron *al vacío*. La purificación por cromatografía sobre sílice, eluyente DCM:MeOH:NH_3 (95:5:0) aumentando gradualmente a DCM:MeOH:NH_3 (90:9:1) dio el

compuesto del título en forma de un sólido amarillo pálido (180 mg, 17% en 2 etapas).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,88 (d, 2H), 4,03 (t, 2H), 3,75 (dt, 2H), 3,59-3,50 (m, 2H), 2,89-2,76 (m, 3H), 2,40 (s, 2H), 2,15-2,05 (m, 2H), 2,03-1,93 (m, 2H), 1,96 (s, 6H), 1,88 (ddd, 2H), 1,49 (s a, 1H), 1,07 (d, 6H).

Ejemplo 22: Dimetil-[4-[4-(4-pirrolidin-1-ilbutoxi)fenil]tetrahidro-piran-4-ilmetil]amina

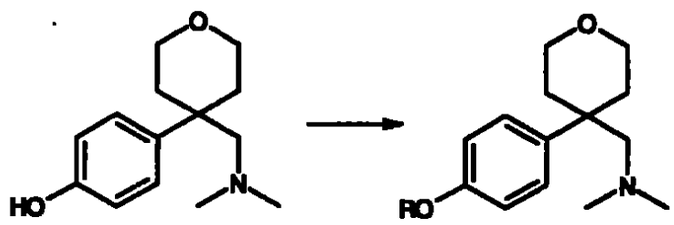


Se hizo reaccionar de forma conjunta 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (1,5 g, 6,38 mmol), 1-bromo-4-clorobutano (1,5 ml, 12,77 mmol), DMF (20 ml) y K_2CO_3 (3,5 g, 25,53 mmol) de acuerdo con el procedimiento general B. La purificación de una fracción del producto en bruto (900 mg) por cromatografía en alúmina, eluyente acetato de etilo:heptanos (12: 88) proporcionó una mezcla de bromo y cloro fenoxi éter (220 mg) que se usó en la siguiente etapa. La mezcla purificada (220 mg, 0,68 mmol) y pirrolidina (0,17 ml, 2,03 mmol) se calentaron a reflujo en EtOH (3 ml, 15 vol) durante una noche. La reacción se concentró *al vacío* y se dividió entre NaOH 2 M (10 ml) y acetato de etilo (10 ml). La fase acuosa se extrajo con acetato de etilo (3 x 5 ml). Las fases de acetato de etilo combinadas se lavaron con salmuera (3 x 5 ml), se secaron sobre $MgSO_4$, se filtraron, se lavaron con acetato de etilo y se concentraron *al vacío*. La purificación por cromatografía sobre sílice, eluyente 95:3:2 (DCM:MeOH:NH_3) seguido de una segunda columna eluyendo con

DCM:MeOH:NH_3 (96,5:3:0,5), dio el compuesto del título en forma de un aceite incoloro (134 mg, 55%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,21 (d, 2H), 6,86 (d, 2H), 3,97 (t, 2H), 3,75 (dt, 2H), 3,59-3,50 (m, 2H), 2,57-2,45 (m, 6H), 2,40 (s, 2H), 2,14-2,05 (m, 2H), 1,96 (s, 6H), 1,92-1,65 (m, 10H).

Procedimiento General C:



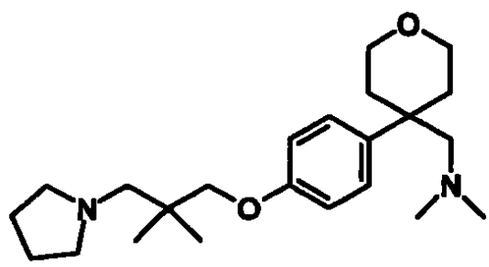
Se mezcló 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (1 eq.), alcohol (R-OH) (0,8 eq.) y PPh_3 (1 eq.) en THF (10 vol) y se enfrió a 0ºC en una atmósfera de N_2. A la reacción se le añadió lentamente DIAD (1 eq.) en THF (10 vol) y se dejó calentar a temperatura ambiente durante una noche. La reacción se inactivó con una solución de HCl 2 M (10 vol) y se extrajo con acetato de etilo (3 x 10 vol). La fase acuosa se basificó a pH 14 con NaOH (~30 vol) y se extrajo con acetato de etilo (3 x 10 vol). La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró *al vacío* a 35ºC. La purificación del material en bruto por cromatografía sobre sílice, eluyente (MeOH al 10% en DCM) proporcionó el compuesto del título.

Intermedio 23: 2,2-Dimetil-3-pirrolidin-1-il-propan-1-ol

Se calentó pirrolidina (1,82 g, 25 mmol), K_2CO_3 (3,0 g, 1,04 eq.), 3-bromo-2,2-dimetil-propan-1-ol (8,45 g, 50 mmol, 2 eq.) a 90ºC durante una noche. La reacción se dejó enfriar a temperatura ambiente y se inactivó con una solución de HCl 2 M (50 ml) y se extrajo con TBME (3 x 50 ml). La fase

acuosa se basificó a pH 14 con una solución de NaOH 2 M y se extrajo con DCM (3 x 50 ml). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron, se lavaron con DCM y se concentraron *al vacío* dando el compuesto del título (1,03 g, 26%) en forma de un aceite amarillo pálido.

Ejemplo 23: {4-[4-(2,2-Dimetil-3-pirrolidin-1-il-propoxi)-fenil]-tetrahidropiran-4-ilmetil}-dimetil-amina



Se hizo reaccionar de forma conjunta 4-(4-dimetilaminometil-tetrahidropiran-4-il)-fenol (0,28 g, 1,19 mmol), 2,2-dimetil-3-pirrolidin-1-il-propan-1-ol (0,15 g, 0,96 mmol), PPh_3 (0,31 g, 1,19 mmol), THF (3 ml) y DIAD (0,24 ml, 1,19 mmol) de acuerdo con el procedimiento general C. El material en bruto se sometió a cromatografía sobre sílice eluyendo con DCM:MeOH:NH_3 (97:2:1) proporcionando el compuesto del título (85 mg, 24%) en forma de un sólido blanquecino.

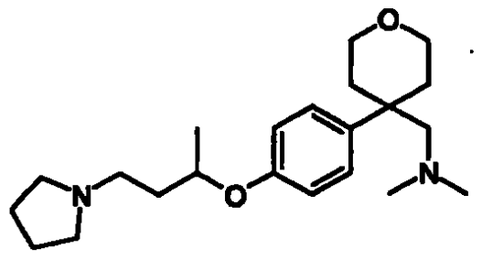
^{1}H RMN (400 MHz, $CDCl_3$) δ 7,23 (d, 2H), 6,91 (d, 2H), 3,84-3,69 (m, 4H), 3,69-3,54 (m, 2H), 2,67-2,56 (m, 4H), 2,50 (s, 2H), 2,44 (s, 2H), 2,18-2,08 (m, 2H), 2,01 (s, 6H), 1,92 (ddd, 2H), 1,79-1,67 (m, 4H), 1,04 (s, 6H).

Intermedio 24: 4-Pirrolidin-1-il-butan-2-ol

Se mezclaron pirrolidina (2 ml, 24 mmol), THF (20 ml) y metil vinilcetona (2,5 ml, 31 mmol) y se agitó durante una noche. A la mezcla de reacción se le añadió $NaBH_4$ (1,17 g, 31 mmol) y se agitó durante 3 horas. La reacción se

inactivó con agua (20 ml) y se extrajo con TBME (2 x 20 ml). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron, se lavaron con TBME y se concentraron *al vacío*. El producto en bruto se purificó por cromatografía en columna, eluyendo con DCM:MeOH:NH_3 (94 :5 :1), dando el compuesto del título en forma de un aceite amarillo pálido (1,3 g, 38%).

Ejemplo 24: Dimetil-[4-[4-(1-metil-3-pirrolidin-1-ilpropoxi)fenil]-tetrahidropiran-4-ilmetil]amina



Se hizo reaccionar de forma conjunta 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (1,03 g, 4,40 mmol), 4-pirrolidin-1-il-butan-2-ol (0,5 g, 3,50 mmol), PPh_3 (1,15 g, 4,40 mmol), THF (10 ml) y DIAD (0,86 ml, 4,40 mmol) de acuerdo con el procedimiento general C. El producto en bruto se purificó por HPLC preparativa, eluyendo con acetonitrilo/agua/TFA al 0,1% en forma de gradiente, dando el compuesto del título en forma de un aceite amarillo (125 mg, 10%).

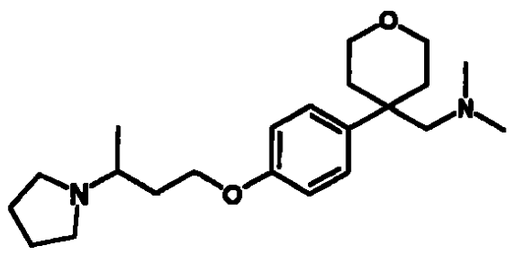
^{1}H RMN (400 MHz, $CDCl_3$) δ 7,19 (d, 2H), 6,86 (d, 2H), 4,43 (m, 1H), 3,75 (dt, 2H), 3,60-3,51 (m, 2H), 2,67-2,46 (m, 6H), 2,40 (s, 2H), 2,14-2,04 (m, 2H), 1,97 (s, 6H), 1,93-1,73 (m, 8H), 1,31 (d, 3H).

Intermedio 25: 3-Pirrolidin-1-il-butan-1-ol

Se calentó a reflujo pirrolidina (28,15 g, 0,4 mol), tolueno (200 ml), p-TsOH catalítico (200 mg) y acetoacetato de etilo (20 g, 0,15 mol) en un aparato

Dean-Stark en una atmósfera de N_2 durante 3 horas. La reacción se enfrió a temperatura ambiente y se concentró *al vacío*. Se disolvió $NaBH_4$ (3,1 g, 82 mmol) en MeOH (50 ml) y se enfrió a 0-5ºC. A la mezcla de reacción se le añadió una porción de la reacción en bruto previa (5 g, 27 mmol) en MeOH (25 ml) y se agitó durante 72 horas. La reacción se inactivó con una solución acuosa de NaOH (1% p/p, 50 ml) y se concentró *al vacío*. La fase acuosa se extrajo con TBME (3 x 50 ml). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron, se lavaron con TBME y se concentraron *al vacío* dando una mezcla de el compuesto del título, éster etílico del ácido 3-pirrolidin-1-il-butanoico y TBME residual (3,5 g). La mezcla (3,5 g) en THF (20 ml) se añadió a una solución de $LiALH_4$ (1 M en THF, 33,5 ml, 33,5 mmol) a 0-5ºC en una atmósfera de N_2. La reacción se dejó calentar a temperatura ambiente y se agitó durante 3 horas. La reacción se inactivó con una solución acuosa de NaOH (1% p/p, 50 ml) a 0-5ºC, se filtró y se lavó con THF (3 x 20 ml). Las fases orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron, se lavaron con THF y se concentraron *al vacío* dando el compuesto del título en forma de un aceite amarillo (2 g, 73%).

Ejemplo 25: Dimetil-[4-[4(3-pirrolidin-1-il-butoxi)-fenil]-tetrahidro-piran-4-ilmetil]-amina

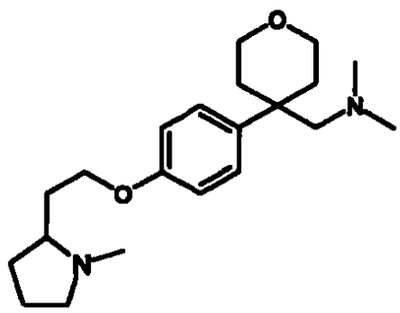


Se hizo reaccionar de forma conjunta 4-(4-dimetilaminometil-tetrahidro-

piran-4-il)-fenol (925 mg, 3,93 mmol), 3-pirrolidin-1-il-butan-1-ol (450 mg, 3,14 mmol), PPh_3 (1,03 g, 3,93 mmol), THF (9 ml) y DIAD (0,77 ml, 3,93 mmol) de acuerdo con el procedimiento general C. El material en bruto se sometió a cromatografía sobre sílice eluyendo con DCM:MeOH (99,5:0,5) proporcionando el compuesto del título (268 mg, 24%) en forma de un aceite incoloro.

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,21 (d, 2H), 6,88 (d, 2H), 4,11-3,97 (m, 2H), 3,75 (dt, 2H), 3,55 (td, 2H), 2,66-2,52 (m, 5H), 2,40 (s, 2H), 2,19-2,05 (m, 3H), 1,96 (s, 6H), 1,93-1,70 (m, 7H), 1,16 (d, 3H).

Ejemplo 26: Dimetil-(4-{4[2-(1-metilpirrolidin-2-il)etoxi]fenil}-tetrahidropiran-4-ilmetil)amina

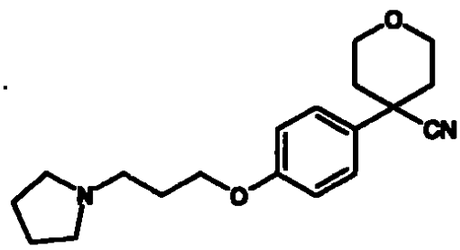


Se hizo reaccionar de forma conjunta 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (405 mg, 1,72 mmol), 2-(1-metil-pirrolidin-2-il)-etanol (178 mg, 1,38 mmol), PPh_3 (451 mg, 1,72 mmol), THF (8 ml) y DIAD (348 mg, 1,72 mmol) de acuerdo con el procedimiento general C. El producto en bruto se sometió a cromatografía en alúmina eluyendo con acetato de etilo:heptano (50:50) proporcionando el compuesto del título (130 mg, 27%) en forma de un aceite incoloro.

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,21 (d, 2H), 6,87 (d, 2H), 4,09-3,95 (m, 2H), 3,75 (dt, 2H), 3,55 (td, 2H), 3,09 (m, 1H), 2,40 (s, 2H), 2,35 (s, 3H), 2,30-1,99 (m,

6H), 1,96 (s, 6H), 1,93-1,63 (m, 6H).

Ejemplo 27: 4-[4(3-Pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-carbonitrilo



Se hizo reaccionar de forma conjunta 4-(4-hidroxi-fenil)-tetrahidro-piran-4-carbonitrilo (2 g, 9,86 mmol), 1-(3-cloro-propil)-pirrolidina (2,33 g, 15,78 mmol), DMF (40 ml) y K_2CO_3 (5,45 g, 39,44 mmol) de acuerdo con el procedimiento general E. El producto de reacción en bruto se diluyó con una solución de HCl 2 M (200 ml) y se lavó con acetato de etilo (3 x 50 ml). La fase acuosa se basificó a pH 14 con NaOH 2 M (200 ml) y se extrajo con acetato de etilo (4 x 50 ml). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron, se lavaron con acetato de etilo y se concentraron *al vacío* dando un sólido blanco. El sólido se suspendió en TBME (15 ml) y heptano (15 ml), se filtró, se lavó con heptano (8 ml) y se secó en el filtro durante 2 horas dando el compuesto del título en forma de un sólido blanco (1,6 g, 53%).

^{1}H RMN (400 MHz, DMSO-D_6) δ 7,43 *(d,* 2H), 6,99 (d, 2H), 4,08-3,94 (m, 4H), 3,64 (dt, 2H), 2,57-2,47 (m, 2H), 2,46-2,36 (m, 4H), 2,12-1,94 (m, 4H), 1,87 (p, 2H), 1,73-1,62 (m, 4H).

Alternativamente, puede prepararse 4-[4-(3-Pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-carbonitrilo con las siguientes etapas:

Etapa 1:

Se disolvió cianuro de 4-hidroxibencilo (20 g, 0,15 mol) en DMF (500 ml)

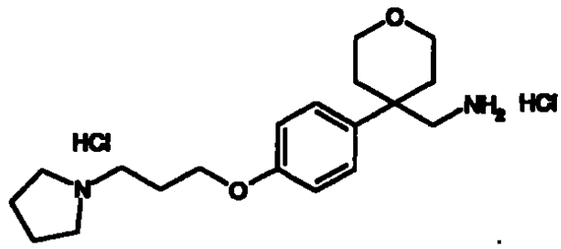
y después se le añadió K_2CO_3 (41,4 g, 0,3 mol) y NaI (7,8 g, 0,052 mol) seguido de la adición gota a gota cloruro de 3-(1-pirrolidin)-propilo (26,5 g, 0,18 mol) a 60 °C. Se continuó calentando a 90 °C durante 3 horas y después la mezcla se calentó durante una noche a 60 °C. Se añadió otra vez cloruro de 3-(1-pirrolidin)-propilo (10 g, 0,067 mol) ya que la reacción no se había completado y se siguió calentando durante 6 horas más. La mezcla de reacción se concentró y se recogió en EtOAc. La fase orgánica se lavó con agua, finalmente con salmuera. El [4-(3-pirrolidin-1-ilpropoxi)fenil]acetonitrilo en bruto se purificó por DCM/MeOH 9,5/0,5 con una columna de gel de sílice. Rendimiento: 25,5 g (70 %).

^1H-RMN (400 MHz, $CDCl_3$) δ 1,77 (m. 4H); 1,98 (m, 2H); 2,50 (m, 4H); 2,59 (t, 2H); 3,66 (s, 2H); 4,00 (t, 2H); 6,87(d, 2H); 7,19(d, 2H).

Etapa 2:

Se suspendió NaH (14,6 g, 0,61 mol) en DMF (100 ml). Se disolvió [4-(3-Pirrolidin-1-ilpropoxi)fenil]acetonitrilo (25,5 g, 0,10 mol) en DMF (100 ml) y se añadió gota a gota a la suspensión refrigerada en hielo de NaH. La mezcla de reacción se agitó a temperatura ambiente durante 30 minutos seguido de la adición gota a gota de 2-bromoetiléter (36,2 g, 0,16 mol) en DMF (200 ml) enfriado en hielo. La mezcla de reacción se vertió en agua enfriada con hielo. El sólido se filtró, se lavó con agua, se secó y el sólido resultante se lavó con EtOAc al 5% en hexano dando el compuesto del título (22 g, 67 %).

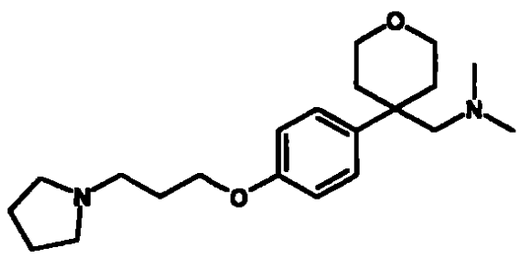
Ejemplo 28: Diclorhidrato de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il}metilamina



A una suspensión agitada de $LiAlH_4$ (1,81 g, 47,7 mmol, 5 eq) en Et_2O/DCM (1:1, 30 ml) a una temperatura de 0 a 5ºC en una atmósfera de nitrógeno se le añadió 4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-carbonitrilo (3 g, 9,55 mmol) en Et_2O/DCM (1:1, 30 ml) durante 15 minutos manteniendo la temperatura entre 5 y 10ºC. La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó hasta que se completó. Se añadió gota a gota hidróxido sódico (2 N, 15 ml) y los sólidos resultantes se filtraron, se lavaron con Et_2O/DCM (1:1, 6 x 50 ml) y se concentraron *al vacío* a 40ºC. Una porción del producto en bruto de la reacción anterior (0,5 g, 1,57 mmol) se disolvió en dioxano (5 ml) y se añadió HCl 4 M en dioxano (1,18 ml) en una atmósfera de N_2. La reacción se agitó durante 3 horas y se filtró bajo una capa de N_2 (higroscópica), se lavó con TBME y se secó en un horno a 40ºC dando el compuesto del título en forma de un sólido blanco (0,5 g, 81%).

^1H RMN (400 MHz, DMSO-D_6) δ 11,24 (s a, 1H), 8,00 (s a, 3H), 7,33 (d, 2H), 6,98 (d, 2H), 4,08 (t, 2H), 3,76-3,63 (m, 2H), 3,60-3,46 (m, 2H), 3,45-3,18 (m, 4H), 3,07-2,87 (m, 4H), 2,25-1,77 (m, 10H).

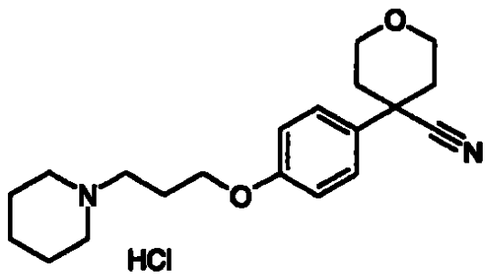
Ejemplo 29: Dimetil-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]-tetrahidro-piran-4-ilmetil]amina:



A una mezcla de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il} metilamina (2,5 g, 7,86 mmol), ácido acético (6 ml) y agua (12,5 ml) se le añadió formaldehído (11,5 ml) y se agitó durante 15 minutos. Se añadió STAB (10 g, 4,72 mmol) en porciones y se agitó durante una hora. A la mezcla de reacción se le añadió lentamente hidróxido sódico (2 M, 100 ml) para conseguir un pH de 9. La mezcla resultante se extrajo con DCM (3x100 ml) y las fases orgánicas combinadas se secaron sobre $MgSO_4$, se filtraron y se concentraron *al vacío* a 35ºC. La mezcla en bruto se purificó por cromatografía en columna sobre sílice eluyendo con DCM:MeOH:NH_3 (95:4:1) dando el compuesto del título en forma de un sólido blanco (1,09 g, 40%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,21 (d, 2H), 6,87 (d, 2H), 4,02 (t, 2H), 3,75 (dt, 2H), 3,55 (td, 2H), 2,65 (t, 2H), 2,56 (s a, 4H), 2,40 (s, 2H), 2,15-1,74 (m, 10H), 1,97 (s, 6H).

Ejemplo 30: 4-[4-(3-Piperidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-carbonitrilo

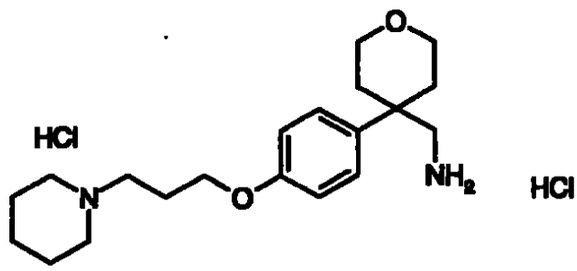


Una mezcla de 4-(4-hidroxifenil)tetrahidro-2*H*-piran-4-carbonitrilo (1,0 g, 5 mmol), 1-(3-cloropropil)piperidina (1,2 g, 7,5 mmol) obtenida siguiendo el procedimiento descrito en la *Patente DD 60557*, carbonato de cesio (2,4 g, 7,5 mmol), KI (1,2 g, 7,5 mmol) en DMF (50 ml) se calentó a 70ºC durante una noche. Después de retirar el DMF a presión reducida, el residuo se inactivó con agua y se extrajo con DCM. La fase orgánicas se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo se purificó por cromatografía ultrarrápida (50 g de gel de sílice, DCM / MeOH) proporcionando el compuesto del título (1,45 g, 88%).

La sal clorhidrato como muestra analítica se preparó con éter/HCl 2 M en diclorometano y cristalización en éter.

^{1}H RMN (500 MHz, $CDCl_3$) δ 12,14 (sa, 1H), 7,32 (d, 2H), 6,83(d,2H), 4,07 - 3,97 (m, 4H), 3,85 -3,78 (m, 2H), 3,57-3,48 (m, 2H), 3,14-3,07 (m, 2H), 2,67 - 2,56 (m, 2H), 2,45 - 2,36 (m, 2H), 2,32 - 2,19 (m, 2H), 2,06 - 1,92 (m, 4H), 1,90-1,75 (m, 4H), 1,43-1,32 (m, 1H).

Ejemplo 31: Diclorhidrato de {4-[4(3-piperidin-1-ilpropoxi)fenil]tetrahidropiran-4-il}metilamina

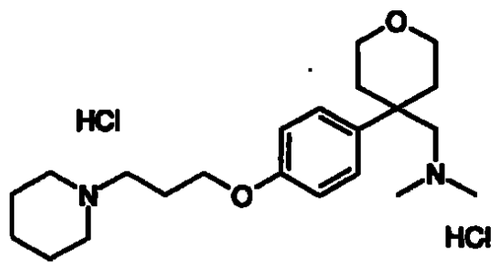


Una mezcla de 4-[4-(3-piperidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-carbonitrilo (1,45 g, 4,4 mmol), isopropanol (12 ml), HCl concentrado (350 µl) y PtO_2 (115 mg) se agitó y se hidrogenó a 50ºC durante una noche a presión

atmosférica. La mezcla se filtró sobre tierra de diatomeas y se concentró. El residuo se disolvió en una mezcla de DCM /MeOH y se lavó con NaOH (1 M). La fase orgánicas se secaron sobre Na_2SO_4, se filtraron y se concentraron, se purificó por cromatografía ultrarrápida (10 g de gel de sílice, DCM/ MeOH (NH_3 al 10%)) proporcionando el compuesto del título en forma de base libre (0,650 g, 44,5%). Esto se convirtió después en la sal diclorhidrato.

^{1}H RMN (400 MHz, DMSO-D_6) δ 10,66 (sa, 1H), 7,74 (sa, 3H), 7,32 (d, 2H), 6,97 (d, 2H), 4,07 (t, 2H), 3,73-3,65 (m, 2H), 3,47-3,28 (m, 4H), 3,18-3,10 (m, 2H), 2,98-2,81 (m, 4H), 2,25-2,16 (m, 2H), 2,14-2,06 (m, 2H), 1,90-1,67 (m, 7H), 1,44-1,31 (m, 1H).

Ejemplo 32: Diclorhidrato de dimetil-{4-[4-(3-piperidin-1-ilpropoxi)fenil]tetrahidro-piran-4-ilmetil}amina



A (0,50 g, 1,5 mmol) de diclorhidrato de {4-[4-(3-piperidin-1-ilpropoxi)fenil]tetrahidropiran-4-il}metilamina se le añadió 1,5 ml de formaldehído (solución al 37% p/p en H_2O). Se le añadió 1,9 ml de ácido fórmico y la mezcla se calentó a 100°C durante 1,5 horas. Después de enfriar, se añadió agua y la mezcla se extrajo con éter. A la fase acuosa se le añadió NaOH y la mezcla se extrajo 3 veces con éter. Los extractos orgánicos se lavaron con salmuera, se secaron sobre Na_2SO_4 se filtraron y se concentraron *al vacío*. El residuo se purificó por cromatografía ultrarrápida (25 g de gel de

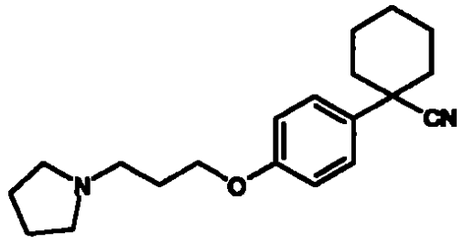
sílice, DCM/ MeOH/NH_3 al 10%). Esto se convirtió después en la sal diclorhidrato.

^{1}H RMN (400 MHz, DMSO-D_6) δ 10,63 (sa, 1H), 9,73 (sa, 1H), 7,43 (d, 2H), 6,99(d, 2H), 4,11-4,03 (t, 2H), 3,76-3,67 (m, 2H), 3,47-3,29 (m, 7H), 3,19-3,11 (m, 2H), 2,92-2,81 (m, 2H), 2,41-2,35 (m, 5H), 2,32-2,16 (m, 4H), 1,95-1,66 (m, 7H), 1,45-1,32 (m, 1H).

Intermedio 26: 1-(4-hidroxifenil)ciclohexanocarbonitrilo

A una solución de 1-(4-metoxifenil)ciclohexanocarbonitrilo (2 g, 9,29 mmol) en DCM (40 ml) a 0ºC en una atmósfera de N_2 se le añadió gota a gota BBr_3 (2,63 ml, 27,87 mmol). La reacción se dejó calentar a temperatura ambiente y se agitó durante 48 horas. La mezcla se agitó durante 3 horas a 0ºC y se inactivó con agua (30 ml). La mezcla se separó y la fase orgánica se lavó con una solución acuosa saturada de $NaHCO_3$ y después con agua. Los extractos orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, se concentraron *al vacío* y se purificaron por cromatografía en columna sobre gel de sílice eluyendo con DCM:acetona (97:3) dando el compuesto del título (1,71 g, 91%).

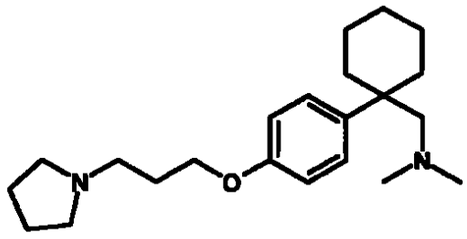
Ejemplo 33: 1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexanocarbonitrilo



1-(4-Hidroxifenil)ciclohexanocarbonitrilo (1,70 g, 8,45 mmol), 1-(3-cloro-propil)-pirrolidina (1,87 g, 12,67 mmol), acetona (50 ml), yoduro sódico (0,444 g, 2,96 mmol) y K_2CO_3 (5,45 g, 39,44 mmol) se calentaron a 50ºC durante una

noche. El disolvente se evaporó y el producto en bruto se recogió en DCM, se lavó con NaOH 0,5 N, se extrajo con una solución de HCl 0,5 N y se lavó con DCM. La fase acuosa se basificó con NaOH 0,5 N y se extrajo con DCM. Los extractos orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, se lavaron con DCM y se concentraron *al vacío* dando un sólido amarillento. El sólido se suspendió en éter, se filtró, se lavó con éter dando el compuesto del título en forma de un sólido blanco (1,34 g, 51%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,30 (d, 2H), 6,83 (d, 2H), 3,95 (t, 2H), 2,54 (t, 2H), 2,44 (m, 4H), 2,06 (m, 2H), 1,92 (m, 2H), 1,84-1,58 (m, 12H).

Ejemplo 34: *N*-({1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil}metil)-*N*,*N*-dimetilamina



Etapa 1:

A una suspensión agitada de $LiAlH_4$ (0,607 g, 16 mmol) en éter dietílico (15 ml) enfriara a 0ºC se le añadió gota a gota una solución de 1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexanocarbonitrilo (1 g, 3,2 mmol) en éter dietílico (10 ml). Después de agitarse a temperatura ambiente durante 30 minutos, la mezcla de reacción se calentó a reflujo durante otros 30 minutos. La mezcla se enfrió a 0ºC y se añadió sucesivamente gota a gota agua (1,38 ml), una solución acuosa 5 N de hidróxido sódico (1,38 ml) y agua (5,52 ml). Después de agitarse durante 15 minutos a temperatura ambiente, la mezcla se filtró

sobre tierra de diatomeas y se concentró. La {1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil}metilamina en bruto (0,961 g, 95%) se usó en la siguiente etapa sin purificación adicional.

Etapa 2:

A {1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil}metilamina (0,96 g, 3 mmol) se le añadió ácido fórmico (5 ml) seguido de formaldehído (solución al 37% p/p en H_2O, 0,915 ml, 33 mmol). La mezcla se calentó a reflujo durante 3 horas y se dejó agitar durante una noche a temperatura ambiente. Después, se diluyó con DCM, se basificó a pH 12 con una solución acuosa de NaOH y la mezcla se extrajo con DCM. Los extractos orgánicos se secaron sobre Na_2SO_4, se filtraron, se concentró *al vacío* y se purificó por cromatografía en columna sobre gel de sílice eluyendo con un gradiente de DCM:MeOH:NH_3 (de 99:0:1 a 90:10:1) proporcionando el compuesto del título (0,447 g, 43%) en forma de un aceite.

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,18 (d, 2H), 6,78 (d, 2H), 3,94 (t, 2H), 2,55 (t, 2H), 2,45 (m, 4H), 2,22 (m, 2H), 2,06-1,86 (m, 10H), 1,72 (m, 4H), 1,58-1,19 (m, 8H).

Intermedio 27: 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbaldehído

Etapa 1:

Una solución de 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbonitrilo (20 g, 0,0636 mol) en ácido clorhídrico concentrado (200 ml, 10 vol) se calentó y se agitó a reflujo durante 16 horas después de lo cual el análisis LC/LCEM mostró que la reacción se había estancado en un 85-90% de conversión. La solución se evaporó a sequedad *al vacío*, formó un azeótropo

con metanol (200 ml, 20 vol) y tolueno (2x 200 ml, 2x 20 vol) produciendo ácido 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxílico en forma de un sólido beige que se usó directamente (no se registraron los datos RMN).

Etapa 2:

Una suspensión de ácido 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxílico (23,5 g, 0,0636 mol) en metanol (235 ml, 10 vol) se agitó y se enfrió a una temperatura de 0 a -5°C en una atmósfera de nitrógeno. Se cargó gota a gota cloruro de tionilo (9,3 ml, 0,1272 mol, 0,40 vol) durante 20 minutos, manteniendo la temperatura entre -5 y +5°C. La suspensión resultante se calentó y se agitó a reflujo en una atmósfera de nitrógeno durante 16 horas después de lo cual el análisis LC mostró un 1,4% en área de ácido restante. La solución se evaporó a sequedad *al vacío* a 40°C dando un lodo pardo. El lodo se disolvió en acetato de etilo (118 ml, 5 vol) y agua (235 ml, 10 vol) y las fases se separaron. La fase acuosa se lavó con acetato de etilo (118 ml, 5 vol) y se basificó a pH 11 con carbonato potásico acuoso saturado (118 ml, 5 vol). El producto se extrajo en diclorometano (3x 118 ml, 3x 5 vol) y los extractos combinados se secaron sobre sulfato de magnesio (23 g) y se concentraron *al vacío* a 40°C produciendo 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxilato de metilo (21,7 g, 98% a partir del nitrilo) en forma de un sólido de color crema.

Etapa 3:

Se cargó rápidamente tetrahidrofurano anhidro (141 ml, 10 vol) en hidruro de aluminio litio agitado y enfriado (0-5°C) (6,2 g, 0,1634 mol, 0,44 peso) en una atmósfera de nitrógeno. La suspensión resultante se enfrió a 0-5°C y después se le añadió gota a gota una solución de 4-[4-(3-pirrolidin-1-

ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxilato de metilo (14,1 g, 0,04058 mol) en tetrahidrofurano (99 ml, 7 vol) durante 30 minutos manteniendo 0-5°C. Al completar la adición la reacción se dejó calentar a temperatura ambiente durante 30 minutos y se agitó a 18-25°C durante 30 minutos, el análisis LC mostró que la reacción se había completado. La mezcla se enfrió a 0 a 5°C, se añadió muy lentamente una mezcla 1:1 de tetrahidrofurano y agua (18,6 ml, 1,32 vol). La mezcla se inactivó después con una solución de hidróxido sódico al 20% p/v (6,2 ml, 0,44 vol) y agua (18,6 ml, 1,32 vol) y la suspensión blanca resultante se agitó enérgicamente durante 30 minutos a 18-25°C. Las sales se retiraron por filtración y se aclararon con tetrahidrofurano (3x 150 ml). Los filtrados combinados se evaporaron a sequedad a 40°C produciendo {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metanol (12,1 g, 94%) en forma de un sólido blanco.

Etapa 4:

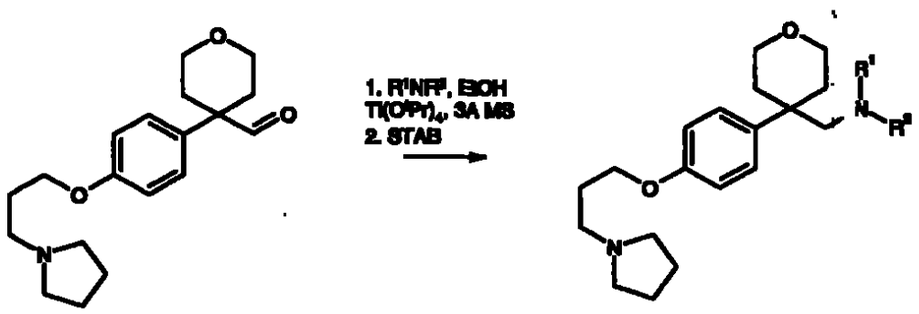
Se cargó clorocromato de piridinio (20,3 g, 0,09415 mol, 1,69 peso) a una suspensión agitada de celite (24 g, 2 peso) y {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metanol (12,03 g, 0,03766 mol) en diclorometano (120 ml, 10 vol) con agitación. La mezcla se agitó a 18-25°C durante 3,5 horas después de lo cual el análisis LC mostró que la reacción se había completado al 70%. Se añadió sulfato de magnesio (12 g, 1 peso) y la suspensión resultante se filtró a través de una capa de óxido de aluminio (activado, básico, Brockmann I, calidad convencional, malla ~150) (481 g, 40 peso) eluyendo con metanol/diclorometano al 1%. Las fracciones limpias se combinaron y se evaporaron a sequedad a 40°C. El sólido pardo resultante se agitó en *terc*-butilmetiléter (120 ml, 10 vol). El residuo no disuelto se retiró por

filtración y se aclaró con *terc*-butilmetiléter (3x120 ml, 3x 10 vol). Los filtrados combinados se evaporaron a 40°C produciendo 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbaldehído (6,0 g, 50,2%) en forma de un sólido beige ceroso.

Alternativamente, puede prepararse 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbaldehído como se indica a continuación:

A una solución de 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbonitrilo (250 mg, 0,79 mmol) en tolueno anhidro (2 ml) a -78°C se le añadió gota a gota una solución 1,5 M de hidruro de diisobutil aluminio en tolueno (1,59 ml, 2,38 mmol, 3 equiv). La mezcla de reacción se agitó durante 2 h a -78°C. Después se añadió acetato de etilo seguido de una solución saturada de tartrato de sodio potasio y diclorometano. Después de agitar a temperatura ambiente durante 1 hora, la fase orgánica se separó. La fase acuosa se extrajo tres veces con diclorometano. Los extractos orgánicos combinados se secaron sobre sulfato sódico, se filtraron y se concentraron a presión reducida dando una mezcla 8:2 del aldehído deseado y del nitrilo de partida en forma de un aceite naranja.

Procedimiento General D:

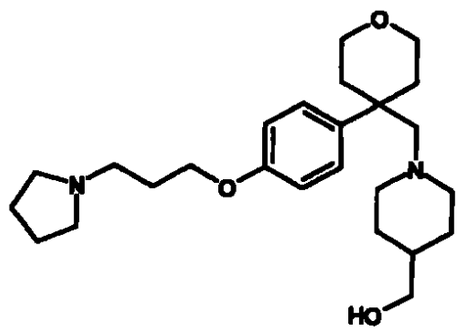


Una solución del 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-

carbaldehído (700 mg, 2,205 mmol, 1 peso) y amina secundaria (NR^1R^2) (4,21 mmol) en etanol puro (28 ml, 40 vol) se agitó a una temperatura de 18 a 25ºC en una atmósfera de nitrógeno sobre tamices moleculares 3A activados (700 mg, 1 peso). Se añadió gota a gota isopropóxido de titanio (IV) (3,25 ml, 11,025 mmol, 4,62 vol) durante 2 minutos. La solución resultante se agitó a 18 a 25ºC en una atmósfera de nitrógeno durante un periodo de 20 a 24 horas, después de lo cual se observó una precipitación. Después se añadió triacetoxiborohidruro sódico (3,97 g, 0,0187 mol, 5,67 peso) en una porción (Nota: No se observó un desprendimiento de gas exotérmico, sino suave) y la reacción se agitó durante un periodo de 1 a 8 horas hasta que el análisis LC mostró que la reacción se había completado o se había estancado en un 1-10% de aldehído en área). La mezcla de reacción se decantó de los tamices y se evaporó a sequedad *al vacío* a 40ºC. Se añadió *terc*-butilmetiléter (28 ml, 40 vol), solución de Rochelle al 50% p/v (28 ml, 40 vol) y una solución de carbonato potásico acuoso saturado (28 ml, 40 vol) y la mezcla se agitó enérgicamente durante 1 a 2 horas hasta que las dos capas eran visibles (la fase orgánica era transparente, la fase acuosa turbia). Las fases se separaron y la fase acuosa se extrajo otra vez con éter de *terc*-butilmetilo (28 ml, 40 vol). Los extractos se combinaron, se lavaron con una solución de cloruro sódico acuoso saturado (28 ml, 40 vol), se secaron sobre sulfato de magnesio (700 mg, 1 peso) y se evaporaron *al vacío* a 40ºC produciendo un aceite viscoso. El aceite se purificó por cromatografía en columna sobre sílice (20 g, 28,6 peso) eluyendo con DCM(95):MeOH(4):NH_3(1) retirando el aldehído no reaccionado, el subproducto alcohólico (típicamente 1-10% en área) y el exceso de amina secundaria produciendo el producto puro en forma de un aceite viscoso

contaminado con diclorometano después de la evaporación. El aceite se disolvió en etanol (5 ml, 7,1 vol) y se evaporó a sequedad *al vacío* a 40ºC, después en un horno de vacío a 40ºC durante 12 a 24 horas produciendo la amina terciaria requerida en forma de un aceite viscoso o un sólido ceroso.

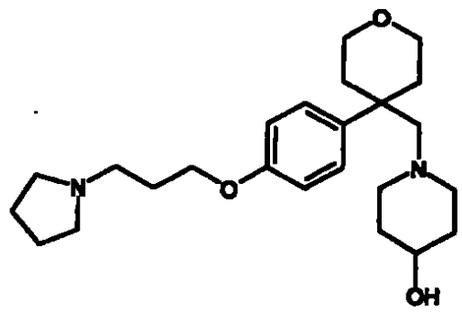
Ejemplo 35: (1-{4-[4-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil}piperidin-4-il)-metanol



Se hizo reaccionar 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbaldehído (700 mg, 2,205 mmol, 1 peso), 4-piperidinametanol (485 mg, 4,21 mmol), etanol puro (28 ml, 40 vol), tamices moleculares activados 3A (700 mg), isopropóxido de titanio (IV) (3,25 ml, 11,03 mmol) y STAB (3,97 g, 18,7 mmol) de acuerdo con el procedimiento general D. El sólido ceroso aislado se purificó por cromatografía en columna sobre sílice eluyendo con DCM:MeOH:NH_3 95:4:1 dando el compuesto del título en forma de un aceite transparente (820 mg, 72%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,85 (d, 2H), 4,02 (t, 2H), 3,75 (dt, 2H), 3,59-3,46 (m, 2H), 3,42 (d, 2H), 2,63 (t, 2H), 2,53 (s a, 4H), 2,39-2,26 (m, 4H), 2,15-1,03 (m, 18H).

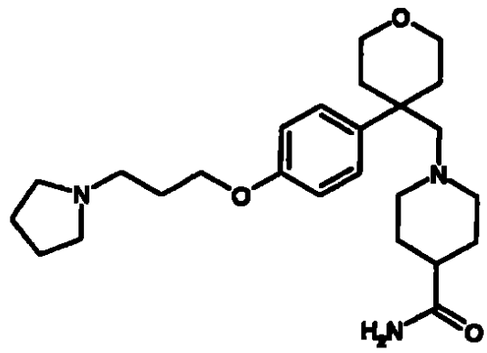
Ejemplo 36: 1-{4-[4-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil}piperidin-4-ol



Se hizo reaccionar 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbaldehído (420 mg, 1,30 mmol, 1 peso), 4-hidroxipiperidina (268 mg, 2,60 mmol), etanol puro (17 ml, 40 vol), tamices moleculares activados 3A (420 mg), isopropóxido de titanio (IV) (1,94 ml, 4,62 vol) y STAB (2,34 g, 11,1 mmol) de acuerdo con el procedimiento general D. El sólido ceroso aislado se purificó por HPLC preparativa eluyendo con acetonitrilo/agua/TFA al 0,1% como gradiente, dando el compuesto del título en forma de un sólido blanco (380 mg, 73%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,21 (d, 2H), 6,86 (d, 2H), 4,02 (t, 2H), 3,75 (dt, 2H), 3,59-3,47 (m, 2H), 2,63 (t, 2H), 2,53 (s a, 4H), 2,35 (s, 2H), 2,33-2,25 (m, 2H), 2,13-1,96 (m, 6H), 1,93-1,83 (m, 2H), 1,82-1,76 (m, 4H), 1,72-1,59 (m, 3H), 1,47-1,29 (m, 3H).

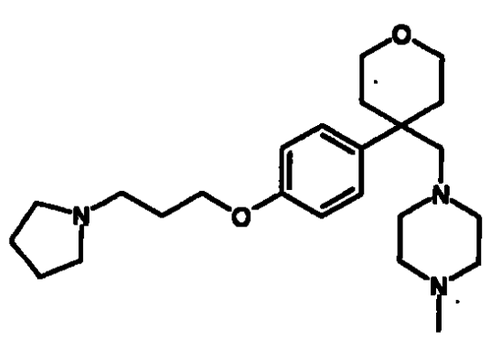
Ejemplo 37: Amida del ácido 1-[4-[4(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil]-piperidin-4-carboxílico



Se hizo reaccionar 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbaldehído (500 mg, 1,58 mmol), isonipecotamida (434 mg, 3,03 mmol), etanol puro (20 ml), tamices moleculares activados 3A (500 mg), isopropóxido de titanio (IV) (2,31 ml, 7,88 mmol) y STAB (2,84 g, 13,6 mmol) de acuerdo con el procedimiento general D. El producto aislado en bruto se purificó por cromatografía en columna sobre sílice eluyendo con DCM:MeOH:NH_3 (97:2:1) dando el compuesto del título en forma de un sólido incoloro (400 mg, 59%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,85 (d, 2H), 5,45 (s a, 2H), 4,01 (t, 2H), 3,79-3,69 (m, 2H), 3,57-3,46 (m, 2H), 2,63 (t, 2H), 2,53 (s a, 4H), 2,35 (s, 2H), 2,31 (s a, 1 H), 2,14-1,72 (m, 14H), 1,67-1,51 (m, 4H).

Ejemplo 38: 1-Metil-4-{4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil}-piperazina

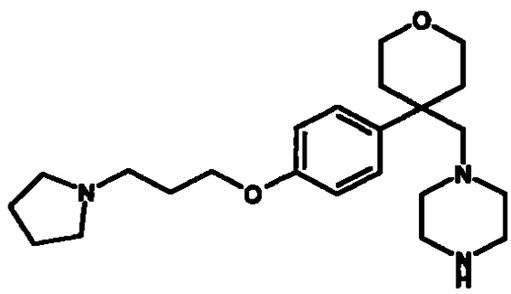


Se hizo reaccionar una solución de 4-[4-(3-pirrolidin-1-ilpropoxi)feniltetrahidro-2*H*-piran-4-carbaldehído (500 mg, 1,58 mmol, 1 peso), 1-metilpiperazina (300 mg, 2,99 mmol), etanol puro (20 ml, 40 vol), tamices moleculares activados 3A (500 mg), isopropóxido de titanio (IV) (2,32 ml, 7,83 mmol) y STAB (1,43 g, 6,73 mmol) de acuerdo con el procedimiento general D. El aceite aislado se purificó por cromatografía en columna sobre sílice (20 g, 28,6 peso) eluyendo con DCM(95):MeOH(4):NH_3(1) dando el compuesto del

título en forma de un aceite viscoso transparente (360 mg, 56%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,21 (d, 2H), 6,86 (d, 2H), 4,02 (t, 2H), 3,75 (dt2H), 3,60-3,47 (m, 2H), 2,63 (t, 2H), 2,53 (s a, 4H), 2,38 (s, 2H), 2,34-2,14 (m, 11H), 2,13-1,73 (m, 10H).

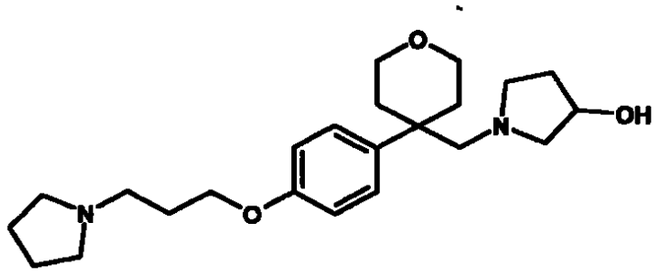
Ejemplo 39: 1-[4-[4-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil]piperazina.



Se hizo reaccionar 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbaldehído (350 mg, 1,103 mmol), éster terc-butilo del ácido 4-piperazin-1-carboxílico (372 mg, 1,98 mmol), etanol puro (40 ml), tamices moleculares activados 3A (350 mg), isopropóxido de titanio (IV) (1,62 ml, 5,48 mmol) y STAB (2,0 g, 9,74 mmol) de acuerdo con el procedimiento general D. El producto aislado en bruto se purificó por cromatografía en columna sobre sílice eluyendo con DCM:MeOH:NH_3 (98:1:1) dando un sólido blanco (295 mg, 69%). Este sólido se volvió a disolver en metanol (3,2 ml) y 1,4-dioxano (8 ml), se le añadió HCl en dioxano (4 M, 1,95 ml). La mezcla se agitó durante una noche y se concentró *al vacío* a 40°C. Se añadieron TBME (13 ml) y NaOH (acuoso 2 M) para lograr un pH de 12-14. La fase orgánica se separó y se secó sobre $MgSO_4$ y se concentró *al vacío* a 35°C. El producto en bruto se sometió a cromatografía sobre sílice eluyendo con DCM:MeOH:NH_3 (94:4:2) dando el compuesto del título en forma de un aceite amarillo (100 mg, 23%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,21 (d, 2H), 6,85 (d, 2H), 4,02 (t, 2H), 3,80-3,70 (m, 2H), 3,58-3,46 (m, 2H), 2,73-2,66 (m, 4H), 2,63 (t, 2H), 2,53 (s a, 4H), 2,34 (s, 2H), 2,17-1,48 (m, 15H).

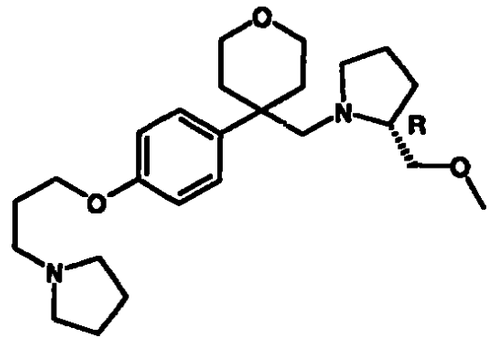
Ejemplo 40: 1-{4-[4-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil}pirrolidin-3-ol



Se hizo reaccionar 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbaldehído (350 mg, 1,103 mmol), 3-pirrolidinol (200 mg, 2,02 mmol), etanol puro (40 ml), tamices moleculares activados 3A (350 mg), isopropóxido de titanio (IV) (1,62 ml, 5,48 mmol) y STAB (2,0 g, 9,74 mmol) de acuerdo con el procedimiento general D. El producto aislado en bruto se purificó por cromatografía en columna sobre sílice eluyendo con DCM:MeOH:NH_3 (97:2:1) dando el compuesto del título en forma de un sólido blanco (390 mg, 91%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,87 (d, 2H), 4,10-4,01 (m, 3H), 3,81-3,68 (m, 3H), 3,55 (t, 2H), 2,67-2,48 (m, 9H), 2,28-1,61 (m, 15H).

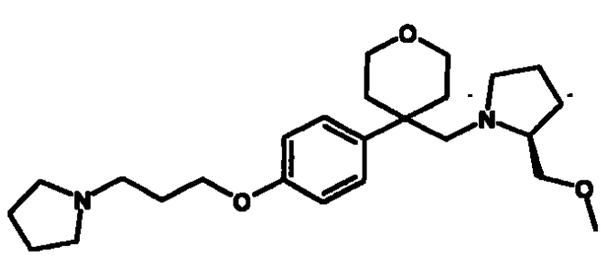
Ejemplo 41: (*R*)-2-Metoximetil-1-{4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil}-pirrolidina



Se hizo reaccionar 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbaldehído (500 mg, 1,575 mmol), (*R*)-2-(metoximetil)pirrolidina (347 mg, 4,21 mmol), etanol puro (20 ml), tamices moleculares activados 3A (500 mg), isopropóxido de titanio (IV) (2,33 ml, 7,88 mmol) y STAB (2,84 g, 13,4 mmol) de acuerdo con el procedimiento general D. El sólido ceroso aislado se purificó por cromatografía en columna sobre sílice eluyendo con DCM:MeOH:NH_3 95:14:1 dando el compuesto del título en forma de aceite amarillo pálido viscoso (390 mg, 59%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,18 (d, 2H), 6,86 (d, 2H), 4,02 (t, 2H), 3,85-3,69 (m, 2H), 3,59 (td, 1H), 3,45 (td, 1H), 3,27 (s, 3H), 3,10 (dd, 1H), 3,02 (dd, 1H), 2,94 (d, 1H), 2,63 (t, 2H), 2,58-2,45 (m, 6H), 2,39 (m,1 H), 2,21 (m, 1H), 2,07-1,67 (m, 11H), 1,57-1,33 (m, 3H).

Ejemplo 42: (*S*)-2-Metoximetil-1-{4-[4-(3-pirrolidin-1-ilpropoxi)-fenil]tetrahidropiran-4-ilmetil}pirrolidina

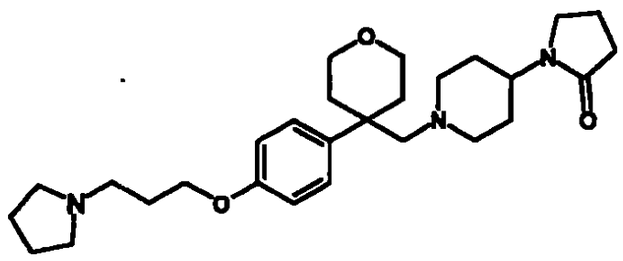


Se hizo reaccionar 4-[4-(3-pirrolidin-1-il-propoxi)fenil]tetrahidro-2*H*-piran-

4-carbaldehído (350 mg, 1,103 mmol), (*S*)-(+)-2-(metoximetil)pirrolidina (230 mg, 200 mmol), etanol puro (40 ml), tamices moleculares activados 3A (350 mg), isopropóxido de titanio (IV) (1,62 ml, 5,48 mmol) y STAB (2,0 g, 9,74 mmol) de acuerdo con el procedimiento general D. El producto aislado en bruto se purificó por cromatografía en columna sobre sílice eluyendo con DCM:MeOH:NH_3 (98:1:1) dando el compuesto del título en forma de un sólido blanco (330 mg, 72%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,18 (d, 2H), 6,86 (d, 2H), 4,02 (t, 2H), 3,84-3,70 (m, 2H), 3,59 (td, 1H), 3,45 (td, 1H), 3,27 (s, 3H), 3,10 (dd, 1H), 3,02 (dd, 1H), 2,94 (d, 1H), 2,63 (t, 2H), 2,59-2,45 (m, 5H), 2,39 (m,1 H), 2,21 (m, 1H), 2,06-1,34 (m, 15H).

Ejemplo 43: 1-(1-{4-[4-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil}piperidin-4-il)pirrolidin-2-ona

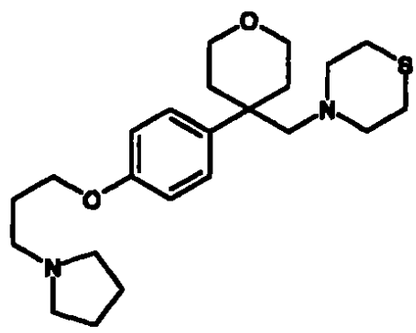


Se hizo reaccionar 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbaldehído (400 mg, 1,260 mmol), clorhidrato de 4-(*N*-2-pirrolidinon)piperidina (493 mg, 4,407 mmol), etanol puro (16 ml), tamices moleculares activados 3A (400 mg), isopropóxido de titanio (IV) (1,86 ml, 6,30 mmol) y STAB (2,27 g, 10,71 mmol) de acuerdo con el procedimiento general D. El sólido ceroso aislado se purificó por cromatografía en columna sobre sílice eluyendo con DCM(95):MeOH(4):NH_3(1) dando el compuesto del título en

forma de un aceite amarillo pálido (133 mg, 22%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,86 (d, 2H), 4,02 (t, 2H), 3,83-3,71 (m, 3H), 3,52 (dt, 2H), 3,32 (t, 2H), 2,63 (t, 2H), 2,53 (s a, 4H), 2,41-2,30 (m, 6H), 2,18 (dt, 2H), 2,12-1,36 (m, 16H).

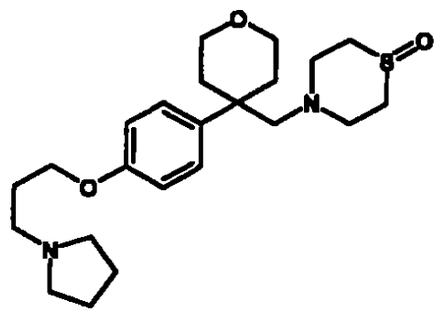
Ejemplo 44: 4-[4-[4-(3-Pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil]tiomorfolina



Se hizo reaccionar 4-[4-(3-pirrolidin-1- ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbaldehído (1,5 g, 4,726 mmol, 1 peso), tiomorfolina (930 mg, 9,027 mmol), etanol puro (60 ml), tamices moleculares activados 3A (1,5 g), isopropóxido de titanio (IV) (6,97 ml, 23,630 mmol) y STAB (8,51 g, 40,15 mmol) de acuerdo con el procedimiento general D. El sólido ceroso aislado se purificó por cromatografía en columna sobre sílice eluyendo con DCM(95):MeOH(4):NH_3(1) dando el compuesto del título en forma de un aceite amarillo pálido (1,06 g, 55%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,86 (d, 2H), 4,02 (t, 2H), 3,75 (dt, 2H), 3,57-3,45 (m, 2H), 2,63 (t, 2H), 2,59-2,39 (m, 12H), 2,36 (s, 2H), 2,14-1,95 (m, 4H), 1,92-1,73 (m, 6H).

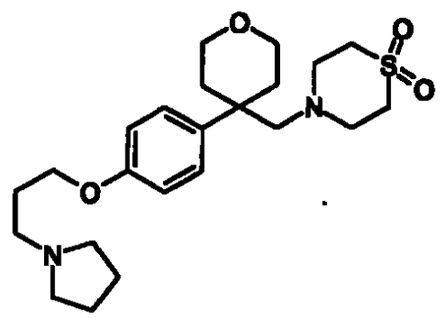
Ejemplo 45: 4-[4-[4-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil]tiomorfolin-1-óxido



A una solución de 4-[4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil]-tiomorfolina (200 mg, 0,494 mmol) en TFA (0,67 ml) a 5 a 10°C se añadió gota a gota una solución de ácido trifluoro-peracético [solución 4 M preparada por adición de H_2O_2 al 27,5% (0,94 ml) a TFA (1,56 ml)] y se agitó a 5 a 10°C durante 1 hora. La mezcla de reacción se diluyó con DCM (5 ml) y se añadió NaOH (solución 5 M, 4 ml) para alcanzar pH14. La mezcla se extrajo con DCM ((2x5 ml), Los extractos de DCM combinados se lavaron con salmuera acuosa saturada (10 ml), se secaron sobre $MgSO_4$, se filtraron y se concentraron *al vacío*. El aceite amarillo aislado se purificó por cromatografía en columna sobre sílice eluyendo con DCM(95):MeOH(4):NH_3(1) dando el compuesto del título en forma de un aceite amarillo (165 mg, 79%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,87 (d, 2H), 4,02 (t, 2H), 3,81-3,69 (m, 2H), 3,59-3,43 (m, 2H), 2,99-2,82 (m, 2H), 2,76-2,2.59 (m, 6H), 2,53 (s a, 4H), 2,46 (s, 2H), 2,31-1,73 (m, 12H).

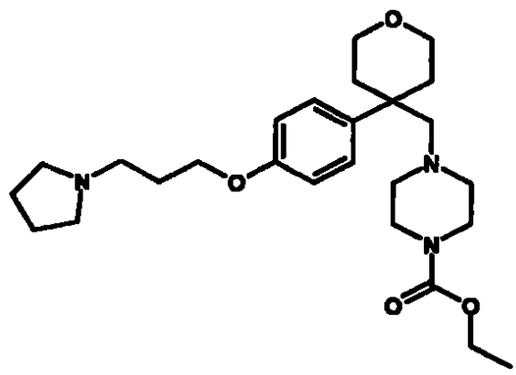
Ejemplo 46: 4-[4-[4-(3-Pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil]tiomorfolina-1,1-dióxido



A una solución de 4-[4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil]-tiomorfolina (230 mg, 0,56 mmol) en TFA (0,77 ml) a 0 a 5ºC se le añadió gota a gota una solución de ácido trifluoro-peracético [solución 4 M preparada por adición de H_2O_2 al 27,5% (0,94 ml) a TFA (1,56 ml)]. La reacción se dejó calentar a temperatura ambiente y se agitó durante una noche. La mezcla de reacción se enfrió a una temperatura de entre 0 y 5ºC, se diluyó con DCM (5 ml) y se inactivó con NaOH (solución 5 M, 5 ml) alcanzando pH14. La mezcla se extrajo con DCM (4x5 ml), Los extractos de DCM combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron *al vacío*. El aceite amarillo aislado se purificó por cromatografía en columna sobre sílice eluyendo con DCM(95):MeOH(4):NH_3(1) dando el compuesto del título en forma de un aceite incoloro (96,6 mg, 39%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,88 (d, 2H), 4,02 (t, 2H), 3,75 (dt, J = 11 y 4 Hz, 2H), 3,57-3,45 (m, 2H), 2,89-2,79 (m, 4H), 2,73-2,65 (m, 4H), 2,63 (t, 2H), 2,55 (s a, 4H), 2,53 (s, 2H), 2,22-2,11 (m, 2H), 2,01 (m, 2H), 1,87-1,73 (m, 6H).

Ejemplo 47: Éster etílico del ácido 4-[4-[4-(3-pirrolidin-1-il-propoxi)fenil]tetrahidropiran-4-ilmetil]piperazin-1-carboxílico



Se hizo reaccionar 4-[4-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbaldehído (500 mg, 1,58 mmol), piperazin-1-carboxilato de etilo (471 mg, 3,00 mmol), etanol puro (20 ml), tamices moleculares activados 3A (500 mg), isopropóxido de titanio (IV) (2,31 ml, 7,88 mmol) y STAB (2,84 g, 13,6 mmol) de acuerdo con el procedimiento general D. El producto aislado en bruto se purificó por cromatografía en columna sobre sílice eluyendo con DCM:MeOH:NH_3 (97:2:1) dando el compuesto del título en forma de un sólido blanco que contenía 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbaldehído residual (350 mg). El material se disolvió en DCM (14 ml) y se añadió PS-AMPS (cargando 2,04 mmol^{-1}, 23 mg) y se agitó durante 24 horas. La resina se filtró y la solución se concentró *al vacío* a 30ºC, El material en bruto se sometió a cromatografía sobre sílice eluyendo con DCM:MeOH:NH_3 (97:2:1) dando el compuesto del título en forma de un sólido blanco (130 mg, 18%).

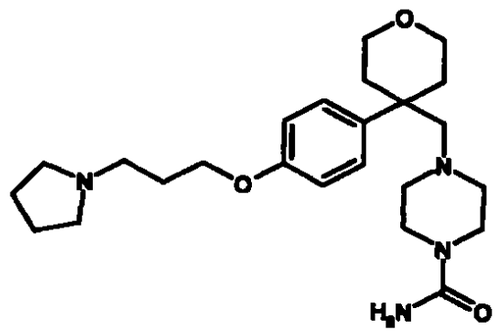
^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,86 (d, 2H), 4,08 (q, 2H), 4,02 (t, 2H), 3,79-3,70 (m, 2H), 3,57-3,47 (m, 2H), 3,27 (s a, 4H), 2,63 (t, 2H), 2,53 (s a, 4H), 2,38 (s, 2H), 2,21-1,73 (m, 14H), 1,21 (t, 3H).

Intermedio 28: Clorhidrato de la amida del ácido piperazin-1-carboxílico

Se mezcló éster *terc*-butilo del ácido 4-piperazin-1-carboxílico (1,0 g, 5,4

mmol), ácido acético (3 ml) y agua (5 ml). Se añadió cianuro potásico (2,25 g, 27,7 mmol) en porciones en forma de una solución en agua (5 ml) y se agitó durante 4 horas, durante lo cual precipitó un sólido. El sólido se filtró, se volvió a disolver en DCM (20 ml), se secó sobre $MgSO_4$, se filtró, la torta del filtro se lavó con DCM (5 vol) y se concentró *al vacío* dando un sólido blanco (0,389). El sólido blanco (0,38 g) se disolvió en metanol (3,8 ml) y 1,4-dioxano (0,7 ml), a la reacción se le añadió HCl 4 M en 1,4-dioxano (2,5 ml, 10 mmol) y se agitó durante una noche. La reacción se concentró *al vacío dando* el compuesto del título (0,28 g, 31% en 2 etapas) en forma de un sólido blanco.

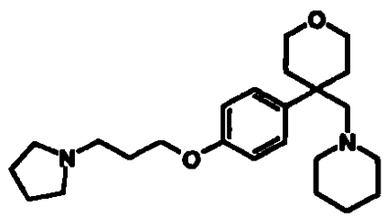
Ejemplo 48: Amida del ácido 4-[4-[4-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil]piperazin-1-carboxílico



Se hizo reaccionar 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2H-piran-4-carbaldehído (317 mg, 1 mmol), clorhidrato de amida del ácido piperazin-1-carboxílico (273 mg, 1,65 mmol), etanol puro (12,7 ml), tamices moleculares activados 3A (320 mg), Et_3N (0,278 ml), isopropóxido de titanio (IV) (1,46 ml, 5,20 mmol) y STAB (1,8 g, 8,5 mmol) de acuerdo con el procedimiento general D. El producto aislado en bruto se purificó por cromatografía en columna sobre sílice eluyendo con DCM:MeOH:NH_3 (98:1:1) dando el compuesto del título en forma de un sólido blanquecino (70 mg, 16%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,21 (d, 2H), 6,86 (d, 2H), 4,30 (s a, 2H), 4,02 (t, 2H), 3,80-3,71 (m, 2H), 3,58-3,48 (m, 2H), 3,23-3,15 (m, 4H), 2,63 (t, 2H), 2,53 (s a, 4H), 2,40 (s, 2H), 2,18-1,73 (m, 14H).

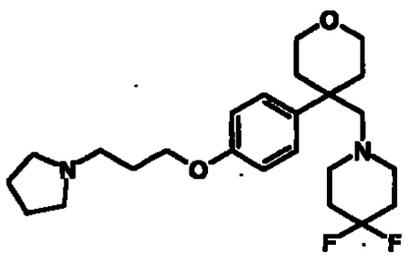
Ejemplo 49: 1-[4-[4-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil]piperidina



Se hizo reaccionar 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbaldehído (272 mg, 0,86 mmol), piperidina (0,161 ml, 1,63 mmol), etanol puro (11 ml), tamices moleculares activados 4A, isopropóxido de titanio (IV) (1,205 ml, 4,28 mmol) y STAB (1,54 g, 7,28 mmol) de acuerdo con el procedimiento general D. El sólido ceroso aislado se purificó por cromatografía en columna sobre sílice eluyendo con un gradiente de DCM:MeOH:NH_3 (de 99:0:1 a 90:9:1) dando el compuesto del título (97,4 mg, 25%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,21(d, 2H), 6,85 (d, 2H), 4,02 (t, 2H), 3,77 -3,72 (m, 2H), 3,54 -3,48 (t, 2H), 2,63 (t, 2H), 2,53 (m, 4H), 2,29 (s. 2H), 2,13-1,87 (m, 10H), 1,79 (quint, 4H), 1,41-1,36 (m, 4H), 1,30-1,26 (m, 2H).

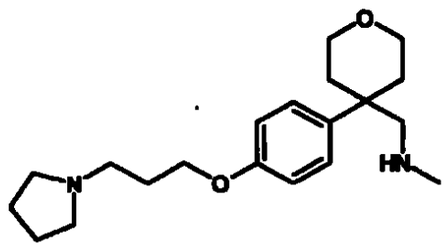
Ejemplo 50: 4,4-difluoro-1-[4-[4-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil]piperidina



Se hizo reaccionar 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbaldehído (260 mg, 0,82 mmol), clorhidrato de 4,4-difluoropiperidina (323 mg, 2,05 mmol), etanol puro (11 ml), tamices moleculares 4A activados, isopropóxido de titanio (IV) (1,209 ml, 4,09 mmol) y STAB (1,475 g, 6,96 mmol) de acuerdo con el procedimiento general D. El sólido ceroso aislado se purificó por HPLC preparativa de fase inversa en una columna Xterra eluyendo con un gradiente de MeCN:H_2O:Et_3N (de 29,9:70:0,1 a 94,9:5:0,1 en 13 minutos) dando el compuesto del título (26 mg, 6%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,21(d, 2H), 6,88 (d, 2H), 4,02 (t, 2H), 3,77 -3,73 (m, 2H), 3,53 -3,47(t, 2H), 2,64 (t, 2H), 2,54 (m, 4H), 2,39 (s, 2H), 2,30-2,24 (m, 6H), 2,13 (d, 2H), 2,02 (m, 2H), 1,90-1,71 (m, 6H).

Ejemplo 51: metil-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]-tetrahidropiran-4-ilmetil]amina



Etapa 1:

A una solución agitada de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il}metilamina (10,83 g, 34,05 mmol) y trietilamina

(10,31 g, 102,16 mmol) en diclorometano anhidro a 0 ° C se le añadió gota a gota una solución de di-*terc*-butildicarbonato (9,65 g, 44,27 mmol) en diclorometano anhidro. Se continuó agitando durante otra hora a 0 °C y después durante una noche a temperatura ambiente. Después, la mezcla de reacción se diluyó con diclorometano, se lavó con agua y salmuera, se secó sobre Na_2SO_4 y se concentró a presión reducida proporcionando a producto en bruto. El producto en bruto se purificó por cromatografía en columna sobre gel de sílice (EtOAc-MeOH-Et_3N) dando éster *terc*-butilo de ácido metil-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-piran-4-ilmetil]carbámico (9,80 g, rendimiento del 69%).

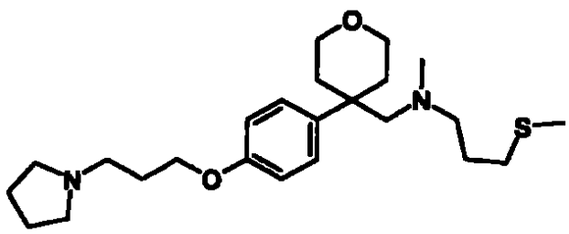
^{1}H RMN (400 MHz, $CDCl_3$) δ 1,37 (s, 9H); 1,75-1,88 (m, 6H); 1,96-2,07 (m, 4H); 2,48-2,55 (m, 4H); 2,61 (t, 2H); 3,28 (d, 2H); 3,51-3,59 (m, 2H); 3,76-3,80 (m, 2H); 4,01 (t, 2H); 4,15 (ma, 1H); 6,89 (d, 2H); 7,16 (d, 2H).

Etapa 2:

A una solución agitada de $LiAlH_4$ (2,59 g, 68,18 mmol) en THF anhidro a 0°C se le añadió gota a gota una solución de éster *terc*-butilo del ácido metil-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-piran-4-ilmetil]carbámico (9,50 g, 22,72 mmol). La mezcla de reacción se llevó a temperatura ambiente y finalmente se calentó a reflujo durante 3 horas. La mezcla de reacción se inactivó con una solución acuosa de NaOH y se filtró sobre una capa corta de celite, se secó sobre Na_2SO_4 y se concentró a presión reducida proporcionando el compuesto del título (7,1 g, rendimiento del 94%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,71-1,78 (m, 4H); 1,80-1,90 (m, 2H); 1,88-2,02 (m, 2H); 2,06-2,14 (m, 2H); 2,23 (s, 3H); 2,46-2,53 (m, 4H); 2,51-2,63 (m, 4H); 3,47- 3,56 (m, 2H); 3,70-3,77 (m, 2H); 3,99 (t, 2H); 6,86 (d, 2H); 7,17 (d, 2H).

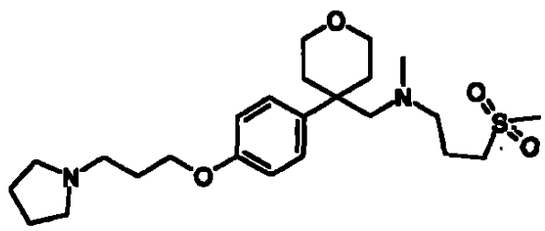
Ejemplo 52: metil-(3-metilsulfanil-propil)-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil}amina



A una solución de metil-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil] tetrahidropiran-4-ilmetil}amina (200 mg, 0,629 mmol) en dicloroetano (5 ml) en una atmósfera de nitrógeno se le añadió ácido acético (45 mg, 1,258 mmol), trietilamina (76 mg, 1,258 mmol) y 3-(metiltio)propanal (108 mg, 1,04 mmol). La mezcla se agitó durante 30 minutos y se le añadió una solución de $NaHB(OAc)_3$ (236 mg, 1,15 mmol) en dicloroetano (5 ml). Después de agita a temperatura ambiente durante una noche, la mezcla de reacción se filtró sobre celite, se concentró *al vacío* y se purificó por cromatografía en columna sobre gel de sílice eluyendo con DCM:MeOH:NH_3 (94,9:5:0,1) dando el compuesto del título (29 mg, 7%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,19 (d, 2H), 6,86 H), 4,02 (t, 2H), 3,78 - 3,73 (m, 2H), 3,54 - 3,49 (m, 2H), 2,67 (t, 2H), 2,59 (m, 4H), 2,42 (s, 2H), 2,35 (t, 2H), 2,22 (t, 2H), 2,11 - 2,00 (m, 7H), 1,91-1,86 (m, 5H), 1,85- 1,82 (m, 4H), 1,56 (q, 2H).

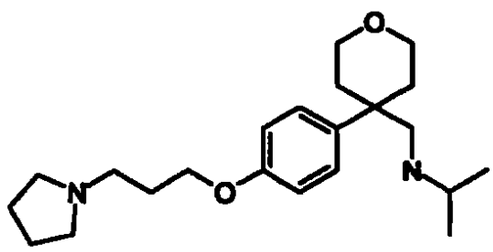
Ejemplo 53: (3-metanosulfonil-propil)-metil-{4-[4-(3-pirrolidin-1-il-propoxi)fenil]tetrahidropiran-4-ilmetil}amina



A una solución de metil-(3-metilsulfanil-propil)-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil)amina (170 mg, 0,404 mmol) en DCM (10 ml) en una atmósfera de nitrógeno a 0°C se le añadió TFA (0,240 ml, 3,2 mmol) seguido de ácido meta-cloroperbenzoico (70% puro, 199 mg, 0,808 mmol). La mezcla de reacción se agitó durante una noche dejándola calentar a temperatura ambiente. Se inactivó con una solución acuosa de $Na_2S_2O_3$. La fase orgánica se separó y se lavó con una solución acuosa de $NaHCO_3$. La fase orgánica se secó sobre sulfato sódico, se filtró, se concentró y se purificó por cromatografía en columna sobre gel de sílice eluyendo con DCM:MeOH:NH_3 (89,9:10:0,1) dando el compuesto del título.

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,18 (d, 2H), 6,88 (d, 2H), 4,03 (t, 2H), 3,78 - 3,73 (m, 2H), 3,53 - 3,48 (m, 2H), 2,82 (s, 3H), 2,69-2,73 (m, 2H), 2,65 (m, 2H), 2,55 (m, 4H), 2,47 (s, 2H), 2,22 (t, 2H), 2,12 - 2,09 (m, 2H), 1,89-2,05 (m, 5H), 1,68-1,85 (m, 8H).

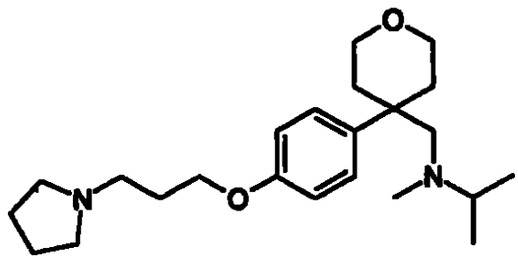
Ejemplo 54: Isopropil-[4-[4(3-pirrolidin-1-ilpropoxi)fenil]-tetrahidro-piran-4-ilmetil}amina



A una solución de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il) metilamina (400 mg, 1,256 mmol) en dicloroetano (10 ml) en una atmósfera de nitrógeno se añadió le ácido acético (180,5 mg, 2,76 mmol), trietilamina (306,4 mg, 2,76 mmol) y acetona (80,2 mg, 1,38 mmol). La mezcla se agitó durante 1 hora a temperatura ambiente y se añadió $NaHB(OAc)_3$ (601 mg, 2,76 mmol). Después de agitar durante una noche, la mezcla de reacción se filtró sobre celite, se concentró *al vacío* y se purificó por cromatografía en columna sobre gel de sílice eluyendo con DCM:MeOH:NH_3 (89:10:1) dando el compuesto del título en forma de un aceite (282 mg, 60%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,13 (d, 2H), 6,82 (d, 2H), 3,96 (t, 2H), 3,68 (m, 2H), 3,49 (m, 2H), 2,61 (s, 2H), 2,56 (t, 2H), 2,46 (m, 5H), 2,04 (m, 2H), 1,94 (m, 2H), 1,84 (m, 2H), 1,72 (m, 4H), 1,19 (s, 1H), 0,83 (d, 6H).

Ejemplo 55: isopropil-metil-{4-[4(3-pirrolidin-1-ilpropoxi)fenil]-tetrahidropiran-4-ilmetil}amina

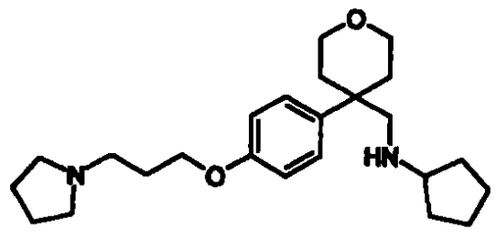


A isopropil-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil)-amina (258 mg, 0,71 mmol) se le añadió formaldehído (solución al 37% p/p en H_2O, 1 ml) y ácido fórmico (1,5 ml). La mezcla resultante se calentó a 60°C durante una noche. Después de enfriar, se añadieron H_2O y acetato de etilo. La fase acuosa se separó, se basificó con NaOH al 30% y se extrajo 3 veces con acetato de etilo. Los extractos orgánicos combinados se secaron sobre

Na_2SO_4, se filtraron y se concentraron *al vacío* dando el compuesto del título en forma de un aceite (170 mg, 65%).

^1H RMN (400 MHz, $CDCl_3$) δ 7,19 (d, 2H), 6,86 (d, 2H), 4,02 (t, 2H), 3,76 (m, 2H), 3,50 (m, 2H), 2,63 (t, 2H), 2,53 (m, 4H), 2,44 (m, 1H), 2,38 (s, 2H), 2,08 (m, 2H), 2,01 (m, 2H), 1,89 (m, 2H), 1,85 (s, 3H), 1,79 (m, 4H), 0,84 (d, 6H).

Ejemplo 56: ciclopentil-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetra-hidropiran-4-ilmetil}amina

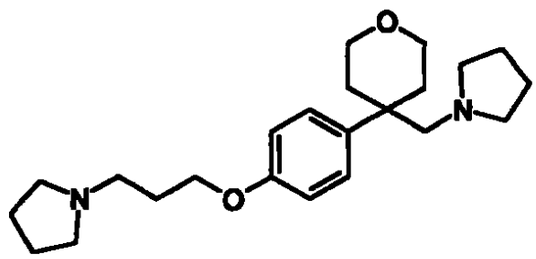


A una solución de (4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il} metilamina (254 mg, 0,798 mmol) en dicloroetano (5 ml) en una atmósfera de nitrógeno se le añadió ácido acético (37 mg, 1,6 mmol), trietilamina (97 mg, 1,6 mmol) y ciclopentanona (10 mg, 1,19 mmol). La mezcla se agitó durante 30 minutos a temperatura ambiente y se le añadió $NaHB(OAc)_3$ (204 mg, 1,6 mmol) a 0ºC. Después de agitar durante una noche, la mezcla de reacción se filtró sobre celite, se concentró *al vacío* y se purificó por cromatografía en columna sobre gel de sílice eluyendo con DCM:MeOH:NH_3 (89:10:1) dando el compuesto del título (226 mg, 58%).

^1H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,88 H), 4,03 (t, 2H), 3,78-3,73 (m, 2H), 3,59-3,53 (m, 2H), 2,84 (q, 1H), 2,73 (t, 2H), 2,65-2,68 (m, 6H), 2,03-2,12 (m, 4H), 1,84-1,94 (m, 6H), 1,65-1,72 (m, 2H), 1,51-1,58 (m, 2H), 1,41-1,46 (m, 2H), 1,07-1,16 (m, 2H).

Ejemplo 57: 1-{4-[4-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-

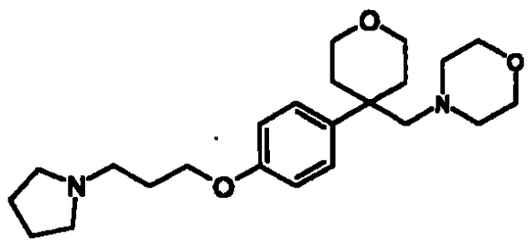
ilmetil}pirrolidina



A una solución agitada de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il} metilamina (150 mg, 0,47 mmol) y 1-bromo-4-cloroetano (54,2 µl, 0,47 mmol) en acetonitrilo anhidro (5 ml) se le añadió carbonato potásico (65 mg, 0,47 mmol). La mezcla se calentó a 60ºC durante una noche se concentró posteriormente a presión reducida. El producto en bruto se purificó por cromatografía en columna sobre gel de sílice eluyendo con DCM:MeOH:NH_3 (94:5:1) dando el compuesto del título (40 mg, rendimiento del 23%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,86 (d, 2H), 4,02 (t, 2H), 3,73 -3,78 (m, 2H), 3,57-3,53 (m, 2H), 2,65 -2,61 (m, 4H), 2,53 (m, 4H), 2,20 (m, 4H), 2,10 -1,88 (m, 6H), 1,56 (m, 4H).

Ejemplo 58: 4-{4-[4(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil}-morfolina

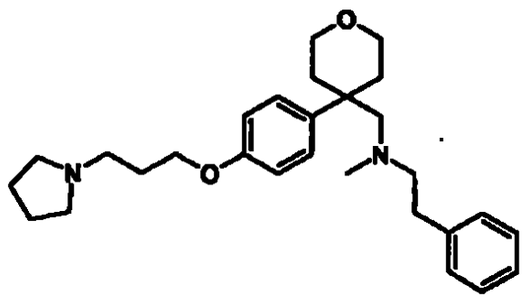


A una solución agitada de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il}metilamina (207 mg, 0,65 mmol) y bis(2-

bromoetil)éter (82 µl, 1,3 mmol) en acetonitrilo anhidro (10 ml) se le añadió carbonato potásico (180 mg, 1,3 mmol). La mezcla se calentó a 60°C durante una noche y después se concentró a presión reducida. El producto en bruto se purificó por cromatografía en columna sobre gel de sílice eluyendo con DCM:MeOH (97:3) con NH_3 al 10% dando el compuesto del título (90 mg, rendimiento del 23%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,22 (d, 2H), 6,83 (d, 2H), 4,04 (m, 2H), 3,73 (m, 2H), 3,51 (m, 6H), 3 (m, 6H), 2,38 (m, 2H), 2,25 (m, 2H), 2,13 - 2,03 (m, 10H), 1,88 (m, 2H).

Ejemplo 59: metil-fenetil-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil]amina

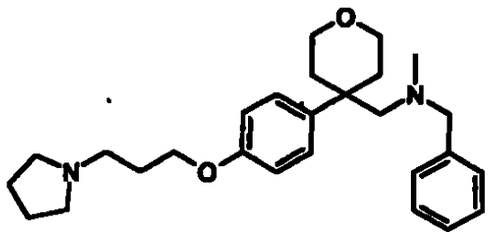


Se trató metil-(4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil)amina (150 mg, 0,45 mmol) con (2-bromoetil)benceno (100 mg, 0,54 mmol) y carbonato potásico (187 mg, 1,35 mmol) en un tubo cerrado herméticamente con microondas (Smith Personal Synthesiser) (55°C) durante 80 minutos. La mezcla de reacción se recogió en DCM (10 ml) y agua (5 ml). La fase orgánica se separó y se lavó dos veces con agua y salmuera. Los extractos orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, se concentraron *al vacío* y se purificaron por cromatografía en columna sobre gel de sílice eluyendo con DCM:MeOH (90:10) con NH_3 al 10% dando el

compuesto del título en forma de un aceite transparente (41,4 mg, 20%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,23 (m, 7H), 6,87 (d, 2H), 4,00 (t, 2H), 3,66 (m, 2H), 3,51 (m, 2H), 3,29 (t, 2H), 3,20 (t, 2H), 2,62 (t, 2H), 2,51 (m, 6H), 2,10 (m, 2H), 1,99 (m, 2H), 1,90 (m, 2H), 1,86 (s, 3H), 1,78 (m, 4H).

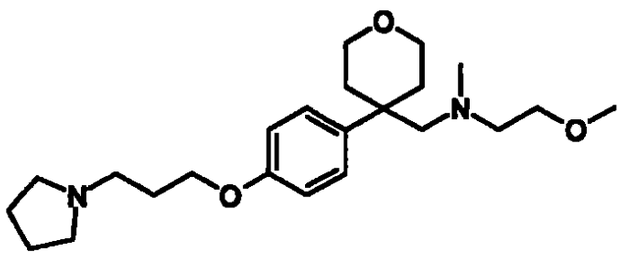
Ejemplo 60: metil-bencil-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil]amina



Este ejemplo se preparó a partir de metil-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil)amina de forma similar al procedimiento usado para el ejemplo 59.

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,28-7,19 (m, 7H), 6,87 (d, 2H), 4,00 (t, 2H), 3,69-3,65 (m, 2H), 3,53-3,48 (t, 2H), 3,29 (s, 2H), 2,61 (t, 2H), 2,54-2,50 (m, 6H), 2,10-2,07 (m, 2H), 2,01-1,97 (m, 2H), 1,93-1,88 (m, 2H), 1,86 (s, 3H), 1,78-1,76 (m, 4H).

Ejemplo 61: (2-metoxietil)-metil-[4-[4-(3-pirrolidin-1-ilpropoxi)-fenil]tetrahidropiran-4-ilmetil)amina

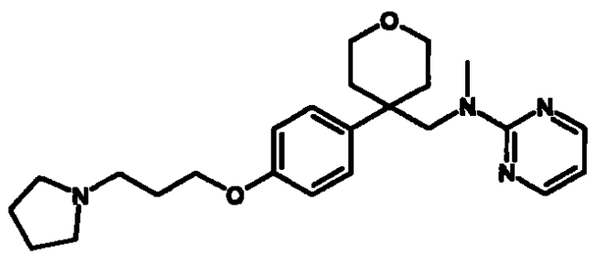


A una solución agitada de metil-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetra-

hidropiran-4-ilmetil)amina (150 mg, 0,45 mmol) y 2-bromoetilmetiléter (43 µl, 0,45 mmol) en acetonitrilo anhidro (5 ml) se le añadió carbonato potásico (62,4 mg, 0,45 mmol). La mezcla se calentó a 60ºC durante una noche y después a 80ºC durante un día y se concentró a presión reducida. El producto en bruto se purificó por cromatografía en columna sobre gel de sílice eluyendo con DCM:MeOH (95:5) con NH_3 al 10% dando el compuesto del título en forma de un aceite (69 mg, rendimiento del 18%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,86 (d, 2H), 4,02 (t, 2H), 3,78 - 3,48 (m, 4H), 3,29 (t, 2H), 3,27 (s, 3H), 2,67 (t, 2H), 2,59 (m, 4H), 2,48 (s, 2H), 2,39 (t, 2H), 2,11 - 2,00 (m, 4H), 1,98 (s, 3H), 1,92 - 1,85 (m, 2H), 1,84 - 1,80 (m, 4H).

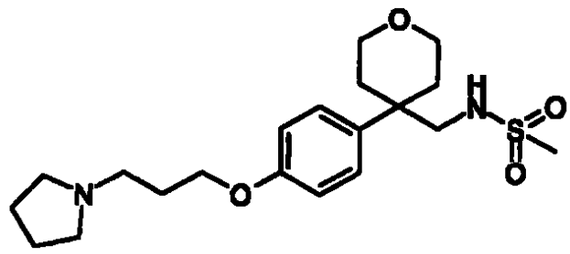
Ejemplo 62: metil-pirimidin-2-il-[4-[4-(3-pirrolidin-1-ilpropoxi)-fenil]-tetrahidropiran-4-ilmetil]amina



A una solución de metil-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil]amina (150 mg, 0,45 mmol) y 2-cloropirimidina (52 mg, 0,45 mmol) en acetonitrilo anhidro (5 ml) se le añadió carbonato potásico (62 mg, 0,45 mmol). La mezcla se calentó a 60ºC durante una noche y después se calentó a reflujo durante 2 días, se filtró y se concentró a presión reducida. El producto en bruto se purificó por cromatografía en columna sobre gel de sílice eluyendo con DCM:MeOH (97:3) con NH_3 al 10% dando el compuesto del título (40 mg, 22% rendimiento).

^{1}H RMN (400 MHz, $CDCl_3$) δ 8,24 (m, 2H), 7,20 (d, 2H), 6,86 (d, 2H), 6,42 (m, 1H), 4,02 (m, 2H), 3,80 (m, 4H), 3,52 (t, 2H), 2,59 (m, 9H), 2,01 (m, 8H), 1,79 (s, 3H).

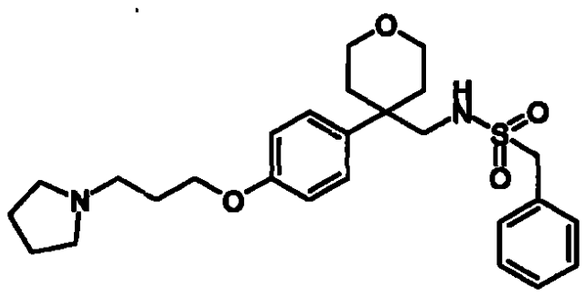
Ejemplo 63: *N*-{4-[4-(3-Pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil}-metanosulfonamida



A una solución agitada de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il}metilamina (200 mg, 0,628 mmol) y trietilamina (106 µl, 0,754 mmol) en diclorometano anhidro (8 ml) en una atmósfera de nitrógeno se añadió gota a gota una solución de cloruro de mesilo (58 µl, 0,754 mmol) en diclorometano anhidro (2 ml). Después de agitar durante una noche, la mezcla de reacción se inactivó con una solución acuosa saturada de $NaHCO_3$. La fase orgánica se separó y se lavó con una solución acuosa saturada de $NaHCO_3$ y agua y después se secó otra vez sobre sulfato sódico, se filtró y se concentró a presión reducida dando el compuesto del título (140 mg, 56 %).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,19 (d, 2H), 6,94 (d, 2H), 4,04 (t, 2H), 3,79 (m, 2H), 3,57 (m, 2H), 3,24 (d, 2H), 2,75 (s, 3H), 2,63 (t, 2H), 2,54 (m, 4H), 2,12 (m, 2H), 2,01 (m, 2H), 1,88 (m, 2H), 1,80 (m, 4H).

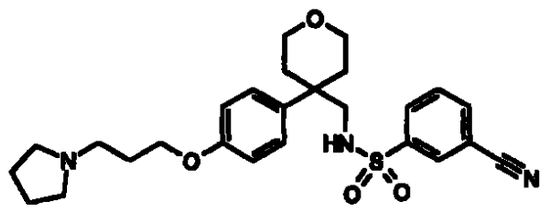
Ejemplo 64: C-Fenil-*N*-{4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidropiran-4-ilmetil}-metanosulfonamida



A una solución agitada de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il} metilamina (200 mg, 0,628 mmol) y trietilamina (106 µl, 0,754 mmol) en diclorometano anhidro (8 ml) en una atmósfera de nitrógeno se le añadió gota a gota una solución de cloruro de α-toluenosulfonilo (143 mg, 0,754 mmol) en diclorometano anhidro (2 ml). Después de agitar durante una noche, la mezcla de reacción se inactivó con una solución acuosa saturada de $NaHCO_3$. La fase orgánica se separó y se lavó con agua, se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida dando el compuesto del título (207 mg, 69 %).

^1H RMN (400 MHz, $CDCl_3$) δ 7,27-7,22 (M, 3H), 7,16-7,14 (M, 2H), 7,07 (D, 2H), 6,83 (D, 2H), 4,05 (S, 2H), 3,95 (T, 2H), 3,68-3,63 (M, 2H), 3,55 (T, 1H), 3,49-3,44 (M, 2H), 3,01(D,2H), 2,57 (T, 2H), 2,47 (S,4H), 2,02-1,93 (M, 4H), 1,78-1,72 (M, 6H).

Ejemplo 65: 3-Ciano-*N*-[4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil]-bencenosulfonamida

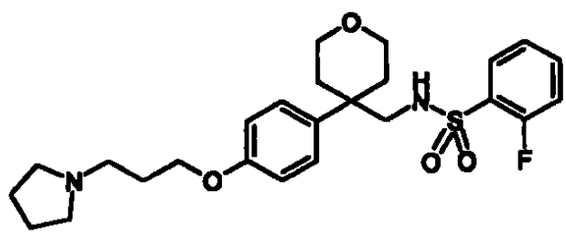


A una solución agitada de (4-[4-(3-pirrolidin-1-

ilpropoxi)fenil]tetrahidropiran-4-il}metilamina (100 mg, 0,314 mmol) y trietilamina (0,1 ml, 0,63 mmol) en diclorometano anhidro (3 ml) en una atmósfera de nitrógeno a 0ºC se le añadió cloruro de 3-cianobencenosulfonilo (100 mg, 0,47 mmol). La mezcla de reacción se agitó durante 2 h dejándola calentar a temperatura ambiente. Después se diluyó con diclorometano y se inactivó con agua. La fase orgánica se separó y se lavó con agua, se secó sobre sulfato sódico, se filtró y se concentró a presión reducida. El producto en bruto se purificó por cromatografía en columna sobre gel de sílice eluyendo con DCM:MeOH (95:5 a 90:10) dando el compuesto del título.

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,97 (s, 1H), 7,93-7,91 (d, 1H), 7,83-7,81 (d, 1H), 7,62-7,58 (m, 1H), 7,11-7,09 (d, 2H), 6,89-6,86 (d, 2H), 4,06-4,03 (m, 3H), 3,77-3,72 (m, 2H), 3,56-3,51 (m, 2H),3,08 (s a,2H), 2,70-2,67 (m, 2H), 3,08 (s a,4H), 2,08-2,01 (m, 4H), 1,85-1,82 (m, 6H).

Ejemplo 66: 2-Fluoro-*N*-{4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil}-bencenosulfonamida

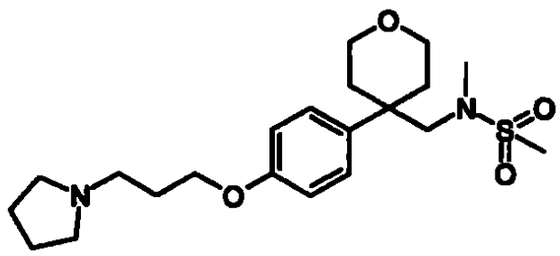


A una solución agitada de {4-(4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il}metilamina (100 mg, 0,314 mmol) y trietilamina (0,1 ml, 0,63 mmol) en diclorometano anhidro (3 ml) en una atmósfera de nitrógeno a 0ºC se le añadió cloruro de 2-fluorobencenosulfonilo (91 mg, 0,47 mmol). La mezcla de reacción se agitó durante 2 horas dejándola calentar a temperatura ambiente. Después se diluyó con diclorometano y se inactivó con

una solución acuosa saturada de $NaHCO_3$. La fase orgánica se separó y se lavó con agua, se secó sobre sulfato sódico, se filtró y se concentró a presión reducida dando el compuesto del título (120 mg, 80%).

^1H RMN (400 MHz, $CDCl_3$) δ 7,86-7,82 (t, 1H), 7,58-7,52 (m, 1H), 7,28-7,24 (m, 1H), 7,13-7,12 (m, 3H), 6,90-6,88 (m, 2H), 4,19 (m, 1H), 4,05-4,02 (t, 2H), 3,73-3,70 (m, 2H), 3,56-3,51 (t, 2H), 3,10-3,08 (d, 2H), 2,66-2,62 (t, 2H), 2,54 (m, 4H), 2,06-1,99 (m, 4H), 1,85-1,8 (m, 6H).

Ejemplo 67: *N*-metil-*N*-{4-[4(3-Pirrolidin-1-il-propoxi)-fenil]-tetra-hidropiran-4-ilmetil}-metanosulfonamida.

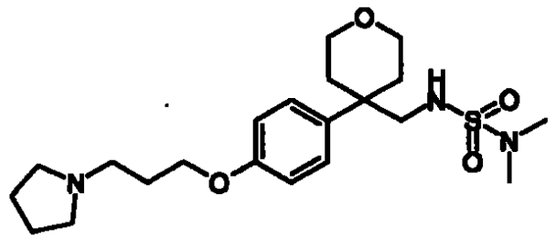


A una solución agitada de metil-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil}amina (200 mg, 0,60 mmol) y trietilamina (102 µl, 0,72 mmol) en diclorometano anhidro (8 ml) en una atmósfera de nitrógeno se le añadió gota a gota una solución de cloruro de mesilo (56 µl, 0,72 mmol) en diclorometano anhidro (2 ml). Después de agitar durante una noche, la mezcla de reacción se inactivó con una solución acuosa saturada de $NaHCO_3$. La fase orgánica se separó, se lavó con agua y después se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida dando el compuesto del título (175 mg, 71 %).

^1H RMN (400 MHz, $CDCl_3$) δ 7,22 (d, 2H), 6,92-6,90 (d, 2H), 4,03 (t, 2H), 3,83-3,78 (m, 2H), 3,52 (t, 2H), 3,16 (s, 2H), 2,88 (s, 3H), 2,64 (t, 2H), 2,54 (m, 4H),

2,19-2,15 (m, 5H), 2,05-1,91 (m,4H), 1,81-1,78 (m, 4H).

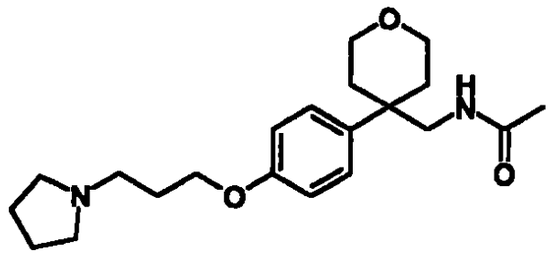
Ejemplo 68 : *N'*-[[4(4-[3-Pirrolidin-1-il-propoxi)-fenil]tetrahidro-2*H*-piran-4-il]metil]-*N,N*-dimetilsulfamida



A una solución agitada de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il}metilamina (200 mg, 0,628 mmol) y trietilamina (106 µl, 0,754 mmol) en diclorometano anhidro (8 ml) en una atmósfera de nitrógeno se le añadió gota a gota una solución de cloruro de dimetilsulfamoílo (81 µl, 0,754 mmol) en diclorometano anhidro (2 ml). Después de agitar durante una noche, la mezcla de reacción se inactivó con una solución acuosa saturada de $NaHCO_3$. La fase orgánica se separó y se lavó con agua y después se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida dando el compuesto del título (207 mg, 77 %).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,19 (D, 2H), 6,93-6,91 (D, 2H), 4,05 (T, 2H), 3,78-3,76 (M, 2H), 3,59-3,54 (M, 2H), 3,17-3,15 (D, 2H), 2,76-2,70 (M, 12H), 2,15-2,06 (M, 4H), 1,90-1,87 (M, 6H).

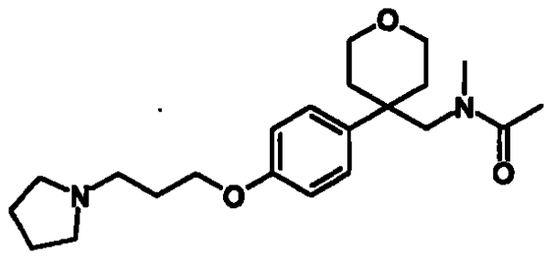
Ejemplo 69: *N*-[4-[4(3-Pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil]-acetamida



A una solución agitada de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il}metilamina (200 mg, 0,628 mmol) y trietilamina (106 µl, 0,754 mmol) en diclorometano anhidro (8 ml) en una atmósfera de nitrógeno se le añadió gota a gota una solución de cloruro de acetilo (54 µl, 0,754 mmol) en diclorometano anhidro (2 ml). Después de agitar durante una noche, la mezcla de reacción se inactivó con una solución acuosa saturada de $NaHCO_3$. La fase orgánica se separó y se lavó con una solución acuosa saturada de $NaHCO_3$ y agua y después se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida dando el compuesto del título (102 mg, 45 %).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,18 (d, 2H), 6,94 (d, 2H), 4,97 (s, 1H), 4,05 (t, 2H), 3,80 (m, 2H), 3,59 (m, 2H), 3,46 (d, 2H), 2,66 (t, 2H), 2,57 (m, 4H), 2,03 (m, 4H), 1,80 (m,8H).

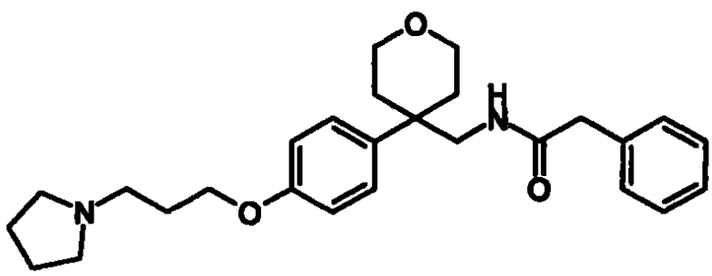
Ejemplo 70: *N*-metil-*N*-{4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil}-acetamida



A una solución agitada de metil-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil}amina (200 mg, 0,60 mmol) y trietilamina (102 µl, 0,72 mmol) en diclorometano anhidro (8 ml) en una atmósfera de nitrógeno se le añadió gota a gota una solución de cloruro de acetilo (52 µl, 0,72 mmol) en diclorometano anhidro (2 ml). Después de agitar durante una noche, la mezcla de reacción se inactivó con una solución acuosa saturada de $NaHCO_3$. La fase orgánica se separó y se lavó con agua y después se secó sobre sulfato de magnesio, se filtró, se concentró a presión reducida y se purificó por cromatografía en columna sobre gel de sílice eluyendo con DCM:MeOH (95:5 a 90:10) dando el compuesto del título (86 mg, 36 %).

^1H RMN (400 MHz, $CDCl_3$) δ Muestra rotámeros 7,19-7,13 (2d, 2H), 6,91-6,88 (d, 2H), 4,05-4,02 (m, 2H), 3,85-3,80 (m, 2H), 3,56-3,45 (m, 4H), 2,67-2,65 (m, 2H), 2,60-2,56 (m, 4H), 2,32-1,96 (varios multipletes, 12H).

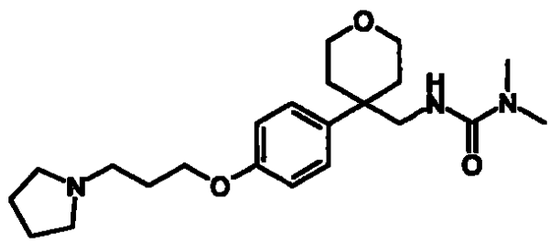
Ejemplo 71: 2-Fenil-*N*-{4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil}-acetamida



A una solución agitada de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il}metilamina (200 mg, 0,63 mmol) y trietilamina (93 µl, 0,66 mmol) en diclorometano anhidro (8 ml) en una atmósfera de nitrógeno a 0ºC se le añadió gota a gota una solución de cloruro de fenilacetilo (93 µl, 0,66 mmol) en diclorometano anhidro (2 ml). Después de agitar durante

3 horas a 0°C, la mezcla de reacción se inactivó con una solución acuosa saturada de $NaHCO_3$. La fase orgánica se separó y se lavó con agua y después se secó sobre sulfato de magnesio, se filtró, se concentró a presión reducida y se purificó por cromatografía en columna sobre gel de sílice eluyendo con DCM:MeOH (98:2) dando el compuesto del título (34 mg, 12 %). ^1H RMN (400 MHz, $CDCl_3$) δ 7,32-7,31 (m, 3H), 7,12-7,10 (m, 2H), 6,89-6,87 (d, 2H), 6,76-6,74 (d, 2H), 4,91 (t, 1 H), 4,02 (t, 2H), 3,79-3,74 (m, 2H), 3,53-3,51 (m, 2H), 3,47 (s, 2H), 3,37-3,35 (d, 2H), 2,62 (m, 6H), 2,08-2,06 (m, 2H), 1,93-1,85 (m, 6H), 1,76-1,74 (m, 2H).

Ejemplo 72: 1,1-Dimetil-3-[4-[4(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil]-urea

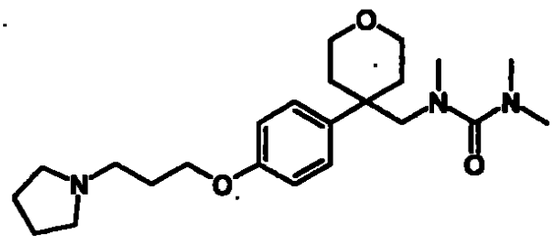


A una solución agitada de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il) metilamina (200 mg, 0,63 mmol) y trietilamina (106 µl, 0,754 mmol) en diclorometano anhidro (9 ml) en una atmósfera de nitrógeno se le añadió gota a gota una solución de cloruro de dimetilcarbamoílo (69 µl, 0,754 mmol) en diclorometano anhidro (1 ml). Después de agitar durante 3 horas a 0°C, la mezcla de reacción se inactivó con una solución acuosa saturada de $NaHCO_3$. La fase orgánica se separó y se lavó con agua y después se secó sobre sulfato de magnesio, se filtró, se concentró a presión reducida y se purificó por cromatografía en columna sobre gel de sílice eluyendo con DCM:MeOH (95:5 a 90:10) dando el compuesto del título (80 mg,

32 %).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,13 (d, 2H), 6,86 (d, 2H), 3,98 (t, 2H), 3,84 (t, 1H), 3,74 (m, 2H), 3,52 (m, 2H), 3,36 (d, 2H), 2,69 (s, 6H), 2,65 (m, 2H), 2,57 (m, 4H), 2,02-1,95 (m,4H), 1,84-1,78 (m, 6H).

Ejemplo 73: 1,1,3-Trimetil-3-{4-[4(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil}-urea

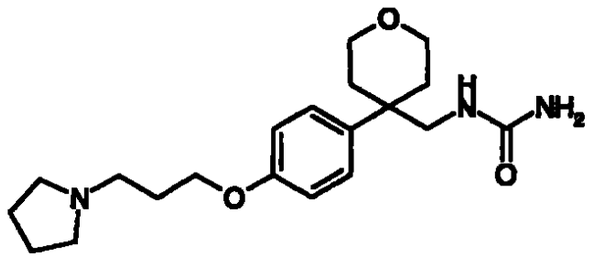


A una solución agitada de metil-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil}amina (200 mg, 0,60 mmol) y trietilamina (102 µl, 0,72 mmol) en diclorometano anhidro (8 ml) en una atmósfera de nitrógeno se le añadió gota a gota una solución de cloruro de dimetilcarbamoílo (67 µl, 0,72 mmol) en diclorometano anhidro (2 ml). Después de agitar durante una noche, la mezcla de reacción se inactivó con una solución acuosa saturada de $NaHCO_3$. La fase orgánica se separó, se lavó con una solución acuosa saturada de $NaHCO_3$ y agua y después se secó sobre sulfato de magnesio, se filtró, se concentró a presión reducida y se purificó por cromatografía en columna sobre gel de sílice eluyendo con DCM:MeOH (95:5) seguido de DCM:MeOH:NH_3 (90:5:5) dando el compuesto del título (84 mg, 39 %).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,19 (d, 2H), 6,90-6,88 (d, 2H), 4,03 (t, 2H), 3,81-3,78 (m, 2H), 3,56-3,52 (m, 4H), 2,70 (s, 6H), 2,66 (t, 2H), 2,29 (s, 3H), 2,05-2,01 (m, 4H), 1,86-1,81 (m, 6H).

Ejemplo 74: {4-[4-(3-Pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-

ilmetil}-urea



A una solución agitada de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il}metilamina (200 mg, 0,63 mmol) y ácido acético (108 µl, 1,89 mmol) en agua (12 ml) se le añadió cianuro potásico en porciones (153 mg, 1,89 mmol). Después de agitar durante una noche, la mezcla de reacción se inactivó con una solución acuosa 0,1 N de NaOH. La fase orgánica se separó y la fase acuosa se extrajo dos veces con diclorometano. Los extractos orgánicos combinados se secaron sobre sulfato de magnesio, se filtró, se concentró a presión reducida y se purificó por cromatografía en columna sobre gel de sílice eluyendo con DCM:MeOH (95:5) seguido de DCM:MeOH (90:10) y DCM:MeOH:NH_3 (90:5:5) dando el compuesto del título (25 mg, 11 %). .

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,18 (d, 2H), 6,92-6,90 (d, 2H), 4,24 (s, 2H), 4,17 (t, 1H), 4,03 (t, 2H), 3,84-3,79 (m, 2H), 3,61-3,55 (m, 2H), 3,36-3,35 (d, 2H), 2,63 (t, 2H), 2,53 (m, 4H), 2,07-1,97 (m, 4H), 1,88-1,79 (m, 6H).

Intermedio 29: 4-aminometil-4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-ciclohexanol

Etapa 1:

Un recipiente de reacción de tres bocas se cargó con [4-(3-pirrolidin-1-ilpropoxi)fenil]acetonitrilo (7 g, 28,6 mmol), hidróxido benciltrimetilamónico (40%

en metanol, 1,3 ml) en acetonitrilo (185 ml). La solución se calentó a reflujo y se le añadió gota a gota acrilato de metilo (25 ml, 286 mmol). Después de calentar a reflujo durante 5 horas, la mezcla se concentró a la mitad, se añadió éter dietílico y los extractos orgánicos se lavaron con HCl 1 N y salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo se purificó por cromatografía ultrarrápida proporcionando éster dimetílico del ácido 4-ciano-4-[4-(3-pirrolidin-1-ilpropoxi)-fenil]-heptanodioico (8,8 g, 74%).

Etapa 2:

A una solución de éster dimetílico del ácido 4-ciano-4-[4-(3-pirrolidin-1-ilpropoxi)-fenil]-heptanodioico (8,8.g, 21,1 mmol) en 1,2-dimetoxietano (176 ml) se cargó en porciones de NaH (dispersión al 60%, 2,55 g, 63,4 mmol). La mezcla de reacción se calentó a reflujo. Después de 4,5 horas, las ¾ del disolvente se evaporaron y la mezcla se enfrió a 20ºC con un baño de hielo y se inactivó con agua (100 ml), HCl 1 N (100 ml). La fase acuosa se extrajo con éter (100 ml). Después de basificar con NaOH las fases acuosas se extrajeron con diclorometano. Los extractos orgánicos combinados se lavaron con agua, se secaron sobre Na_2SO_4, se filtraron y se concentraron proporcionando éster metílico del ácido 5-ciano-2-oxo-5-[4-(3-pirrolidin-1-ilpropoxi)-fenil]-ciclohexano-carboxílico (6,6 g , 81%) en forma de un aceite.

Etapa 3:

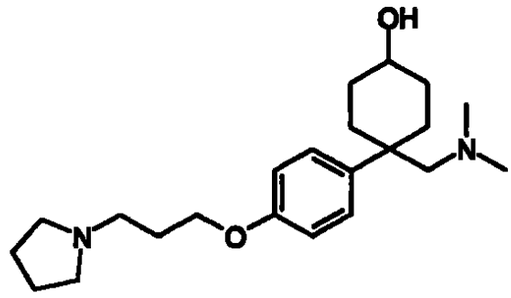
A una solución de éster metílico del ácido 5-ciano-2-oxo-5-[4-(3-pirrolidin-1-ilpropoxi)-fenil]-ciclohexanocarboxílico (6,6 g, 17 mmol) y dimetilsulfóxido (128 ml) se le añadió agua (8,0 ml) y cloruro sódico (6,4 g, 109 mmol). La mezcla de reacción se calentó a 142-146ºC. Después de 5 horas, la mezcla se concentró y el residuo se disolvió en DCM (120 ml), se lavó con

agua (100 ml), y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó por cromatografía ultrarrápida (70 g de gel de sílice, eluyente : gradiente de DCM/MeOH 95/5 a 90/10) proporcionando 4-oxo-1-[4-(3-pirrolidin-1-ilpropoxi)-fenil]-ciclohexanocarbonitrilo como aceite de cristalización (2,2 g 45,5 %). Después de la cristalización en éter, se obtuvieron 0,2 g de muestra analítica.

Etapa 4:

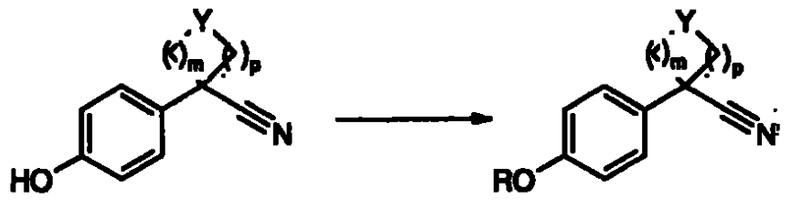
A una suspensión agitada de $LiAlH_4$ (0,59 g, 15 mmol, 10 eq) en éter dietílico (8 ml) se le añadió gota a gota a temperatura ambiente una solución de 4-oxo-1-[4-(3-pirrolidin-1-ilpropoxi)-fenil]-ciclohexanocarbonitrilo (0,5 g, 1,5 mmol) en éter dietílico (25 ml). La mezcla de reacción se calentó a reflujo durante 2 horas. La mezcla de reacción se enfrió a 0ºC y se añadieron sucesivamente gota a gota una solución de agua, hidróxido sódico (15% p/v, 0,68 ml) y agua. Después de agitarse durante 15 minutos a temperatura ambiente, la mezcla se filtró sobre tierra de diatomeas y se concentró. El residuo se purificó por cromatografía ultrarrápida (10 g gel de sílice, DCM/ MeOH (NH_3 al 10%) proporcionando el compuesto del título (0,27 g, 54%) en forma de un aceite.

Ejemplo 75: 4-dimetilaminometil-4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-ciclohexanol



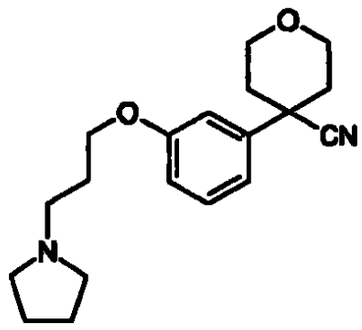
A 4-aminometil-4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-ciclohexanol (0,26 g, 0,78 mmol) se le añadió 0,8 ml de formaldehído (solución al 37% p/p en H_2O). Se le añadió 1 ml de ácido fórmico y la mezcla se calentó a aproximadamente 100ºC durante 20 minutos. Después de enfriarse, se añadió agua y la mezcla se extrajo con éter. A la fase acuosa se le añadió NaOH y la mezcla se extrajo 3 veces con éter. Los extractos orgánicos se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron *al vacío* proporcionando 0,23 g de aceite. El residuo se purificó por cromatografía ultrarrápida (25 g gel de sílice, DCW MeOH (NH_3 al 10%) proporcionando 0,18 g de producto. Después de triturar con 10 ml de hexanos (0,13 g, 46,4%) se obtuvo el compuesto del título. ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,25 (d, 2H), 6,85(d, 2H), 4. (t, 2H), 3,8 (sa, 1 H), 2,62 (t, 2H), 2,56-2,49 (m, 4H), 2,39 (s, 2H), 2,08-1,92 (m, 3H), 1,95 (s,6H), 1,85-1,74 (m, 6H), 1,73-1,64 (m, 4H), 1,62-1,52 (m, 2H).

Procedimiento general E:



El fenol de partida (3,69 mmol), cloruro (5,90 mmol), DMF (15 ml) y K_2CO_3 (14,83 mmol) se calentó a 130°C hasta que se completa la reacción (1 a 2 horas). Se enfrió a temperatura ambiente, se añadió agua (30 ml), se extrajo con EtOAc (3x9 ml) y los extractos orgánicos combinados se lavaron con NaOH (2 M, 2x25 ml). Los extractos orgánicos se secaron sobre $MgSO_4$, se filtraron y se concentraron *al vacío* a 35°C. La purificación del material en bruto por cromatografía sobre sílice, eluyente (MeOH al 10% en DCM) proporcionó los compuesto del título.

Ejemplo 76: 4-[3-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-carbonitrilo

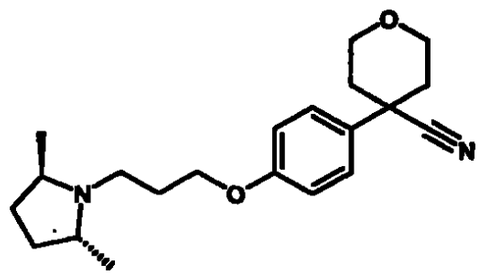


Se hizo reaccionar de forma conjunta 4-(3-hidroxi-fenil)-tetrahidro-2*H*-piran-4-carbonitrilo (1,03 g, 5,10 mmol), 1-(3-cloro-propil)-pirrolidina (600 mg, 4,08 mmol), DMF (6,8 ml) y K_2CO_3 (2,82 g, 20,4 mmol) de acuerdo con el procedimiento general E. La fase orgánica se lavó con NaOH 2 M (3 x 50 ml),

salmuera (3 x 50 ml), se secó sobre $MgSO_4$, se filtró y se concentró *al vacío* a 35°C. La mezcla en bruto se suspendió en TBME:heptano (1:20, 10 ml). El sólido se filtró, se lavó con heptano (10 ml) y se secó en el filtro durante 2 horas dando el compuesto del título (0,4 g, 31%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,32 (t, 1H), 7,07-6,99 (m, 2H), 6,87 (dd, 1H), 4,11-4,04 (m, 2H), 4,05 (t, 2H), 3,90 (td, 2H), 2,63 (t, 2H), 2,57-2,49 (m, 4H), 2,18-1,97 (m, 6H), 1,84-1,75 (m, 4H).

Ejemplo 77: 4-{4-[3-(2,5-Dimetilpirrolidin-1-il)propoxi]fenil}-tetrahidropiran-4-carbonitrilo

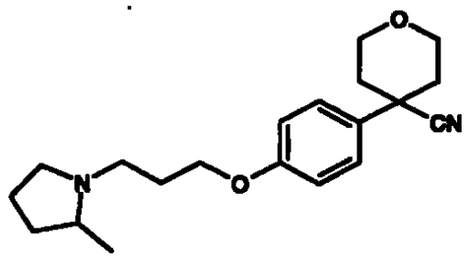


Se hizo reaccionar de forma conjunta 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbonitrilo 318 mg, 1,56 mmol), 1-(3-cloropropil)-2,5-trans-dimetil-pirrolidina (250 mg, 1,42 mmol), DMF (5 ml) y K_2CO_3 (785 mg, 5,70 mmol) de acuerdo con el procedimiento general E. El producto en bruto se disolvió en acetato de etilo (20 ml), se lavó con salmuera (2 x 10 ml), se secó sobre $MgSO_4$, se filtró y se concentró *al vacío* dando el compuesto del título (200 mg, 56%) en forma de un sólido pardo claro.

^{1}H RMN (400 MHz, $CDCl_3$), δ 7,37 (d, 2H), 6,93 (d, 2H), 4,13-3,97 (m, 4H), 3,89 (td, 2H), 3,14-2,98 (m, 2H), 2,76 (m, 1H), 2,55 (m, 1H), 2,16-1,88 (m, 8H), 1,46-1,30 (m, 2H), 0,97 (d, 6H).

Ejemplo 78: 4-{4-[3-(2-Metilpirrolidin-1-il)-propoxi]-fenil}tetra-hidropiran-4-

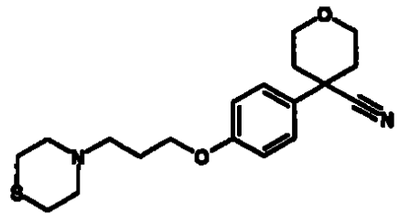
carbonitrilo



Se hizo reaccionar de forma conjunta 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbonitrilo (315 mg, 1,55 mmol), 1-(3-cloropropil)-2-metil-pirrolidina (400 mg, 2,48 mmol), DMF (6 ml) y K_2CO_3 (833 mg, 6,03 mmol) de acuerdo con el procedimiento general E. La purificación por cromatografía sobre sílice, eluyente DCM:MeOH:NH_3 (92:6:2) proporcionó el compuesto del título (450 mg, 88%) en forma de un aceite naranja.

^{1}H RMN (400 MHz, $CDCl_3$), δ 7,37 (d, 2H), 6,93 (d, 2H), 4,12-3,99 (m, 4H), 3,89 (td, 2H), 2,35-1,62 (m, 14H), 1,42 (m, 1H), 1,09 (d, 3H).

Ejemplo 79: 4-[4-[3-Tiomorfolin-4-ilpropoxi)fenil]tetrahidropiran-4-carbonitrilo

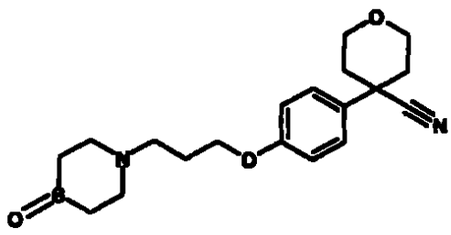


Se hizo reaccionar de forma conjunta 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbonitrilo (750 mg, 3,69 mmol), 4-(3-cloropropil)-tiomorfolina (1,06 g, 5,91 mmol), DMF (15 ml) y K_2CO_3 (2,05 g, 14,83 mmol) de acuerdo con el procedimiento general E. La purificación por cromatografía sobre sílice, eluyente DCM:MeOH:NH_3 (96:3:1) proporcionó el

compuesto del título (365 mg, 29%) en forma de un sólido blanquecino.

^{1}H RMN (400 MHz, $CDCl_3$), δ 7,37 (d, 2H), 6,93 (d, 2H), 4,12-4,04 (m, 2H), 4,01 (t, 2H), 3,89 (td, 2H), 2,77-2,64 (m, 8H), 2,54 (t, 2H), 2,16-1,99 (m, 4H), 1,95 (p, 2H).

Ejemplo 80: 4-[4-[3-(1-Oxo-tiomorfolin-4-il)-propoxi]-fenil]-tetra-hidropiran-4-carbonitrilo

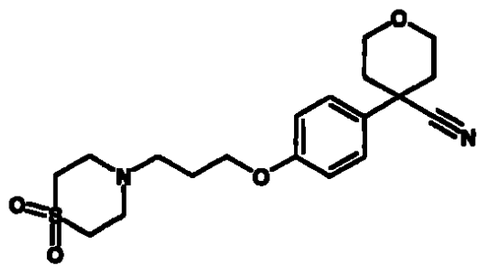


Se calentó tetrahidrato de perborato sódico (221 mg, 1,43 mmol) y ácido acético en hielo (5 ml) a una temperatura de 50 a 60°C y se añadió 4-[4-(3-tiomorfolin-4-ilpropoxi)fenil]tetrahidropiran-4-carbonitrilo (500 mg, 1,43 mmol) en una porción y se continuó calentando durante 3 horas. La mezcla de reacción se enfrió a temperatura ambiente y se filtró. El filtrado se añadió a agua enfriada con hielo (15 ml) y se extrajo con EtOAc (3x5 ml), que se descartó. La fase acuosa se basificó a pH 8-9 con hidróxido sódico 2 M y se extrajo con DCM (3)(25 ml), se secó sobre $MgSO_4$, se filtró y se concentró *al vacío* a 35°C. El material en bruto se sometió a cromatografía sobre sílice eluyendo con DCM:MeOH:NH_3 (97:2:1 a 92:6:2) proporcionando el compuesto del título (300 mg, 58%) en forma de un sólido blanco.

^{1}H RMN (400 MHz, $CDCl_3$), δ 7,38 (d, 2H), 6,92 (d, 2H), 4,11-4,05 (m, 2H), 4,03 (t, 21-1), 3,89 (td, 2H), 3,15-3,03 (m, 2H), 2,94-2,67 (m, 6H), 2,63 (t, 2H), 2,16-1,92 (m, 6H).

Ejemplo 81: 4-[4-[3-(1,1-Dioxo-1λ6-tiomorfolin-4-il)propoxi]-

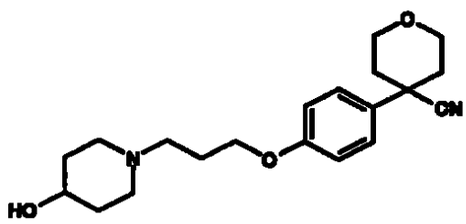
fenil}tetrahidro-piran-4-carbonitrilo



A una solución de 4-[4-(3-tiomorfolin-4-ilpropoxi)fenil]tetrahidropiran-4-carbonitrilo (500 mg, 1,44 mmol) en TFA (1,65 ml) a temperatura de 0 a 5ºC se le añadió gota a gota una solución de ácido trifluoro-peracético (4 M en TFA, 0,72 ml). La reacción se dejó calentar a temperatura ambiente y se agitó durante 3 horas. A la reacción se le añadió otra porción de ácido trifluoro-peracético (4 M en TFA, 0,097 ml) [solución 4 M preparada por adición de H_2O_2 al 27,5% (0,94 ml) a TFA (1,56 ml)] y se agitó durante una noche. La mezcla de reacción se enfrió a 0 a 5ºC, se diluyó con DCM (20 ml) y se inactivó con NaOH (solución 5 M, 12 ml) alcanzando pH 10. La mezcla se extrajo con DCM (3 x 20 ml), Los extractos de DCM combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron *al vacío*. El aceite amarillo aislado se purificó por cromatografía en columna en alúmina básica eluyendo con DCM(95):MeOH(4):NH_3(1) dando el compuesto del título en forma de un sólido blanquecino (230 mg, 42%).

^{1}H RMN (400 MHz, $CDCl_3$), δ 7,39 (d, 2H), 6,92 (d, 2H), 4,12-4,05 (m, 2H), 4,03 (t, 2H), 3,89 (td, 2H), 3,11-2,96 (m, 8H), 2,71 (t, 2H), 2,15-1,99 (m, 4H), 1,96 (p, 2H).

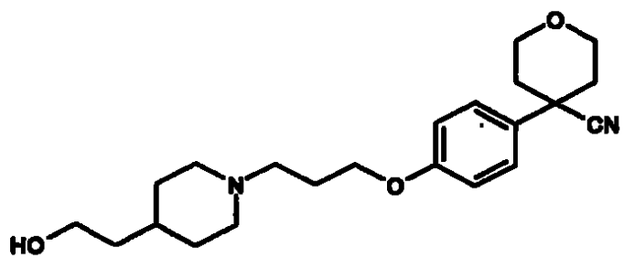
Ejemplo 82: 4-{4-[3-(4-Hidroxipiperidin-1-il)propoxi]fenil}tetrahidro-piran-4-carbonitrilo



Se hizo reaccionar de forma conjunta 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2H-piran-4-carbonitrilo (533 mg, 2,62 mmol), 1-(3-cloro-propil)-piperidin-4-ol (750 mg, 4,22 mmol), DMF (10 ml) y K_2CO_3 (1,44 g, 10,42 mmol) de acuerdo con el procedimiento general E. La purificación por cromatografía sobre sílice, eluyente DCM:MeOH:NH_3 (92:6:2) proporcionó el compuesto del título (550 mg, 61%) en forma de un sólido blanquecino.

^{1}H RMN (400 MHz, $CDCl_3$), δ 7,38 (d, 2H), 6,93 (d, 2H), 4,13-4,04 (m, 2H), 4,02 (t, 2H), 3,89 (td, 2H), 3,70 (m, 1H), 2,87-2,71 (m, 2H), 2,50 (t, 2H), 2,23-1,84 (m, 10H), 1,68-1,49 (m, 3H).

Ejemplo 83: 4-(4-{3-[4-(2-Hidroxietil)-piperidin-1-il]propoxi}fenil) tetrahidro-piran-4-carbonitrilo

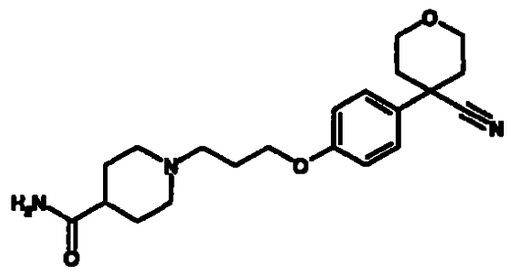


Se hizo reaccionar de forma conjunta 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbonitrilo (185 mg, 0,91 mmol), 2-[1-(3-cloro-propil)-piperidin-4-il]-etanol (300 mg, 1,46 mmol), DMF (4 ml) y K_2CO_3 (497 mg, 3,60 mmol) de acuerdo con el procedimiento general E. La purificación por cromatografía sobre sílice, eluyente DCM: MeOH:NH_3 (92:6:2)

proporcionó el compuesto del título (220 mg, 65%) en forma de sólido rosa pálido.

^{1}H RMN (400 MHz, $CDCl_3$), δ 7,37 (d, 2H), 6,93 (d, 2H), 4,11-4,04 (m, 2H), 4,01 (t, 2H), 3,89 (td, 2H), 3,70 (t, 2H), 2,97-2,87 (m, 2H), 2,48 (t, 2H), 2,15-1,88 (m, 8H), 1,77-1,57 (m, 3H), 1,57-1,38 (m, 3H), 1,35-1,21 (m, 2H).

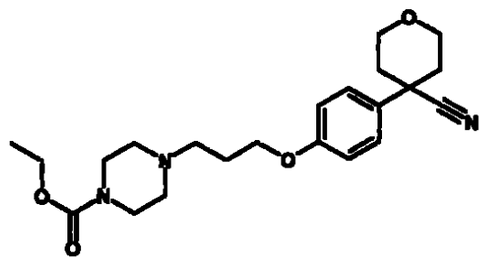
Ejemplo 84: Amida del ácido 1-[3-[4-(4-Ciano-tetrahidro-piran-4-il)-fenoxi]-propil]-piperidin-4-carboxílico



Se hizo reaccionar de forma conjunta 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbonitrilo (200 mg, 0,98 mmol), amida del ácido 1-(3-cloropropil)-piperidin-4-carboxílico (200 mg, 0,98 mmol), DMF (4 ml) y K_2CO_3 (550 mg, 3,98 mmol) de acuerdo con el procedimiento general E. La mezcla de reacción se vertió sobre agua (30 ml), el precipitado resultante se filtró y se volvió a disolver en DCM (20 ml). La solución de DCM se lavó con una solución de NaOH (2 M, 2x5 ml) y agua (5 ml), se secó sobre $MgSO_4$, se filtró y se concentró *al vacío* a 35ºC, desplazando el DCM residual con EtOH proporcionando el compuesto del título (210 mg, 58%) en forma de un sólido blanquecino.

^{1}H RMN (400 MHz, $CDCl_3$), δ 7,38 (d, 2H), 6,93 (d, 2H), 5,45 (s a, 1H), 5,35 (s a, 1H), 4,12-4,05 (m, 2H), 4,02 (t, 2H), 3,89 (td, 2H), 3,03-2,92 (m, 2H), 2,50 (t, 2H), 2,22-1,84 (m, 11H), 1,81-1,67 (m, 2H).

Ejemplo 85: Éster etílico del ácido 4-{3-[4-(4-Cianotetrahidropiran-4-il)-fenoxi]propil}-piperazin-1-carboxílico



Se hizo reaccionar de forma conjunta 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbonitrilo (500 mg, 2,46 mmol), éster etílico del ácido 4-(3-cloropropil)-piperazin-1-carboxílico (570 mg, 2,43 mmol), DMF (10 ml) y K_2CO_3 (1,36 g, 9,84 mmol) de acuerdo con el procedimiento general E. La fase orgánica se lavó con NaOH 2 M (3 x 20 ml), agua (2x 20 ml), se secó sobre $MgSO_4$, se filtró y se concentró *al vacío* a 35ºC. El producto en bruto se sometió a cromatografía sobre sílice eluyendo con DCM:MeOH:NH_3 (97:2:1) proporcionando el compuesto del título (280 mg, 28%) en forma de un sólido blanquecino.

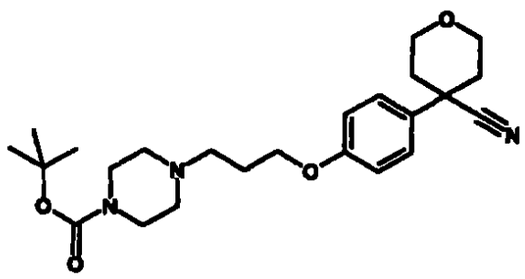
^{1}H RMN (400 MHz, $CDCl_3$), δ 7,38 (d, 2H), 6,93 (d, 2H), 4,14 (q, 2H), 4,11-4,05 (m, 2H), 4,03 (t, 2H), 3,89 (td, 2H), 3,55-3,42 (m, 4H), 2,53 (t, 2H), 2,47-2,36 (m, 4H), 2,15-1,92 (m, 6H), 1,26 (t, 3H).

Intermedio 30: Éster *terc*-butilo del ácido 4-(3-cloro-propil)-piperazin-1-carboxílico

Se hizo reaccionar de forma conjunta éster *terc*-butilo del ácido 4-piperazin-1-carboxílico (4,0 g, 21,5 mmol), acetona (80 ml, 20 vol), una solución de NaOH 5 M (5,16 ml, 1,2 eq.) y 1-bromo-3-cloropropano (10,15 g, 64,5 mmol, 3 eq.) de acuerdo con el procedimiento general A dando el compuesto del título

(2,78 g, 66%) en forma de un aceite incoloro.

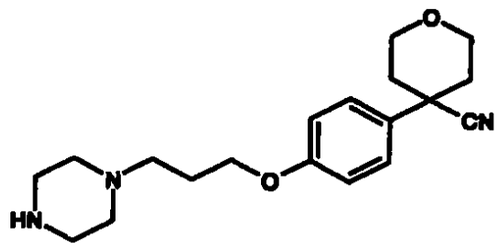
Ejemplo 86: Éster *terc*-butilo del ácido 4[3-[4-(4-Ciano-tetrahidro-piran-4-il)-fenoxi]-propil)-piperazin-1-carboxílico



Se calentó 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbonitrilo (200 mg, 0,99 mmol), éster *terc*-butilo del ácido 4-(3-cloropropil)-piperazin-1-carboxílico (203 mg, 0,76 mmol), DMF (4 ml) y K_2CO_3 (553 g, 4,00 mmol) a 70°C y se trató de acuerdo con el procedimiento general E. La fase orgánica se lavó con NaOH 2 M (3.x 20 ml), agua (2x 20 ml), se secó sobre $MgSO_4$, se filtró y se concentró *al vacío* a 35°C proporcionando el compuesto del título (272 mg, 64%) en forma de un sólido blanquecino.

^{1}H RMN (400 MHz, $CDCl_3$), δ 7,38 (d, 2H), 6,93 (d, 2H), 4,11-4,04 (m, 2H), 4,03 (t, 2H), 3,89 (td, 2H), 3,50-3,37 (m, 4H), 2,53 (t, 2H), 2,45-2,34 (m, 4H), 2,15-2,00 (m, 4H), 1,97 (p, 2H), 1,46 (s, 9H).

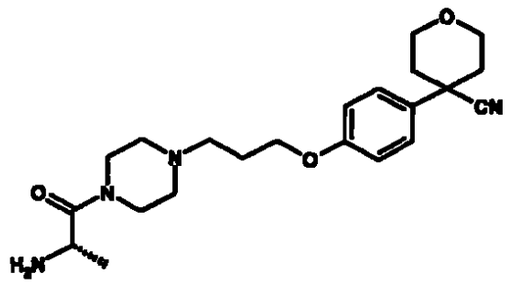
Ejemplo 87: 4-[4-(3-Piperazin-1-ilpropoxi)fenil]tetrahidropiran-4-carbonitrilo



Se agitó éster terc-butilo del ácido 4-[3-[4-(4-Ciano-tetrahidro-piran-4-il)-fenoxi]-propil}-piperazin-1-carboxílico (500 mg, 1,16 mmol), MeOH (5 ml), 1,4-dioxano (1 ml) y HCl en dioxano (4 M, 1,8 ml) a temperatura ambiente durante una noche. La mezcla de reacción se concentró *al vacío* a 40ºC y se diluyó con TBME (5 ml).Se añadió NaOH acuoso (solución 2 M) alcanzando un pH de 14 y la mezcla se separó y se extrajo con TBME (2x5 ml). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron y se concentraron *al vacío* proporcionando compuesto del título en forma de un aceite amarillo (275 mg, 72%).

^{1}H RMN (400 MHz, $CDCl_3$), δ 7,38 (d, 2H), 6,93 (d, 2H), 4,11-4,05 (m, 2H), 4,03 (t, 2H), 3,89 (td, 2H), 2,90 (t, 4H), 2,51 (t, 2H), 2,44 (s a, 4H), 2,15-2,00 (m, 4H), 1,97 (m, 2H), 1,74 (s a, 1H).

Ejemplo 88: 4-{4[3-[4-(2-Aminopropionil)piperazin-1-il]propoxi}fenil)-tetrahidropiran-4-carbonitrilo



Se agitó 4-[4-(3-piperazin-1-ilpropoxi)fenil]tetrahidropiran-4-carbonitrilo (265 mg, 0,81 mmol), DCM (10,6 ml), HOBT (120 mg, 0,89 mmol), FMoc (*L*)-anilina (277 mg, 0,89 mmol) y EDCI.HCl (171 mg, 0,89 mmol) a temperatura ambiente durante una noche. Se añadió agua (10 ml) durante una hora, la mezcla se filtró y la fase orgánica se separó y se lavó con agua (10 ml), la fase

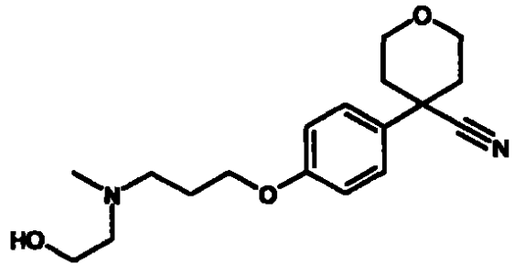
orgánica se secó sobre $MgSO_4$, se filtró y se concentró *al vacío* a 35ºC. El residuo se disolvió en DCM (9 ml) y se añadió piperidina (86 mg, 10 mmol), la mezcla se agitó a temperatura ambiente durante una hora. A la mezcla de reacción se le añadió agua (5 ml) y la fase orgánica se separó, se secó sobre $MgSO_4$, se filtró y se concentró *al vacío* a 35ºC. El material en bruto se sometió a cromatografía sobre sílice eluyendo con MeOH al 2% en DCM proporcionando compuesto del título (136 mg, 42%).

^{1}H RMN (400 MHz, $CDCl_3$), δ 7,38 (d, 2H), 6,93 (d, 2H), 4,11-4,05 (m, 2H), 4,03 (t, 2H), 3,89 (td, 2H), 3,77 (q, 1H), 3,65 (s a, 2H), 3,49 (s a, 2H), 2,55 (t, 2H), 2,45 (s a, 4H), 2,14-2,00 (m, 4H), 1,97 (m, 2H), 1,58 (s a, 2H), 1,25 (d, 3H).

Intermedio 31: 2-[(3-Cloro-propil)-metil-amino]-etanol

Se hizo reaccionar de forma conjunta 2-(metilamino)-etanol (1,0 g, 13,3 mmol), acetona (20 ml, 20 vol), una solución de NaOH 5 M (3,19 ml, 1,2 eq.) y 1-bromo-3-cloropropano (6,28 g, 39,9 mmol, 3 eq.) de acuerdo con el procedimiento general A dando el compuesto del título (1,14 g, 55%) en forma de un aceite incoloro.

Ejemplo 89: 4-(4-{3-[(2-Hidroxietil)metilamino]propoxi}-fenil)tetrahidropiran-4-carbonitrilo

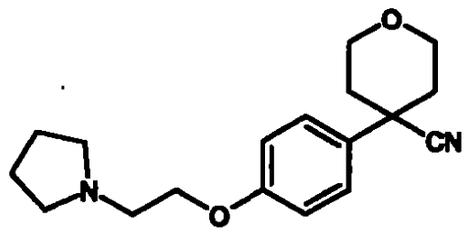


Se hizo reaccionar de forma conjunta 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbonitrilo (800 mg, 3,94 mmol), 2-[(3-

cloropropil)-metil-amino]-etanol (595 mg, 3,94 mmol), DMF (8 ml) y K_2CO_3 (2,18 g, 15,76 mmol) de acuerdo con el procedimiento general E. La fase orgánica se lavó con NaOH 2 M (3.x 20 ml), agua (2x 20 ml), se secó sobre $MgSO_4$, se filtró y se concentró *al vacío* a 35ºC proporcionando el compuesto del título (550 mg, 44%) en forma de un aceite amarillo pálido.

^{1}H RMN (400 MHz, $CDCl_3$), δ 7,37 (d, 2H), 6,92 (d, 2H), 4,11-4,04 (m, 2H), 3,88 (dt, 2H), 3,60 (t, 2H), 2,61 (t, 2H), 2,56 (t, 2H), 2,37 (s a, 1H), 2,29 (s, 3H), 2,15-1,91 (m, 6H)

Ejemplo 90: 4-[4-(2-Pirrolidin-1-iletoxi)fenil]tetrahidropiran-4-carbonitrilo

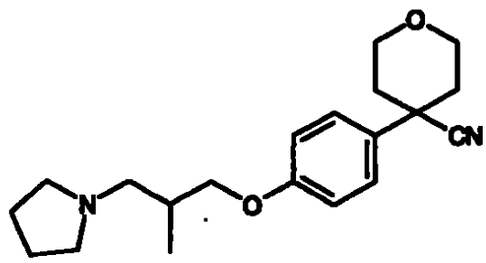


Se hizo reaccionar de forma conjunta 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbonitrilo (570 mg, 2,82 mmol), 1-(2-cloro-etil)-pirrolidina (300 mg, 2,25 mmol), DMF (5,7 ml) y K_2CO_3 (1,56 g, 1,13 mmol) de acuerdo con el procedimiento general E. La fase orgánica se lavó con NaOH 2 M (3 x 20 ml), agua (2x 20 ml), se secó sobre $MgSO_4$, se filtró y se concentró *al vacío* a 35ºC. El material en bruto se sometió a cromatografía sobre sílice eluyendo con MeOH al 5% en DCM y gradiente de MeOH al 10% en DCM proporcionando el compuesto del título (400 mg, 47%) en forma de un sólido blanquecino.

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,38 (d, 2H), 6,95 (d, 2H), 4,13 (t, 2H), 4,10-4,03 (m, 2H), 3,89 (td, 2H), 2,92 (t, 2H), 2,64 (s a, 4H), 2,15-1,99 (m, 4H), 1,88-1,76 (m, 4H).

393

Ejemplo 91: 4-[4-(2-Metil-3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-piran-4-carbonitrilo



Se hizo reaccionar de forma conjunta 4-(4-hidroxi-fenil)-tetrahidro-piran-4-carbonitrilo (790 mg, 3,87 mmol), 1-(3-cloro-2-metil-propil)-pirrolidina (500 mg, 3,10 mmol), DMF (5 ml) y K_2CO_3 (2,14 g, 15,50 mmol) de acuerdo con el procedimiento general E. La fase orgánica se lavó con NaOH 2 M (3 x 20 ml), agua *(2 x* 20 ml), se secó sobre $MgSO_4$, se filtró y se concentró *al vacío* a 35ºC proporcionando el compuesto del título (979 mg, 96%) en forma de un sólido amarillo.

^{1}H RMN (400 MHz, $CDCl_3$), δ 7,37 (d, 2H), 6,95 (d, 2H), 4,11-4,03 (m, 2H), 4,02 (dd, 1H), 3,89 (td, 2H), 3,77 (dd, 1H), 2,60-2,42 (m, 5H), 2,32 (dd, 1H), 2,22-1,99 (m, 5H), 1,82-1,72 (m, 4H), 1,07 (d, 3H).

Intermedio 32: Clorhidrato de 1-(3-Cloro-1-metil-propil)-pirrolidina

Etapa 1:

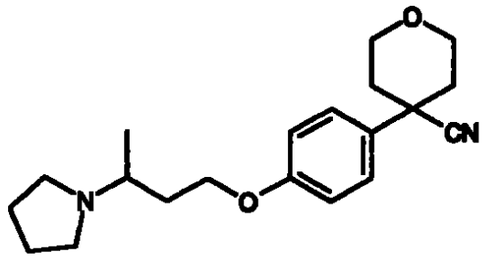
Se calentó a reflujo pirrolidina (28,15 g, 0,4 mol), tolueno (200 ml), *p*-TsOH catalítico (200 mg) y acetoacetato de etilo (20 g, 0,15 mol) con un aparato Dean-Stark en una atmósfera de N_2 durante 3 horas. La reacción se enfrió a temperatura ambiente y se concentró *al vacío*. Se disolvió $NaBH_4$ (3,1 g, 82 mmol) en MeOH (50 ml) y se enfrió a 0-5ºC. A la mezcla de reacción se le añadió una porción del producto de reacción previo (5 g, 27 mmol) en MeOH

(25 ml) y se agitó durante 72 horas. La reacción se inactivó con una solución acuosa de NaOH (1 %p/p, 50 ml) y se concentró *al vacío*. La fase acuosa se extrajo con TBME (3 x 50 ml). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron, se lavaron con TBME y se concentraron *al vacío* dando una mezcla del compuesto del título, éste etílico del ácido 3-pirrolidin-1-il-butanoico y TBME residual (3,5 g). La mezcla (3,5 g) en THF (20 ml) se añadió a una solución de $LiALH_4$ (1 M en THF, 33,5 ml, 33,5 mmol) a 0-5ºC en una atmósfera de N_2. La reacción se dejó calentar a temperatura ambiente y se agitó durante 3 horas. La reacción se inactivó con una solución acuosa de NaOH (1%p/p, 50 ml) a 0-5ºC, se filtró y se lavó con THF (3 x 20 ml). Los extractos orgánicos combinados se secaron sobre $MgSO_4$, se filtraron, se lavaron con THF y se concentraron *al vacío* dando 3-pirrolidin-1-il-butan-1-ol en forma de un aceite amarillo (2 g, 73%).

Etapa 2:

Se disolvió 3-pirrolidin-1-il-butan-1-ol (1,0 g, 7 mmol) en DCM (20 ml). La reacción se enfrió a 0-5ºC y se añadió lentamente cloruro de tionilo (1,65 g, 14 mmol). La reacción se dejó calentar a temperatura ambiente y se agitó durante una noche. La reacción se concentró *al vacío* y formó un azeótropo con DCM (20 ml) dando el compuesto del título (1,4 g, 100%) en forma de un aceite pardo.

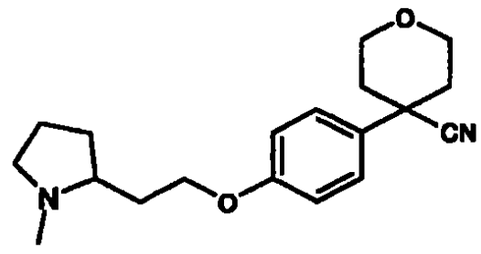
Ejemplo 92: 4-[4-(3-Pirrolidin-1-ilbutoxi)fenil]tetrahidropiran-4-carbonitrilo.



Se hizo reaccionar de forma conjunta 4-(4-hidroxi-fenil)-tetrahidro-piran-4-carbonitrilo (1,0 g, 4,9 mmol), 1-(3-cloro-1-metil-propil)-pirrolidina (780 mg, 3,90 mmol), DMF (20 ml) y K_2CO_3 (2,71 g, 19,60 mmol) de acuerdo con el procedimiento general E. La fase orgánica se lavó con NaOH 2 M (3 x 20 ml), agua (2 x 20 ml), se secó sobre $MgSO_4$, se filtró y se concentró *al vacío* a 35°C y se purificó por HPLC preparativa, eluyendo con acetonitrilo/agua/TFA al 0,1% como gradiente, proporcionando el compuesto del título (120 mg, 9%) en forma de un aceite amarillo.

^{1}H RMN (400 MHz, $CDCl_3$), δ 7,38 (d, 2H), 6,93 (d, 2H), 4,15-3,98 (m, 4H), 3,89 (td, 2H), 2,75-2,51 (m, 5H), 2,22-1,74 (m, 10H), 1,17 (d, 3H).

Ejemplo 93: 4-[4-[2-(1-Metilpirrolidin-2-il)etoxi]fenil]tetrahidro-piran-4-carbonitrilo

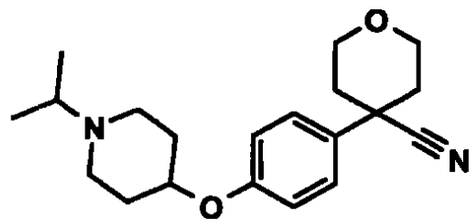


Se hizo reaccionar de forma conjunta 4-(4-hidroxi-fenil)-tetrahidro-piran-4-carbonitrilo (1,0 g, 4,9 mmol), 2-(2-cloro-etil)-1-metil-pirrolidina (722 mg, 3,90 mmol), DMF (20 ml) y K_2CO_3 (2,71 g, 19,60 mmol) de acuerdo con el

procedimiento general E. La fase orgánica se lavó con NaOH 2 M (3 x 20 ml), agua (2 x 20 ml), se secó sobre $MgSO_4$, se filtró y se concentró *al vacío* a 35ºC y se purificó por TLC prep, eluyendo con DCM:MeOH:NH_3 (95:5:3), proporcionando el compuesto del título (180 mg, 15%) en forma de un aceite amarillo.

^{1}H RMN (400 MHz, $CDCl_3$), δ 7,38 (d, 2H), 6,93 (d, 2H), 4,12-4,03 (m, 4H), 3,89 (td, 2H), 3,08 (m, 1H), 2,35 (s, 3H), 2,29-1,94 (m, 8H), 1,85-1,65 (m, 2H), 1,62-1,50 (m, 2H).

Ejemplo 94: 4-[4-(1-isopropilpiperidin-4-iloxi)fenil]tetrahidropiran-4-carbonitrilo



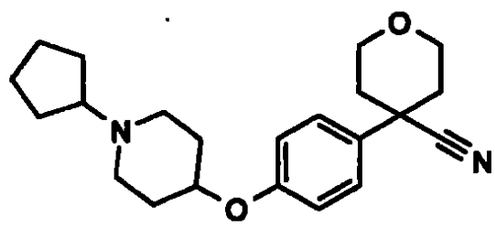
Se añadió 4-(4-hidroxi-fenil)-tetrahidro-piran-4-carbonitrilo (459 mg, 2,26 mmol) en DMF (2 ml) a una solución de NaH (100 mg, 2,5 mmol) en DMF (2 ml) a temperatura ambiente en una atmósfera de N. La reacción se agitó durante 1 hora y se añadió lentamente una solución de éster 1-isopropil-piperidin-4-ilo del ácido metanosulfónico (400 mg, 1,81 mmol) en DMF (1,3 ml). La reacción se calentó a 75ºC y se agitó durante 6 horas. La reacción se dejó enfriar a temperatura ambiente y se diluyó con TBME (20 ml), agua (10 ml) y una solución de NaOH 5 M (10 ml). La fase orgánica se lavó con NaOH 2,5 M (2 x 20 ml), salmuera (2 x 20 ml), se secó sobre $MgSO_4$, se filtró y se concentró *al vacío*. La reacción en bruto se purificó por cromatografía sucesiva en columna, eluyendo con DCM:MeOH : NH_3 (98 :1 :1) dando el compuesto del

397

título en forma de un sólido amarillo pálido (116 mg, 19%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,37 (d, 2H), 6,93 (d, 2H), 4,30 (m, 1H), 4,12-4,02 (m, 2H), 3,89 (td, 2H), 2,84-2,68 (m, 3H), 2,45-2,34 (m, 2H), 2,15-1,96 (m, 6H), 1,88-1,75 (m, 2H), 1,06 (d, 6H).

Ejemplo 95: 4-[4-(1-Ciclopentilpiperidin-4-iloxi)fenil]tetrahidropiran-4-carbonitrilo



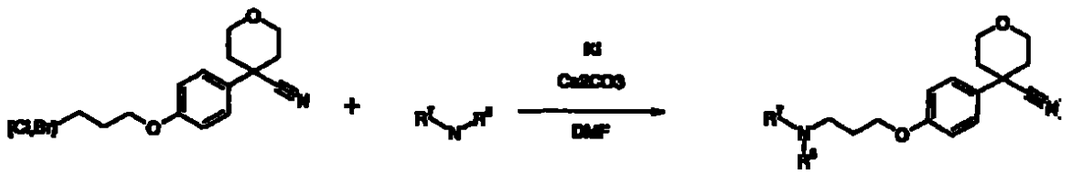
Se añadió 4-(4-hidroxi-fenil)-tetrahidro-piran-4-carbonitrilo (459 mg, 2,26 mmol) en DMF (2 ml) a una solución de NaH (100 mg, 2,5 mmol) en DMF (2 ml) a temperatura ambiente en una atmósfera de N_2. La reacción se agitó durante 1 hora y se añadió lentamente una solución de éster 1-ciclopentil-piperidin-4-ilo del ácido metanosulfónico (447 mg, 1,81 mmol) en DMF (1,3 ml). La reacción se calentó a 75ºC y se agitó durante 6 horas. La reacción se dejó enfriar a temperatura ambiente y se diluyó con TBME (20 ml), agua (10 ml) y una solución de NaOH 5 M (10 ml). La fase orgánica se lavó con NaOH 2,5 M (2 x 20 ml), salmuera (2 x 20 ml), se secó sobre $MgSO_4$, se filtró y se concentró *al vacío*. La reacción en bruto se purificó por cromatografía sucesiva en columna, eluyendo con DCM:MeOH : NH_3 (98 :1 :1) dando el compuesto del título en forma de un sólido amarillo pálido (81 mg, 13%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,37 (d, 2H), 6,93 (d, 2H), 4,36 (m, 1H), 4,11-4,04 (m, 2H), 3,89 (td, 2H), 2,91-2,77 (m, 2H), 2,67-2,25 (m, 2H), 2,15-1,99 (m, 7H), 1,95-1,81 (m, 4H), 1,78-1,64 (m, 2H), 1,62-1,39 (m, 4H).

Intermedios 33 y 34: 4-[4-(3-cloro-propoxi)-fenil]-tetrahidropiran-4-carbonitrilo y 4-[4-(3-bromo-propoxi)-fenil]-tetrahidropiran-4-carbonitrilo

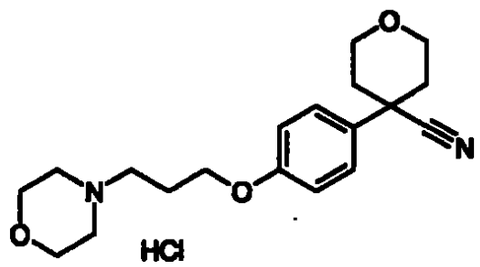
Se recogió 4(4-hidroxi-fenil)-tetrahidro-piran-4-carbonitrilo (3,4 g, 16,73 mmol) en DMF (75 ml) y después se añadió Cs_2CO_3 (4,84 g, 25,095 mmol) seguido de adición gota a gota de 1-bromo-3-cloropropano (2,45 ml) a 60 °C. Se continuó calentando a 60 °C durante una noche. Primero, la mezcla de reacción se concentró y se inactivó añadiendo agua y se extrajo con acetato de etilo. El compuesto se purificó por cromatografía en columna (0-14 %, acetato de etilo-hexano). Rendimiento: 3,3 g (70 % de una mezcla 10:3 de compuesto de cloro y bromo).

Procedimiento general F:



Una mezcla de haluro (0,7 mmol), Cs_2CO_3 (0,350 g, 1,07 mmol), yoduro potásico (0,180 g, 1,07 mmol) y amina (NR^7R^8) (1,07 mmol) en DMF (7 ml) se calentó a 70°C durante una noche. La mezcla se enfrió a temperatura ambiente, se añadió agua y la mezcla resultante se extrajo con diclorometano y los extractos orgánicos se secaron sobre Na_2SO_4, se filtraron y se concentraron *al vacío*. La purificación del material en bruto se realizó por cromatografía ultrarrápida (20 g de gel de sílice, gradiente de DCM/ MeOH).

Ejemplo 96: 4-[4-(3-morfolino-4-ilpropoxi)fenil]tetrahidropiran-4-carbonitrilo

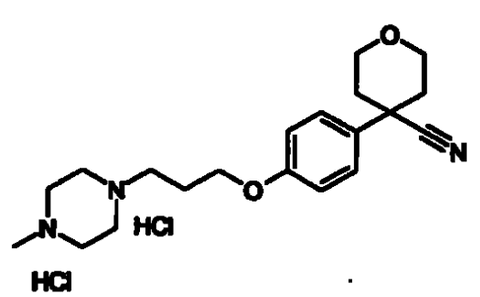


El compuesto se obtuvo de acuerdo con el procedimiento general F, usando morfolina como amina. La muestra analítica de sal clorhidrato se preparó con éter/HCl 2 M en diclorometano y cristalización en éter.

Rendimiento = 34%

^{1}H RMN (400 MHz, DMSO-D_6) δ 1,95-2,12 (m, 4H); 2,16-2,25 (m, 2H); 3,01-3,12 (m, 2H); 3,19-3,27 (m, 2H); 3,40-3,48 (m, 2H); 3,60-3,69 (t, 2H); 3,80-3,89 (m, 2H); 3,91-4,03 (m, 4H); 4,08-4,13 (m, 2H); 7,20 (d, 2H); 7,46 (d, 2H); 11,33 (sa, 1H)

Ejemplo 97: 4-[4-[3-(4-metil-piperazin-1-il)-propoxi]fenil]tetrahidro-piran-4-carbonitrilo



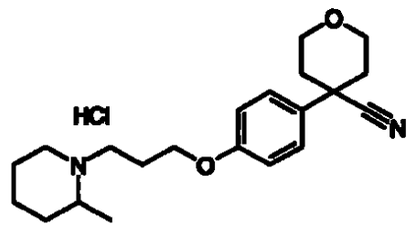
El compuesto se obtuvo de acuerdo con el procedimiento general F, usando 1-metilpiperazina como amina. La muestra analítica de sal clorhidrato se preparó con éter/HCl 1 M en diclorometano y se trituró con pentano.

Rendimiento = 57%

^{1}H RMN (400 MHz, DMSO-D_6) δ 11,85 (sa, 1H), 7,46 (d, 2H), 7,02 (d, 2H), 4,13

-4,07 (m, 2H), 4,03 -3,96 (m, 2H), 3,84-3,18 (m, 12H), 2,87-2,78 (m, 3H), 2,24 - 2,13 (m, 2H), 2,11 -1,96 (m, 4H).

Ejemplo 98: 4-{4-[3-(2-metil-piperidin-1-il)-propoxi]fenil}-tetrahidro-piran-4-carbonitrilo

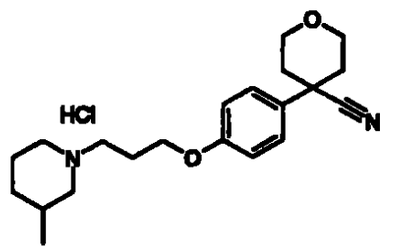


El compuesto se obtuvo de acuerdo con el procedimiento general F, usando 2-metilpiperidina como amina. La muestra analítica de sal clorhidrato se preparó con éter/HO 1 M en diclorometano y trituración con pentano.

Rendimiento = 28%

^{1}H RMN (400 MHz, DMSO-D_6) δ 10,22 (sa, 1H), 7,46 (d, 2H), 7,01(d, 2H), 4,13-4,06 (m, 2H), 4,03-3,96 (dd, 2H), 3,69-3,60 (t, 2H), 3,48-3,38 (m, 1H), 3,25-3,06 (m, 3H), 3,01-2,90 (m, 1H), 2,21-1,95 (m, 7H), 1,88-1,57 (m, 5H), 1,56-1,39 (m, 1 H), 1,32 (d, 2H), 1,24 (d, 1 H).

Ejemplo 99: 4-{4-[3-(3-metil-piperidin-1-il)-propoxi]fenil}-tetrahidro-piran-4-carbonitrilo

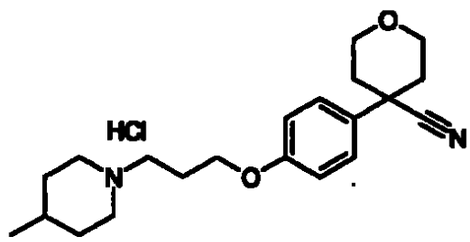


El compuesto se obtuvo de acuerdo con el procedimiento general F, usando 3-metilpiperidina como amina. La muestra analítica de sal clorhidrato se preparó con éter/HCl 1 M en diclorometano y trituración con pentano.

Rendimiento = 52%

^{1}H RMN (400 MHz, DMSO-D_6) δ 10,32 (sa, 1H), 7,46 (d, 2H), 7,01(d, 2H), 4,11-4,05 (t, 2H), 4,03-3,96 (dd, 2H), 3,69-3,60 (t, 2H), 3,48-3,35 (m, 2H), 3,19-3,11 (m, 2H), 2,82-2,72 (m, 1H), 2,58-2,45 (m, 1H), 2,24-2,16 (m, 2H), 2,12-1,90 (m, 5H), 1,85-1,70 (m, 3H), 1,12-1,02 (m, 1H), 0,89 (d, 3H).

Ejemplo 100: 4-{4-[3-(4-metil-piperidin-1-il)-propoxi]fenil}-tetrahidro-piran-4-carbonitrilo

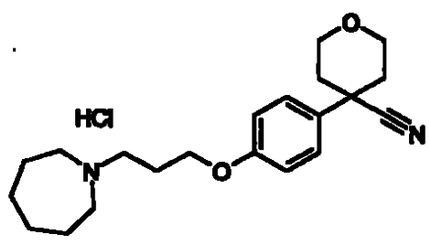


El compuesto se obtuvo de acuerdo con el procedimiento general F, usando 4-metilpiperidina como amina. La muestra analítica de sal clorhidrato se preparó con éter/HCl 1 M en diclorometano y trituración con pentano.

Rendimiento = 60%

^{1}H RMN: (400 MHz, DMSO-D_6) δ 10,18 (sa, 1H), 7,46 (d, 2H), 7,01(d, 2H), 4,11-4,05 (t, 2H), 4,03-3,96 (dd, 2H), 3,69-3,60 (t, 2H), 3,49-3,42 (m, 2H), 3,19-3,11 (m, 2H), 2,94-2,83 (m, 2H), 2,22-2,13 (m, 2H), 2,11-1,95 (m, 4H), 1,81-1,73 (m, 2H), 1,65-1,54 (m, 1H), 1,53-1,41 (m, 2H), 0,91 (d, 3H).

Ejemplo 101: 4-[4-(3-azepan-1-ilpropoxi)fenil]tetrahidropiran-4-carbonitrilo

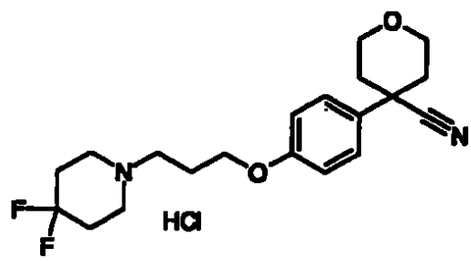


El compuesto se obtuvo de acuerdo con el procedimiento general F, usando hexametilenimina como amina. La muestra analítica de sal clorhidrato se preparó con éter/HCl 1 M en diclorometano y trituración con éter.

Rendimiento = 9%

^{1}H RMN (400 MHz, DMSO-D_6) δ 10,54 (sa, 1 H), 7,41 (d, 2H), 7,01(d, 2H), 4,11-4,05 (t, 2H), 4,03-3,96 (dd, 2H), 3,69-3,60 (dt, 2H), 3,41-3,30 (m, 2H), 3,24-3,17 (m, 2H), 3,16-3,06 (m, 2H), 2,24-2,16 (m, 2H), 2,12-1,95 (m, 4H), 1,92-1,76 (m, 4H), 1,72-1,52 (m, 4H).

Ejemplo 102: 4-[4-[3-(4,4-difluoro-piperidin-1-il)-propoxi]fenil]-tetra-hidropiran-4-carbonitrilo

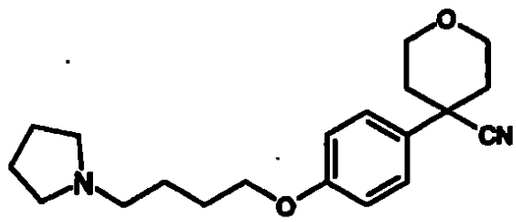


El compuesto se obtuvo de acuerdo con el procedimiento general F, usando clorhidrato de 4,4-difluoropiperidina como amina (añadir $(C_2H_5)_3N$ para obtener la base libre). La muestra analítica de sal clorhidrato se preparó con éter/HCl 1 M en diclorometano y trituración con éter.

Rendimiento = 9%

^{1}H RMN : (400 MHz, DMSO-D_6) δ 10,28 (sa, 1H), 7,46 (d, 2H), 7,01(d, 2H), 4,12-4,07 (t, 2H), 4,03-3,96 (dd, 2H), 3,69-3,59 (dt, 4H), 3,33-325 (m, 2H), 3,21-3,11 (m, 2H), 2,39-2,27 (m, 2H), 2,27-2,17 (m, 2H), 2,12-1,95 (m, 4H).

Ejemplo 103: 4-[4-(5-Pirrolidin-1-ilpentiloxi)fenil]tetrahidropiran-4-carbonitrilo



Se hizo reaccionar de forma conjunta 4-(4-hidroxi-fenil)-tetrahidro-piran-4-carbonitrilo (1,5 g, 7,39 mmol), 1-bromo-4-clorobutano (1,7 ml, 14,77 mmol), DMF (20 ml) y K_2CO_3 (4,1 g, 29,56 mmol) de acuerdo con el procedimiento general E. La purificación por cromatografía sobre sílice, eluyente acetato de etilo:heptanos (33:66) proporcionó una mezcla de bromo y cloro fenoxi éter (1,3 g, 60%) que se usó en la siguiente etapa. Una porción de la mezcla (0,5 g, 1,70 mmol) y pirrolidina (0,42 ml, 5,11 mmol) se calentó a reflujo en EtOH (5 ml, 10 vol) durante una noche. La reacción se concentró *al vacío* y se dividió entre NaOH 2 M (10 ml) y acetato de etilo (10 ml). La fase acuosa se extrajo con acetato de etilo (3 x 10 ml). Las fases de acetato de etilo combinadas se lavaron con salmuera (3 x 10 ml), se secaron sobre $MgSO_4$, se filtraron, se lavaron con acetato de etilo y se concentraron *al vacío*. La purificación por cromatografía sobre sílice, eluyente DCM:MeOH:NH_3 (95:4:1) aumentando gradualmente a DCM:MeOH:NH_3 (93:6:1), dio el compuesto del título en forma de un sólido amarillo pálido (350 mg, 63%).

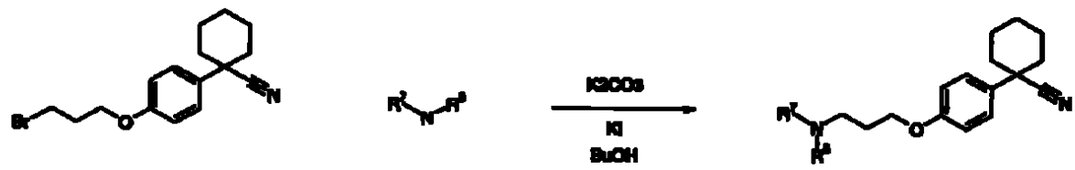
^{1}H RMN (400 MHz, DMSO-d_6) δ 7,38 (d, 2H), 6,92 (d, 2H), 4,11-4,03 (m, 2H), 3,99 (t, 2H), 3,89 (td, 2H), 2,58-2,43 (m, 6H), 2,15-1,99 (m, 4H), 1,89-1,64 (m, 8H).

Intermedio 35: 1-[4-(3-bromo-propoxi)-fenil]-ciclohexanocarbonitrilo

Se recogió 1-(4-hidroxifenil)ciclohexanocarbonitrilo (2,0 g, 10 mmol) en acetona (150 ml) y después se añadió Cs_2CO_3 (8,1 g, 25 mmol) seguido de

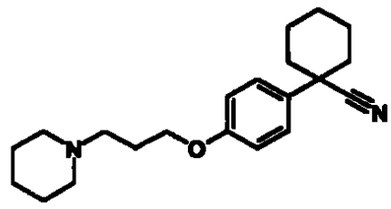
adición gota a gota adición de 1,3-dibromopropano (5,1 ml, 50 mmol). La mezcla se calentó durante 3 horas a 70ºC. Después de enfriar y filtrar, la mezcla se concentró y el residuo se purificó por cromatografía ultrarrápida (50 g gel de sílice, DCM) proporcionando el compuesto del título (2,8 g, 87%). Nota: presencia de derivado alilo como impureza.

Procedimiento general G:



Una mezcla de 1-[4-(3-bromo-propoxi)-fenil]-ciclohexanocarbonitrilo (0,660 g, 2,0 mmol), amina (NR^7R^8) (0,260 g, 3,0 mmol), carbonato sódico (0,320 g, 3 mmol), yoduro potásico (20 mg) y 20 ml de butanol se calentó durante 4 horas a 100ºC. Después de enfriarse, se añadió agua para inactivar la reacción y la mezcla se extrajo con DCM. Los extractos orgánicos se lavaron con una solución acuosa saturada de $NaHCO_3$, agua y se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo se purificó por cromatografía ultrarrápida (DCM y DCM / MeOH (NH_3 al 10%) proporcionando (0,440 g, 67%).

Ejemplo 104: 1-[4-(3-piperidin-1-il-propoxi)-fenil]-ciclohexano-carbonitril

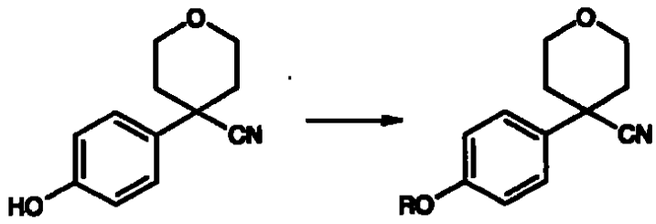


Una mezcla de 1-[4-(3-bromo-propoxi)-fenil]-ciclohexanocarbonitrilo (0,660 g, 2,0 mmol), piperidina (0,260 g, 3,0 mmol), carbonato sódico (0,320 g,

3 mmol), yoduro potásico (20 mg) y 20 ml de butanol se calentó durante 4 horas a 100ºC de acuerdo con el procedimiento general G. Después de enfriarse, se añadió agua para inactivar la reacción y la mezcla se extrajo con DCM. Los extractos orgánicos se lavaron con una solución acuosa saturada de $NaHCO_3$, agua y se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo se purificó por cromatografía ultrarrápida (DCM y DCM / MeOH (NH_3 al 10%) proporcionando el compuesto del título (0,440 g, 67%).

^1H RMN (400 MHz, $CDCl_3$) δ 7,37 (d, 2H), 6,90(d, 2H), 4,00 (t, 2H), 2,49-2,36 (m, 6H), 2,17-2,09 (m, 2H), 1,97 (ct, 2H), 1,88-1,67 (m, 7H), 1,62-1,55 (m, 4H), 1,47-1,40 (m, 2H), 1,32-1,20 (m, 1 H).

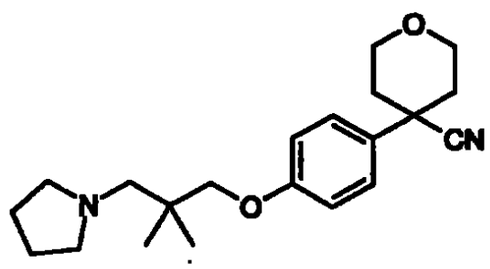
Procedimiento general H:



Se mezclaron 4-(4-hidroxi-fenil)-tetrahidro-piran-4-carbonitrilo (1 eq.), alcohol (R-OH) (0,8 eq.) y PPh_3 (1 eq.) en THF (10 vol) y se enfrió a 0ºC en una atmósfera de N_2. A la reacción se le añadió lentamente DIAD (1 eq.) en THF (10 vol) y se dejó calentar a temperatura ambiente durante una noche. La reacción se inactivó con una solución de HCl 2 M (10 vol) y se extrajo con acetato de etilo (3 x 10 vol). La fase acuosa se basificó a pH 14 con NaOH (~30 vol) y se extrajo con acetato de etilo (3 x 10 vol). Los extractos orgánicos se secaron sobre $MgSO_4$, se filtraron y se concentraron *al vacío* a 35ºC. La purificación del material en bruto por cromatografía sobre sílice, eluyente (MeOH al 10% en DCM) proporcionó los compuestos del título.

406

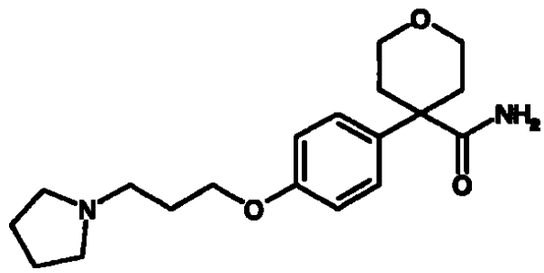
Ejemplo 105: 4-[4-(2,2-Dimetil-3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-carbonitrilo



Se hizo reaccionar de forma conjunta 4-(4-hidroxi-fenil)-tetrahidro-piran-4-carbonitrilo (1,29 g, 6,4 mmol), 2,2-dimetil-3-pirrolidin-1-il-propan-1-ol (0,8 g, 5.1 mmol), PPh_3 (1,67 g, 6,4 mmol), THF (16 ml) y DIAD (1,25 ml, 6,4 mmol) de acuerdo con el procedimiento general H. El material en bruto se sometió a cromatografía sobre sílice eluyendo con DCM:MeOH (98 :2). El sólido resultante se suspendió en TBME:heptanos (1:2, 1 ml) proporcionando el compuesto del título (120 mg, 5%) en forma de un sólido blanco.

^{1}H RMN (400 MHz, $GDCl_3$), δ 7,37 (d, 2H), 6,94 (d, 2H), 4,12-4,03 (m, 2H), 3,89 (td, 2H), 3,71 (s, 2H), 2,57 (s a, 4H), 2,47 (s, 2H), 2,15-1,99 (m, 4H), 1,70 (sa, 4H), 1,00 (s, 6H).

Ejemplo 106: Amida del ácido 4-[4-(3-Pirrolidin-1-il-propoxi)-fenil]-tetrahidro-2*H*-piran-4-carboxílico



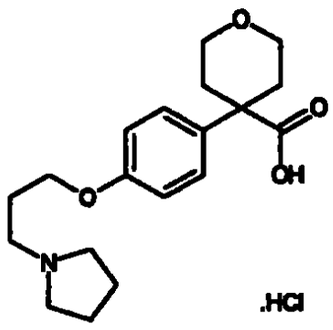
Se trató 4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-carbonitrilo

407

(400 mg, 1,27 mmol) con ácido polifosfórico a 80ºC durante una noche. Después de dejar enfriar la mezcla a temperatura ambiente, se añadió acetato de etilo y agua. La fase orgánica se separó. La fase acuosa se basificó a pH 10 con NaOH concentrado y se extrajo con DCM. Los extractos orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, se concentraron *al vacío* y se purificaron por cromatografía en columna sobre gel de sílice eluyendo dando el compuesto del título (88 mg, 26%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,29 (d, 2H), 6,91(d, 2H), 5,64-5,30 (d, 2H), 4,02 (t, 2H), 3,76 (t, 4H), 2,62 (t, 2H), 2,52 (m, 4H), 2,37-2,30 (m, 2H), 2,08-1,96 (m, 4H), 1,81-1,75 (m, 4H).

Ejemplo 107: Ácido 4-[4-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxílico



Una solución de 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbonitrilo (20 g, 0,0636 mol) en ácido clorhídrico concentrado (200 ml, 10 vol) se calentó y se agitó a reflujo durante 16 horas después de lo cual el análisis LC/LCEM mostró que la reacción se había estancado en 85-90% de conversión. La solución se evaporó a sequedad *al vacío*, formó un azeótropo con metanol (200 ml, 20 vol) y tolueno (2x 200 ml, 2x 20 vol) produciendo compuesto del título en forma de un sólido beige que se usó directamente.

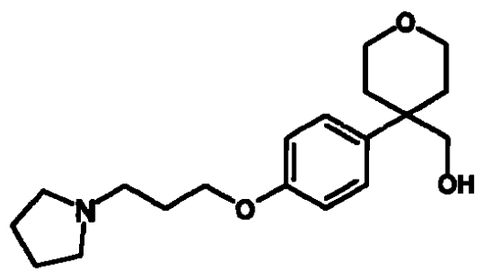
^{1}H RMN (400 MHz, $CDCl_3$) δ 7,18 (d, 2H), 6,96 (d, 2H), 4,12 (t, 2H), 3,94-3,84 (m, 2H), 3,74-3,66 (m, 2H), 3,60 (dt, 2H), 3,42 (t, 2H), 2,50-2,44 (m, 2H), 2,26-2,00 (m, 8H), 2,96-2,84 (m, 2H);

EMAR (IEN$^+$) 334,2013 $(M+H)^+$.

Intermedio 38: 4-[4(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxilato de metilo

Una suspensión de ácido 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxílico (23,5 g, 0,0636 mol) en metanol (235 ml, 10 vol) se agitó y se enfrió a una temperatura de 0 a -5ºC en una atmósfera de nitrógeno. Se cargó gota a gota cloruro de tionilo (9,3 ml, 0,1272 mol, 0,40 vol) durante 20 minutos, manteniendo la temperatura entre -5 y +5ºC. Después, la suspensión se calentó y se agitó a reflujo en una atmósfera de nitrógeno durante 16 horas después de lo cual el análisis LC mostró un 1,4% en área de ácido restante. La solución se evaporó a sequedad *al vacío* a 40ºC dando un lodo pardo. El lodo se disolvió en acetato de etilo (118 ml, 5 vol) y agua (235 ml, 10 vol) y las fases se separaron. La fase acuosa se lavó con acetato de etilo (118 ml, 5 vol) y se basificó a pH 11 con carbonato potásico acuoso saturado (118 ml, 5 vol). El producto se extrajo en diclorometano (3x 118 ml, 3x 5 vol) y los extractos combinados se secaron sobre sulfato de magnesio (23 g, 1 peso) y se concentraron *al vacío* a 40ºC produciendo compuesto del título (21,7 g, 98% a partir del nitrilo) en forma de un sólido de color crema.

Ejemplo 108: {4-[4-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metanol



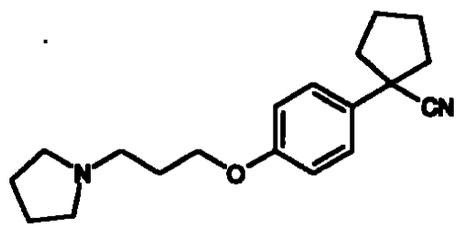
Se cargó rápidamente tetrahidrofurano anhidro (141 ml, 10 vol) en hidruro de aluminio litio agitado y enfriado (0-5ºC) (6,2 g, 0,1634 mol, 0,44 peso) en una atmósfera de nitrógeno (Nota: muy exotérmico). La suspensión resultante se enfrió a 0-5ºC y después se añadió gota a gota una solución de 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxilato de metilo (14,1 g, 0,04058 mol) en tetrahidrofurano (99 ml, 7 vol) durante 30 minutos manteniendo 0-5ºC. Al completar la adición, se dejó calentar a temperatura ambiente durante 30 minutos y se agitó a 18-25ºC durante 30 minutos, El análisis LC mostró que la reacción se había completado. La mezcla se enfrió a 0 a 5ºC, se añadió muy lentamente una mezcla 1:1 de tetrahidrofurano y agua (18,6 ml, 1,32 vol) (Nota: muy exotérmica, desprendimiento de gas, temperatura mantenida por debajo de 16ºC, hacia el final de la desactivación la mezcla de reacción sedimenta y se vuelve más libre con agitación continua) La mezcla se inactivó posteriormente con una solución de hidróxido sódico al 20% p/v (6,2 ml, 0,44 vol) y agua (18,6 ml, 1,32 vol) y la suspensión blanca resultante se agitó enérgicamente durante 30 minutos a 18-25ºC. Las tablillas se retiraron por filtración y se aclararon con tetrahidrofurano (3x 150 ml). Los filtrados combinados se evaporaron a sequedad a 40ºC produciendo compuesto del título (12,1 g, 94%) en forma de un sólido blanco.

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,25 (d, 2H), 6,90 (d, 2H), 4,05 (t, 2H), 3,80 (dt,

410

2H), 3,55 (td, 2H), 2,60 (t, 2H), 2,62-2,41 (m, 4H), 2,10 (dt, 2H), 2,00 (p, 2H), 2,00-1,85 (m, 2H), 1,95-1,72 (m, 4H).

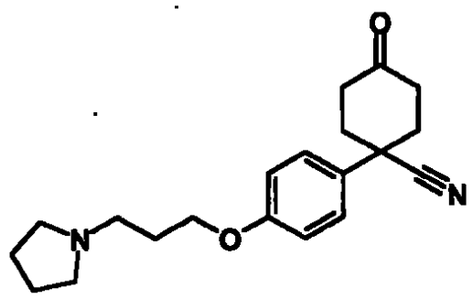
Ejemplo 109: 1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclo-pentano-carbonitrilo



A una suspensión de NaH (60%, 0,574 g, 14,35 mmol) en DMF (8 ml) a 0°C se le añadió gota a gota [4-(3-pirrolidin-1-ilpropoxi)fenil]acetonitrilo (1 g, 4,10 mmol) en DMF (3 ml). La mezcla de reacción se agitó a 0°C durante 5 minutos y después a temperatura ambiente durante 30 minutos. Después de enfriarse a 0°C, se añadió gota a gota 1,4-dibromobutano (0,980 ml, 8,2 mmol) en DMF (2 ml) se añadió gota a gota. La mezcla de reacción se dejó calentar a temperatura ambiente después se calentó a 50°C durante una noche. Se vertió en agua enfriada en hielo y se extrajo con DCM. Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron *al vacío*. La mezcla en bruto se purificó por cromatografía en columna, eluyendo con un gradiente de DCM:MeOH:NH_3 (de 99:0:1 a 90:10:1) dando el compuesto del título (0,443 g, 36%).

^{1}H RMN (400 MHz, DMSO-D_6) δ 7,29 (d, 2H), 6,79 (d, 2H), 4,02 (m, 2H), 3,18 (m, 2H), 2,47-2,28 (m, 4H), 2,19-1,75 (m, 11H), 1,19 (m, 3H).

Ejemplo 110: 4-oxo-1-[4-(3-pirrolidin-1-ilpropoxi)-fenil]-ciclohexano-carbonitrilo



Etapa 1:

Un recipiente de reacción de tres bocas se cargó con [4-(3-pirrolidin-1-ilpropoxi)fenil]acetonitrilo (7 g, 28,6 mmol), hidróxido benciltrimetilamónico (40% en metanol, 1,3 ml) en acetonitrilo (185 ml). La solución se calentó a reflujo y se añadió gota a gota acrilato de metilo (25 ml, 286 mmol). Después de calentar a reflujo durante 5 horas, la mezcla se concentró a la mitad, se añadió éter dietílico y los extractos orgánicos se lavaron con HCl 1 N y salmuera, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El residuo se purificó por cromatografía ultrarrápida proporcionando éster dimetílico del ácido 4-ciano-4-[4-(3-pirrolidin-1-ilpropoxi)-fenil]-heptanodioico (8,8 g, 74%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,28 (d, 2H); 6,95 (d, 2H); 4,08-4,0 (m, 2H); 3,6 (s, 6H); 2,68-2,60 (m, 2H); 2,58-2,45 (m, 6H); 2,40-2,20 (m, 4H); 2,20-2,12 (m, 2H); 2,08-2,0 (m, 2H); 1,80-1,75 (m, 4H)

Etapa 2:

A una solución de éster dimetílico de ácido 4-ciano-4-[4-(3-pirrolidin-1-ilpropoxi)-fenil]-heptanodioico (8,8 g, 21,1 mmol) en 1,2-dimetoxietano (176 ml) se le añadieron porciones de NaH (dispersión al 60%; 2,55 g, 63,4 mmol). La mezcla de reacción se calentó a reflujo. Después de 4,5 horas, los ¾ del disolvente se evaporaron y la mezcla se enfrió a 20°C con un baño de hielo y se inactivó con agua (100 ml), HCl 1 N (100 ml). La fase acuosa se extrajo con

éter (100 ml). Después de la basificación con NaOH la fase acuosas se extrajeron con diclorometano. Los extractos orgánicos combinados se lavaron con agua, se secaron sobre Na_2SO_4, se filtraron y se concentraron proporcionando éster metílico del ácido 5-ciano-2-oxo-5-[4-(3-pirrolidin-1-ilpropoxi)-fenil]-ciclohexanocarboxílico (6,6 g, 81%) en forma de un aceite.

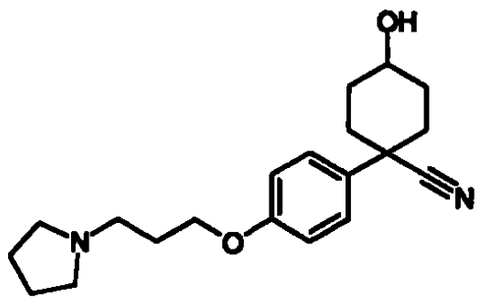
^{1}H RMN (400 MHz, $CDCl_3$) δ 12,2 (sa, 1H); 7,33 (d, 2H); 6,95 (d, 2H); 4,08-4,00 (m, 2H); 3,75 (s, 3H); 2,95 (d, 1H); 2,80-2,70 (m, 1H); 2,65-2,60 (m, 2H); 2,50-2,42 (m, 6H); 2,30-2,15 (m, 2H); 2,05-1,95 (m, 2H); 1,90-1,85 (m, 4H).

Etapa 3:

A una solución de éster metílico de ácido 5-ciano-2-oxo-5-[4-(3-pirrolidin-1-ilpropoxi)-fenil]-ciclohexanocarboxílico (6,6 g, 17 mmol) y dimetilsulfóxido (128 ml) se le añadió agua (8,0 ml) y cloruro sódico (6,4 g, 109 mmol). La mezcla de reacción se calentó a 142-146ºC. Después de 5 horas, la mezcla se concentró y el residuo se disolvió en DCM (120 ml), se lavó con agua (100 ml), y salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó por cromatografía ultrarrápida (70 g gel de sílice, eluyente: gradiente de DCM/MeOH 95/5 a 90/10) proporcionando 4-oxo-1-[4-(3-pirrolidin-1-ilpropoxi)-fenil]-ciclohexanocarbonitrilo en forma de un aceite de cristalización (2,2 g, 45,5%). Después de cristalización en éter, se obtuvieron 0,2 g de muestra analítica.

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,32 (d, 2H), 6,88 (d, 2H), 4,1 (t, 2H), 2,95-2,8 (m, 2H), 2,65-2,38 (m, 10H), 2,3-2,15 (m, 2H), 2,0-1,9 (m, 2H), 1,8-1,7 (m, 4H).

Ejemplo 111: 4-hidroxi-1-[4-(3-pirrolidin-1-ilpropoxi)-fenil]ciclo-hexanocarbonitrilo



A una suspensión agitada de $LiAlH_4$ (0,070 g, 1,85 mmol, 5 eq) en éter dietílico (1,9 ml) se le añadió gota a gota a 0ºC una solución de 4-oxo-1-[4-(3-pirrolidin-1-ilpropoxi)-fenil]-ciclohexanocarbonitrilo (0,12 g, 0,37 mmol) en éter dietílico (5,5 ml). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se enfrió a 0ºC y se añadieron sucesivamente una solución de agua, hidróxido sódico (15% p/v, 0,08 ml) y agua. Después de agitarse durante 15 minutos a temperatura ambiente, la mezcla se filtró sobre tierra de diatomeas y se concentró. El residuo se purificó por cromatografía ultrarrápida (10 g gel de sílice, DCM/ MeOH (NH_3 al 10%) proporcionando 0,050 g de compuesto del título.

^{1}H RMN (400 MHz, DMSO-D_6) δ 10,6 (sa, 1H), 7,42 (d, 2H), 7(d, 2H), 4,1-3,95 (m, 2H), 3,6-3,2 (m, 5H), 3,03-2,87 (m, 2H), 2,15-1,8 (m, 10H), 1,65-1,5 (m, 2H).

Intermedio 37: (*R*)-2-Metilpirrolidina

Pueden obtenerse enantiómeros puros de 2-metil pirrolidina por resolución con +/- ácido tartárico como se describe en *Acta. Pharm. Suecica* 15, 255-263; 1978.

Intermedio 38: 3-[(2*R*)-2-Metilpirrolidin-1-il]propan-1-ol

Se añadió 3-bromopropan-1-ol (5,28 ml, 58,4 mmol) a una solución de (R)-2-metilpirrolidina (7,1 g, 58,4 mmol) en agua (200 ml). Después se añadió

KOH (7,53 g, 134 mmol) y la mezcla se agitó a temperatura ambiente durante 48 horas. La mezcla de reacción se extrajo con diclorometano (5 x 80 ml) y acetato de etilo (5 x 80 ml). Los extractos orgánicos combinados se secaron usando $MgSO_4$, se filtraron y se concentraron *al vacío*. El compuesto se purificó por cromatografía en columna sobre gel de sílice Biotage®, eluyendo con diclorometano:metanol:amoniaco, (90:10:1) dando el compuesto del título en forma de un aceite pardo pálido (5,44, 65 %).

LCEM (APCI$^+$) 144 $(M+H)^+$.

Intermedio 39: (3*S*)-3-metoxipirrolidina-1-carboxilato de *terc*-butilo

Se añadió hidruro sódico (dispersión al 80% en aceite mineral, 940 mg, 0,024 mmol) en dos porciones a 0ºC a una solución de (3*S*)-3-hidroxipirrolidina-1-carboxilato de *terc*-butilo (4,00 g, 0,02 mmol). La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 1 hora antes de enfriarse otra vez a 0ºC. Se añadió lentamente yoduro de metilo (2,00 ml, 0,032 mmol) y la mezcla de reacción se calentó a temperatura ambiente durante una noche. La mezcla se vertió lentamente en 200 ml de hielo y se agitó hasta que el hielo se descongeló completamente. El producto se extrajo usando diclorometano (2 x 250 ml), se secó (Na_2SO_4) y se concentró *al vacío*. El compuesto se purificó por cromatografía en columna sobre gel de sílice Biotage®, eluyendo con diclorometano dando el producto en forma de un aceite incoloro (2,88 g, 67 %).

Intermedio 40: (3*S*)-3-Metoxipirrolidina

A solución de ácido trifluoroacético (2,5 ml) en diclorometano (5 ml) se le añadió lentamente a 0 ºC a una solución de (3*S*)-3-metoxipirrolidina-1-carboxilato de *terc*-butilo (2,88 g, mmol) y la reacción se dejó calentar a temperatura ambiente y se agitó durante 2,5 horas. La mezcla de reacción se

inactivó con una solución de carbonato sódico saturado (100 ml) y se extrajo con diclorometano (2 x 200 ml). Los extractos orgánicos se combinaron, se secaron sobre sulfato de magnesio y se concentraron *al vacío*. El residuo se recogió en diclorometano (30 ml) y se enfrió a 0°C en un baño de hielo. Se burbujeó cloruro de hidrógeno gaseoso a través de la suspensión durante 1 hora y la mezcla de reacción se dejó agitar a temperatura ambiente durante 48 horas. La mezcla de reacción se basificó con una solución de hidrogenocarbonato sódico saturado (100 ml) y se extrajo con diclorometano (2 x 200 ml) y acetato de etilo (3 x 150 ml). La fase acuosa se concentró *al vacío* y después se extrajo con metanol caliente produciendo el producto del título, 2,00 g.

Intermedio 41: (3*R*)-1-Bencil-3-metoxipirrolidina

Se preparó (3*R*)-1-bencil-3-metoxipirrolidina como se describe en la siguiente patente WO 91/08206 y se usó en la siguiente etapa en forma de mezcla en bruto.

Intermedio 42: (3*R*)-3-Metoxipirrolidina

Una solución de (3*R*)-1-Bencil-3-metoxipirrolidina (2,35 g, 12,3 mmol) en metanol (50 ml) que contenía HCl concentrado (1 ml) se hidrogenó a temperatura ambiente a 50 psi en presencia de una cantidad catalítica de $Pd(OH)_2$ al 10% sobre carbono (250 mg, 10% p/p). La mezcla de reacción se filtró sobre celite y se aclaró con diclorometano (60 ml) y metanol (60 ml) para retirar el catalizador. La fase orgánica se basificó con NaOH (2,0 M, 10 ml) y se extrajo con dietiléter (3 x 30 ml). La fase acuosa se acidificó posteriormente a pH 3 usando HCl concentrado, se concentró *al vacío* y formó un azeótropo con tolueno dando el producto en forma de un sólido amarillo que se usó

posteriormente sin purificación.

Intermedio 43: 2,2-Dimetilpirrolidina

Etapa 1: 1-Bencil-2,2-dimetilpirrolidina se preparó de acuerdo con el procedimiento descrito en la siguiente referencia. S. M. Denton y A. Wood, *Synlett*, 1999, 55.

Etapa 2: una solución de 1-Bencil-2,2-dimetilpirrolidina (1,02 g, 5,40 mmol) en etanol (80 ml) y HCl concentrado (0,5 ml) se hidrogenó sobre $Pd(OH)_2$ al 20% (100 mg, 10% p/p) a 60 psi a temperatura ambiente durante 4 horas. La mezcla de reacción se filtró sobre arbocel retirando el catalizador y se añadieron 2 ml más de HCl concentrado al producto en bruto. La mezcla de reacción se concentró al *vacío* y se secó azeotrópicamente usando tolueno dando el producto en forma de un sólido pardo, que parecía ser ligeramente higroscópico (732 mg, 100 %).

Intermedio 44: (2*R*,5*S*)-2,5-Dimetilpirrolidina

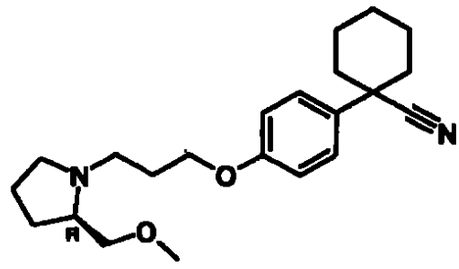
La base libre de *cis*-2,5-dimetilpirrolidina se preparó como se describe en C. G. Overberger, L C. Palmer, B. S. Marks y N. R. Byrd, *J. Am. Chem. Soc.*, 1955, 77, 4100. Esto se acidificó posteriormente usando HCl (solución 2,0 M en dietiléter) que, después de la filtración y recristalización posterior en acetonitrilo e alcohol *i*-propílico dio el compuesto del título en forma de un sólido cristalino (5,29 g, 22 %) con una relación de aproximadamente 10:1 de *cis*:*trans*.

Intermedios 45 y 46: 1-[4-(3-bromo-propoxi)fenil]ciclohexano-carbonitrilo y 1-[4-(3-cloro-propoxi)-fenil]-ciclohexano-carbonitrilo

Se añadió K_2CO_3 (3,02 g, 21,9 mmol) a una solución de 1-(4-hidroxifenil)ciclohexanocarbonitrilo (4,0 g, 19,9 mmol) en DMF (50 ml). Después se añadió gota a gota 1-bromo-3-cloropropano (1,97 ml, 19,9 mmol) y la

reacción se calentó a 60ºC durante una noche. La mezcla de reacción se concentró, se inactivó añadiendo agua (50 ml), se extrajo con diclorometano (2 x 50 ml) y los extractos orgánicos se secaron sobre Na_2SO_4, se filtraron y se concentraron *al vacío*. El compuesto se purificó por cromatografía en columna sobre gel de sílice Biotage®, eluyendo con dietiléter:diclorometano, 50:50 a 0:100. Rendimiento: 5,32 g (96% de una mezcla 3:1 de compuesto cloro y bromo).

Ejemplo 112: 1-(4-[3-[(2*R*)-2-(metoximetil)pirrolidin-1-il]propoxi]-fenil)ciclohexanocarbonitrilo

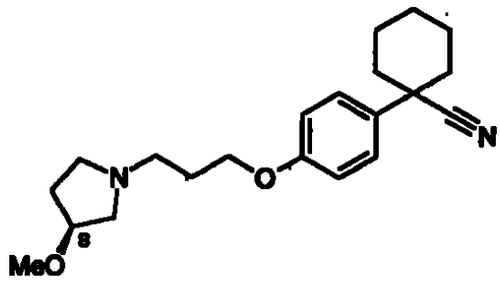


Una mezcla (1:3) de 1-[4-(3-bromo-propoxi)-fenil]-ciclohexanocarbonitrilo y 1-(4-(3-cloro-propoxi)-fenil]-ciclohexanocarbonitrilo (2,00 g, 7,20 mmol), Cs_2CO_3 (2,58 g, 7,20 mmol), yoduro potásico (0,20 g, 1,20 mmol) y (*R*)-(-)-2-(metoximetil)pirrolidina (1,07 ml, 8,60 mmol) en NMP (20 ml) se calentó a 75 ºC durante una noche. La mezcla de reacción se enfrió a temperatura ambiente, se concentró *al vacío*, y se inactivó añadiendo agua (30 ml). El producto en bruto se extrajo con acetato de etilo (30 x ml) y Los extractos orgánicos se secaron sobre Na_2SO_4, se filtraron y se concentraron *al vacío*. El compuesto se purificó por cromatografía en columna sobre gel de sílice Biotage®, eluyendo con diclorometano:metanol:amoniaco, 100:0:0 a 90:10:1 dando el compuesto del título en forma de un aceite pardo (1,39 g, 54%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,38 (d, 2H), 6,70 (d, 2H), 4,02 (t, 2H), 3,46-3,38

(m, 1H), 3,36-3,28 (m, 3H), 3,24-3,16 (m, 1H), 3,12-3,04 (m, 1H), 2,72-2,58 (m, 1H), 2,52-2,44 (m, 1H), 2,30-2,20 (m, 1H), 2,18-2,06 (m, 2H), 1,98 (quintuplete, 2H), 1,92-1,60 (m, 12H), 1,36-1,18 (m, 1H); EMAR (IEN$^+$) 357,2537 $(M+H)^+$.

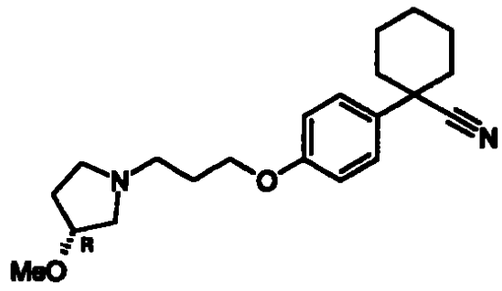
Ejemplo 113: 1-(4-[3-[(3S)-3-metoxipirrolidin-1-il]propoxi}fenil)ciclohexanocarbonitrilo



Una mezcla (1:3) de 1-[4-(3-bromo-propoxi)-fenil]-ciclohexanocarbonitrilo y 1-[4-(3-cloro-propoxi)-fenil]-ciclohexanocarbonitrilo (200 mg, 0,72 mmol), *N,N*-diisopropiletilamina (251 µl, 1,44 mmol) y (*S*)-3-metoxi-pirrolidina (198 mg, 1,96 mmol) en NMP (0,5 ml) se calentó a 160 °C en el microondas (Smith Personal Synthesiser) durante 400 segundos. La mezcla de reacción se inactivó con agua (10 ml) y se extrajo con diclorometano (2 x 10 ml), se secó sobre Na_2SO_4, se filtró y se concentró- *al vacío*. El compuesto se purificó por cromatografía en columna sobre gel de sílice Biotage®, eluyendo con diclorometano:metanol:amoniaco, 97:3:0,3 a 95:5:0,5. dando el producto en forma de un aceite transparente (102 mg, 41%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,36 (d, 2H), 6,90 (d, 2H), 4,02 (t, 2H), 3,96-3,88 (m, 1H), 3,28 (s, 3H), 2,86-2,52 (m, 6H), 2,18-1,96 (m, 5H), 1,88-1,66 (m, 8H), 1,38-1,16 (m, 1H); LCEM (APCI$^+$) 343 $(M+H)^+$.

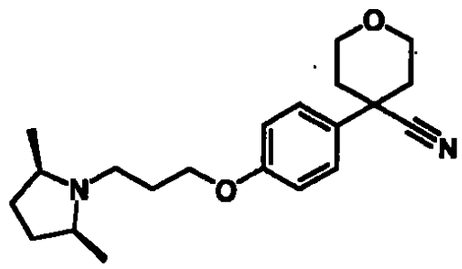
Ejemplo 114: 1-(4-[3-[(3*R*)-3-metoxipirrolidin-1-il]propoxi}fenil)ciclohexancoarbonitrilo



Una mezcla (1:3) de 1-[4-(3-bromo-propoxi)-fenil]-ciclohexanocarbonitrilo y 1-[4-(3-cloro-propoxi)-fenil]-ciclohexanocarbonitrilo (200 mg, 0,72 mmol), *N,N*-diisopropiletilamina (251 µl, 1,44 mmol) y (*R*)-3-metoxi-pirrolidina (198 mg, 1,44 mmol) en NMP (0,5 ml) se calentó a 160 °C en el microondas (Smith Personal Synthesiser) durante 600 segundos. La mezcla de reacción se inactivó con agua (30 ml) y se extrajo con acetato de etilo (2 x 30 ml), se secó sobre Na_2SO_4, se filtró y se concentró *al vacío*. El compuesto se purificó por cromatografía en columna sobre gel de sílice Biotage® eluyendo con diclorometano:metanol:amoniaco, 98:2:0,2 a 95:5:0,5 dando un aceite pardo (37 mg, 11 %).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,38 (d, 2H), 6,90 (d, 2H), 4,02 (t, 2H), 3,94-3,88 (m, 1H), 3,28 (s, 3H), 2,74-2,66 (m, 2H), 2,64-2,56 (m, 2H), 2,46 (quintuplete, 2H), 2,17-1,94 (m, 5H) 1,88-1,66 (m, 8H) 1,32-1,18 (m, 1H); EMAR (IEN$^+$) 343,2380 $(M+H)^+$.

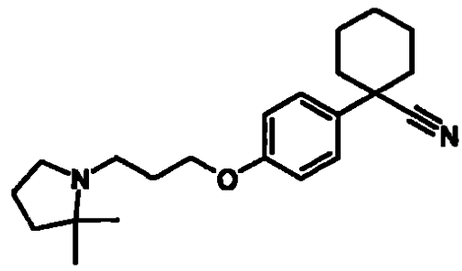
Ejemplo 115: 4-(4-{3-[(2*R*,5*S*)-2,5-dimetilpirrolidin-1-il]propoxi}-fenil)-tetrahidro-2*H*-piran-4-carbonitrilo



Una mezcla (1:3) de 1-[4-(3-bromo-propoxi)-fenil]-ciclohexanocarbonitrilo y 1-[4-(3-cloro-propoxi)-fenil]-ciclohexanocarbonitrilo (150 mg, 0,54 mmol), *N,N*-diisopropiletilamina (187 µl, 1,07 mmol) y (2*R*,5*S*)-2,5-dimetilpirrolidina (145 mg, 1,07 mmol) en NMP (0,5 ml) se calentó a 160°C en el microondas (Smith Personal Synthesiser) durante 400 segundos y después a 170 °C durante 600 segundos. La mezcla de reacción se inactivó con $NaHCO_3$ (15 ml) y se extrajo con acetato de etilo (2 x 15 ml), se secó sobre Na_2SO_4, se filtró y se concentró *al vacío*. El compuesto se purificó por cromatografía en columna sobre gel de sílice Biotage®, eluyendo con diclorometano:metanol:amoniaco, 97:3:0,3 a 90:10:1. Rendimiento = 28 %

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,36 (d, 2H), 6,92 (d, 2H), 4,10-4,04 (m, 2H), 4,00 (t, 2H), 3,88 (dt, 2H), 2,72 (t, 2H), 2,64-2,52 (m, 2H), 2,14-1,98 (m, 4H), 1,94 (quintuplete, 2H), 1,86-1,78 (m, 2H), 1,42-1,28 (m, 2H), 1,10 (d, 6H); EMAR (IEN$^+$) 343,2380 $(M+H)^+$.

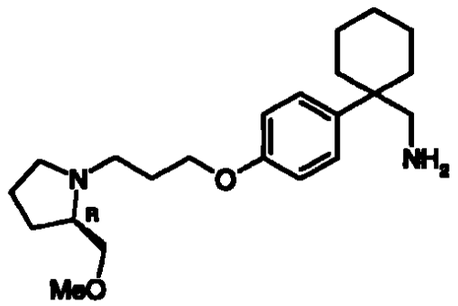
Ejemplo 116: 1-[4-[3-(2,2-dimetilpirrolidin-1-il)propoxi]fenil]-ciclohexanocarbonitrilo



Una mezcla (1:3) de 1-[4-(3-bromo-propoxi)-fenil]-ciclohexanocarbonitrilo y 1-[4-(3-cloro-propoxi)-fenil]-ciclohexanocarbonitrilo (150 mg, 0,54 mmol), *N,N*-diisopropiletilamina (188 µl, 1,08 mmol) y 2,2-dimetil-pirrolidina (131 mg, 1,08 mmol) en NMP (0,5 ml) se calentó a 180°C en el microondas (Smith Personal Synthesiser) durante 600 segundos. La mezcla de reacción se inactivó con agua (15 ml) y se extrajo con acetato de etilo (2 x 15 ml), se secó sobre Na_2SO_4, se filtró y se concentró *al vacío*. El compuesto se purificó por cromatografía en columna sobre gel de sílice Biotage®, eluyendo con diclorometano:metanol:amoniaco, 98:2:0,2 a 95:5:0,5 dando el compuesto del título en forma de un aceite pardo (31 mg, 17 %).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,38 (d, 2H), 6,90 (d, 2H), 4,04 (t, 2H), 2,78 (t, 2H), 2,54 (t, 2H), 2,16-2,12 (m, 2H), 1,94 (quintuplete, 2H), 1,90-1,64 (m, 11H), 1,20-1,34 (m, 1H), 0,98 (s, 6H); EMAR (IEN$^+$) 341,2588 $(M+H)^+$.

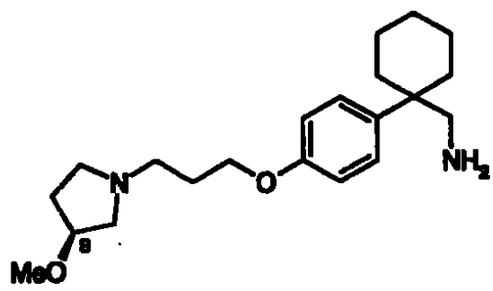
Ejemplo 117: 1-[1-(4-{3-[(2*R*)-2-(metoximetil)pirrolidin-1-il]propoxi}-fenil)ciclohexil]metanamina



A una suspensión agitada de $LiAlH_4$ (1,0 M en éter dietílico, 13,7 ml, 13,7 mmol) a 0ºC en una atmósfera de nitrógeno se le añadió 1-(4-{3-[(2*R*)-2-(metoximetil)pirrolidin-1-il]propoxi}fenil)ciclohexanocarbonitrilo (0,980 g, 2,7 mmol) en Et_2O (15 ml) durante 15 minutos manteniendo la temperatura entre 5 y 10ºC. La mezcla de reacción se dejó calentar a temperatura ambiente durante 20 minutos y después se calentó a reflujo durante 30 minutos hasta que se completó. La mezcla de reacción se enfrió a 0ºC, agua (0,5 ml) se añadió seguido de NaOH (2,0 M, 1,5 ml) y agua (0,5 ml). Se añadió acetato de etilo (5 ml) y la mezcla se filtró a través de una capa de celite, eluyendo con acetato de etilo (2 x 15 ml). Los lavados orgánicos se secaron sobre Na_2SO_4 y se concentraron al vacío. El compuesto se purificó por cromatografía en columna sobre gel de sílice Biotage®, eluyendo con diclorometano:metanol:amoniaco, 98:2:0,2 a 95:5:0,5 dando el compuesto del título en forma de un aceite transparente (309 mg, 32 %).

^1H RMN (400 MHz, $CDCl_3$) δ 7,22 (d, 2H), 6,88 (d, 2H), 4,04-3,96 (m, 2H), 3,32 (m, 3H), 3,26-3,20 (m, 1H), 3,14-3,04 (m, 1H), 2,74-2,62 (m, 1H), 2,60 (s, 2H), 2,56-2,46 (m, 1H), 2,28 (cuadruplete, 1H), 2,12-1,98 (m, 4H), 1,96-1,90 (m, 1H), 1,82-1,70 (m, 2H), 1,68-1,46 (m, 8H), 1,36-1,30 (m, 3H); EMAR (IEN$^+$) 361,2850 $(M+H)^+$.

Ejemplo 118: {[1-(4-{3-[(3S)-3-metoxipirrolidin-1-il]propoxi}-fenil)-ciclohexil]metil}amina.



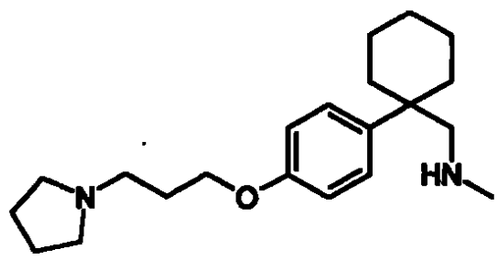
A una suspensión agitada de $LiAlH_4$ (1,0 M en éter dietílico, 1,46 ml, 1,46 mmol) a 0°C en una atmósfera de nitrógeno se añadió una solución de 1-(4-{3-[(3*S*)-3-metoxipirrolidin-1-il]propoxi}fenil)ciclohexanocarbonitrilo (0,10 g, 0,29 mmol) en Et_2O (2 ml) durante 15 minutos manteniendo la temperatura entre 5 y 10°C. La mezcla de reacción se dejó calentar a temperatura ambiente durante 20 minutos después se calentó a reflujo durante 30 minutos hasta que se completó. La mezcla de reacción se enfrió a 0°C, se añadió gota a gota agua (0,5 ml) seguido de hidróxido sódico (2,0 M, 1,5 ml) y agua (0,5 ml). Se añadió acetato de etilo (5 ml) y la mezcla se filtró a través de un capa de celite, eluyendo con acetato de etilo (2 x 15 ml). Los lavados orgánicos se secaron sobre Na_2SO_4 y se concentraron al vacío. El compuesto se purificó por cromatografía en columna sobre gel de sílice Biotage®, eluyendo con diclorometano:metanol:amoniaco, 97:3:0,3 a 90:10:1 dando el compuesto del título en forma de un aceite transparente (75 mg, 75 %).

^1H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,86 (d, 2H), 4,02 (t, 2H), 3,94-3,88 (m, 1H), 3,28 (s, 3H), 2,76-2,68 (m, 2H), 2,58-2,66 (m, 3H), 2,45-2,52 (m, 1H), 2,12-2,04 (m, 3H), 1,98 (quintuplete, 2H), 1,84-1,74 (m, 1H), 1,56-1,44 (m, 5H), 1,38-1,30 (m, 3H), 1,16-1,25 (m, 2H);

EMAR (IEN$^+$) 347,2693 $(M+H)^+$.

Ejemplo 119: *N*-metil-1-[1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclo-

hexil}metanamina



A una solución agitada de ((1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil}metil)amina (0,60 g, 1,90 mmol) y *N,N*-diisopropiletilamina (330 µl, 1,90 mmol) en diclorometano anhidro (6 ml) a 0ºC se le añadió gota a gota una solución de di-*terc*-butildicarbonato (455 mg, 2,09 mmol) en diclorometano anhidro (4 ml). La reacción se dejó calentar a temperatura ambiente y se agitó durante 2 horas más. La mezcla de reacción se concentró al vacío, se dividió entre $NaHCO_3$ (20 ml) y diclorometano (20 ml) y se extrajo con 20 ml más de diclorometano. La fase orgánicas se combinaron, se secaron sobre Na_2SO_4 y se concentraron a presión reducida proporcionando el producto en bruto. El compuesto se purificó por cromatografía en columna sobre gel de sílice, eluyendo con DCM/MeOH/NH_3 (95:5:0,5) dando ({1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil)metil)-carbamato de terc-butilo en forma de un aceite transparente (642 mg, 81 %).

^{1}H RMN complicada por presencia de rotámeros.

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,24 (d, 2H), 6,90 (d, 2H), 4,12 (sa, 1H), 4,02 (t, 2H), 3,24-3,06 (m, 2H), 2,66 (t, 2H) 2,56-2,46 (m, 4H), 2,08-1,94 (m, 4H), 1,84-1,72 (m, 4H), 1,62-1,54 (m, 4H), 1,48-1,28 (m, 13H)

LCEM (IEN$^+$) 417 $(M+H)^+$ 439 $(M+Na)^+$.

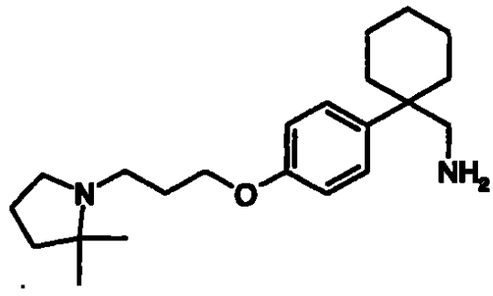
Etapa 2:

Una solución de ({1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil}metil)-

carbamato de terc-butilo (600 mg, 1,44 mmol) en Et_2O (5 ml) se le añadió gota a gota a una solución agitada de $LiAlH_4$ (solución 1,0 M en Et_2O, 4,32 ml, 4,32 mmol) a 0ºC. Se añadió THF (5 ml) y la mezcla de reacción se calentó a reflujo durante una noche. La mezcla de reacción se enfrió a 0ºC se inactivó con agua (0,5 ml), NaOH acuoso (2,0 M, 0,5 ml) y agua (0,5 ml). Se añadieron diclorometano y acetato de etilo y la mezcla se filtró sobre una capa de celite y se concentró al vacío. El compuesto se purificó por cromatografía en columna sobre gel de sílice Biotage®, eluyendo con diclorometano:metanol:amoniaco, 96:4:0,4 a 90:10:1 dando el compuesto del título en forma de un aceite transparente (230 mg, 48 %).

^1H RMN (400 MHz, $CDCl_3$) δ 7,16 (d, 2H), 6,88 (d, 2H), 4,02 (t, 2H), 2,64 (t, 2H) 2,54 (s, 2H), 2,50-2,58 (m, 4H), 2,26 (s, 3H), 2,14-2,08 (m, 2H), 1,98 (quintuplete, 2H), 1,84-1,76 (m, 4H), 1,68-1,56 (m, 2H), 1,52-1,32 (m, 6H); EMAR (IEN$^+$) 331,2744 $(M+H)^+$.

Ejemplo 120: [(1-{4-[3-(2,2-dimetilpirrolidin-1-il)propoxi]fenil}-ciclohexil)metil]amina

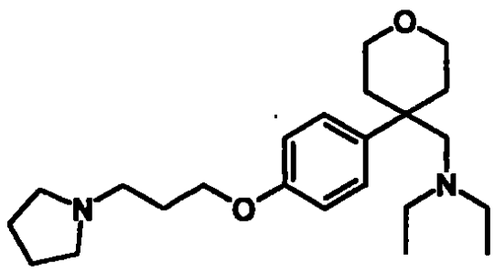


A una suspensión agitada de $LiAlH_4$ (1,0 M en éter dietílico, 0,4 ml, 0,40 mmol) a 0ºC en una atmósfera de nitrógeno se le añadió 1-{4-[3-(2,2-dimetilpirrolidin-1-il)propoxi]fenil}ciclohexanocarbonitrilo (27 mg, 0,079 mmol) en Et_2O (15 ml) durante 15 minutos manteniendo la temperatura a 5 a 10ºC. La

mezcla de reacción se dejó calentar a temperatura ambiente durante 20 minutos después se calentó a reflujo durante 30 minutos hasta que se completa. La mezcla de reacción se enfrió a 0ºC, se añadió agua (0,5 ml) seguido de NaOH (2,0 M, 1,5 ml) y agua (0,5 ml). Se añadió acetato de etilo (5 ml) y la mezcla se filtró a través de una capa corta de celite, eluyendo con acetato de etilo (2 x 15 ml) y se concentró *al vacío*. El compuesto se purificó por cromatografía en columna sobre gel de sílice Biotage®, eluyendo con diclorometano:metanol:amoniaco, 97:3:0,3 dando el compuesto del título en forma de un aceite transparente (10 mg, 37 %).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,22 (d, 2H), 6,84 (d, 2H), 4,02 (t, 2H), 2,86-2,76 (m, 2H), 2,66 (s, 2H), 2,58-2,50 (m, 2H), 2,16-2,06 (m, 2H), 2,00-2,90 (m, 2H), 1,84-1,72 (m, 2H), 1,70-1,64 (m, 2H), 1,56-1,46 (m, 4H), 1,40-1,32 (m, 4H), 1,02 (s, 6H). EMAR (IEN$^+$) 345,2901 $(M+H)^+$.

Ejemplo 121: N-etil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)etanamina



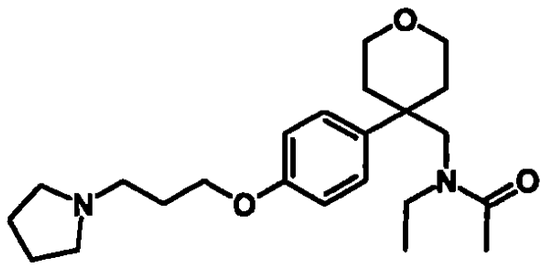
Una solución de *N*-etil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)acetamida (119 mg, 0,307 mmol) en tetrahidrofurano (1 ml) se añadió gota a gota a 0ºC a una solución de $LiAlH_4$ (1,0 M en dietiléter, 0,614 ml, 0,614 mmol) en una atmósfera de nitrógeno. La mezcla de reacción se dejó calentar a temperatura ambiente durante una noche. La mezcla de reacción se

A280
479

enfrió a 0°C, después se añadió gota a gota agua (0,5 ml) seguido de hidróxido sódico (2,0 M, 0,5 ml) y agua (0,5 ml) otra vez. El sólido resultante se filtró sobre una pequeña capa de celite, se lavó con DCM (100 ml) y se concentró al vacío. El compuesto se purificó por cromatografía en columna sobre gel de sílice Biotage®, eluyendo con diclorometano:metanol:amoniaco, 94,5:5,5:0,55 a 91:9:0,9 dando el compuesto del título en forma de un aceite amarillo pálido (61 mg, 53%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,18 (d, 2H), 6,86 (d, 2H), 4,02 (t, 2H), 3,70-3,78 (m, 2H), 3,48 (dt, 2H), 2,64 (t, 2H), 2,58-2,46 (m, 4H), 2,38 (s, 2H), 2,20 (cuadruplete, 4H), 2,13-1,96 (m, 4H), 1,92-1,86 (m, 2H), 1,82-1,78 (m, 4H), 0,82 (t, 6H); EMAR (IEN$^+$) 375,3006 $(M+H)^+$.

Ejemplo 122: *N*-etil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)acetamida



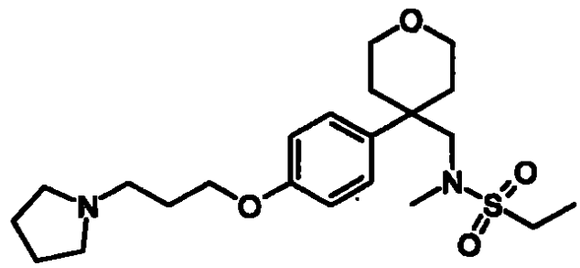
Se añadió gota a gota cloruro de acetilo (14 µl, 0,20 mmol) a una solución de *N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)etanamina (70 mg, 0,20 mmol) y trietilamina (28 µl, 0,20 mmol) en THF (0,50 ml) a 0°C y la reacción se agitó durante 2 horas. La reacción se inactivó usando $NaHCO_3$ (10 ml), se extrajo con diclorometano (3 x 10 ml) y los extractos orgánicos se secaron sobre Na_2SO_4, se filtraron y se concentraron *al vacío*. El compuesto se purificó por cromatografía en columna sobre sílice,

eluyendo con DCM/MeOH/NH_3 (95:5:0,5) proporcionando el compuesto del título en forma de un aceite transparente (33 mg, 42 %).

^{1}H RMN complicada por presencia de rotámeros.

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20-7,12 (m, 2H), 6,92-6,86 (m, 2H), 4,06-4,00 (m, 2H), 3,88-3,76 (m, 2H), 2,56-2,48 (m, 2H), 3,42 (s, 2H), 2,66 (t, 2H), 2,58-2,52 (m, 4H), 2,48 (cuadruplete, 2H), 2,08 (s, 3H), 2,06-1,92 (m, 6H), 1,84-1,76 (m, 4H), 0,98 (t, 0,6 H) 0,86 (t, 2,4H). EMAR (IEN$^+$) 389,2799 $(M+H)^+$.

Ejemplo 123: *N*-metil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]-tetrahidro-2*H*-piran-4-il}metil)etanosulfonamida

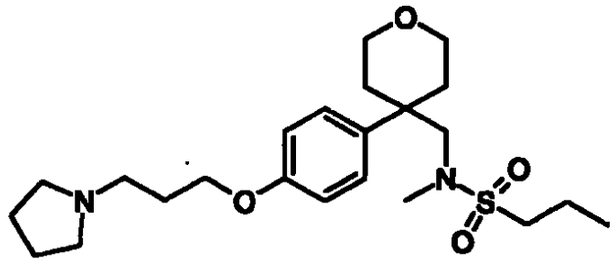


Se añadió gota a gota cloruro de etanosulfonilo (43 µl, 0,456 mmol) a una solución de trietilamina (58 µl, 0,418 mmol) y *N*-metil-1-(1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil)metanamina (125 mg, 0,38 mmol) en diclorometano (1 ml) a 0ºC y la reacción se agitó durante 30 minutos. La reacción se inactivó con $NaHCO_3$ (20 ml), se extrajo usando diclorometano (3 x 10 ml), se secó usando Na_2SO_4 y se concentró *al vacío*. El compuesto se purificó por cromatografía en columna sobre gel de sílice Biotage®, eluyendo con diclorometano:metanol:amoniaco, 98:2:0,2 a 96:4:0,4 dando el compuesto del título en forma de un aceite pardo pálido (152 mg, 94%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,24 (d, 2H), 6,90 (d, 2H), 4,04 (t, 2H), 3,84-3,76 (m, 2H), 2,56-2,50 (m, 2H), 3,26 (s, 2H), 2,88 (cuadruplete, 2H), 2,68 (t, 2H),

2,60-2,52 (m, 4H), 2,22 (s, 3H), 2,30-2,12 (m, 2H), 2,02 (quintuplete, 2H), 1,98-1,90 (m, 2H), 1,86-1,78 (m, 4H) 1,34 (t, 3H); EMAR (IEN$^+$) 425,2469 $(M+H)^+$.

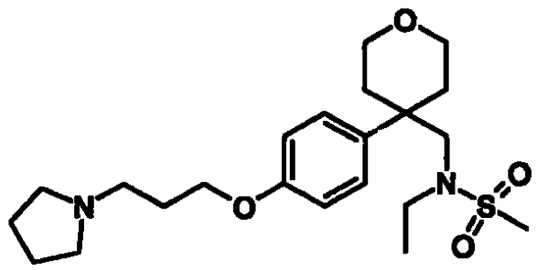
Ejemplo 124: *N*-metil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]-tetrahidro-2*H*-piran-4-il}metil)propano-1-sulfonamida



Se añadió gota a gota cloruro de *n*-propilsulfonilo (33 µl, 0,289 mmol) a una solución de trietilamina (37 µl, 0,265 mmol) y *N*-metil-1-{1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil}metanamina (80 mg, 0,24 mmol) en diclorometano (1 ml) a 0°C y la reacción se agitó durante 1 hora. La reacción se inactivó con $NaHCO_3$ (20 ml), se extrajo usando diclorometano (3 x 15 ml), se secó usando Na_2SO_4 y se concentró *al vacío*. El compuesto se purificó por cromatografía en columna sobre gel de sílice Biotage®, eluyendo con diclorometano:metanol:amoniaco, 98:2:0,2 a 92:8:0,8 dando el compuesto del título en forma de un aceite pardo pálido (62 mg, 59%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,22 (d, 2H), 6,90 (d, 2H), 4,02 (t, 2H), 3,82-3,74 (m, 2H), 3,50 (dt, 2H), 3,20 (s, 2H), 2,74 (dt, 2H), 2,64 (t, 2H), 2,56-2,48 (m, 4H), 2,20 (s, 3H), 2,18-2,12 (m, 2H), 2,02 (quintuplete, 2H), 1,98-1,84 (m, 2H), 1,82-1,68 (m, 6H) 1,00 (t, 3H); EMAR (IEN$^+$) 439,2625 $(M+H)^+$.

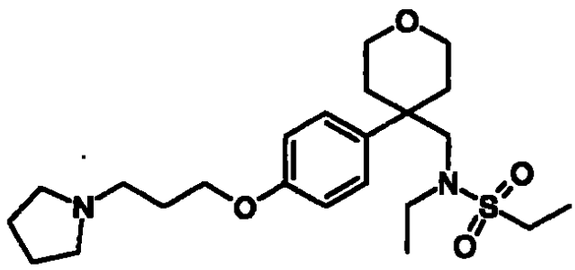
Ejemplo 125: *N*-etil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)metanosulfonamida



Se añadió gota a gota cloruro de metanosulfonilo (19 µl, 0,24 mmol) a una solución de trietilamina (31 µl, 0,22 mmol) y *N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)etanamina (70 mg, 0,20 mmol) en diclorometano (0,5 ml) a 0ºC y después se dejó calentar a temperatura ambiente y se agitó durante una noche. La reacción se inactivó con $NaHCO_3$ (10 ml), se extrajo usando diclorometano (3 x 15 ml), se secó usando Na_2SO_4 y se concentró *al vacío*. El compuesto se purificó por cromatografía en columna sobre gel de sílice Biotage®, eluyendo con diclorometano:metanol:amoniaco, 96,5:3,5:0,35 a 95:5:0,5 dando el compuesto del título en forma de un aceite pardo pálido (60 mg, 71%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,24 (d, 2H), 6,90 (d, 2H), 4,02 (t, 2H), 3,84-3,72 (m, 2H), 3,50 (dt, 2H), 3,28 (s, 2H), 2,72-2,60 (m, 7H), 2,58-2,52 (m, 4H), 2,16 (m, 2H), 2,04 (quintuplete, 2H), 1,96-1,90 (m, 2H), 1,84-1,76 (m, 4H), 0,90 (t, 3H); EMAR (IEN$^+$) 425,2469 $(M+H)^+$.

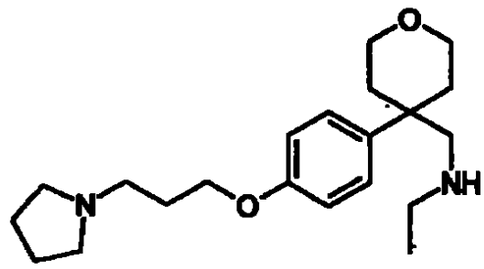
Ejemplo 126: *N*-etil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)etanosulfonamida



Se añadió gota a gota cloruro de etanosulfonilo (26 µl, 0,28 mmol) a una solución de trietilamina (35 µl, 0,25 mmol) y *N*-((4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il)metil)etanamina (78 mg, 0,23 mmol) en diclorometano (0,5 ml) a 0ºC que se dejó calentar a temperatura ambiente y se agitó durante una noche. La reacción se inactivó con $NaHCO_3$ (10 ml), se extrajo usando diclorometano (3 x 10 ml), se secó usando Na_2SO_4 y se concentró *al vacío*. El compuesto se purificó por cromatografía en columna sobre gel de sílice Biotage®, eluyendo con diclorometano:metanol:amoniaco, 96,5:3,5:0,35 a 95:5:0,5 dando el compuesto del título en forma de un aceite pardo pálido (55 mg, 54%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,24 (d, 2H), 6,90 (d, 2H), 4,02 (t, 2H), 3,84-3,72 (m, 2H), 3,48 (t, 2H), 3,32 (s, 2H), 2,76 (cuadruplete, 2H), 2,72-2,60 (m, 4H), 2,60-2,48 (m, 4H), 2,20-2,08 (m, 2H), 2,04 (quintuplete, 2H), 1,98-1,90 (m, 2H), 1,86-1,76 (m, 4H), 1,30 (t, 3H), 0,88 (t, 3H). EMAR (IEN$^+$) 439,2625 $(M+H)^+$.

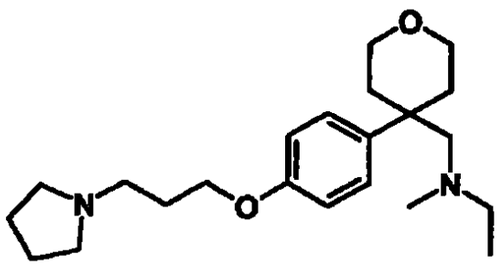
Ejemplo 127: *N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)etanamina



Se añadió gota a gota $LiAlH_4$ (1,0 M en dietiléter, 4,72 ml, 4,72 mmol) a 0ºC a una solución de *N*-[4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil]-acetamida (848 mg, 2,36 mmol) en tetrahidrofurano (2 ml) en una atmósfera de nitrógeno. La mezcla de reacción se dejó calentar a temperatura ambiente durante 2 horas y después se trató a 50ºC durante 10 horas. La mezcla de reacción se enfrió a 0ºC, se añadió gota a gota agua (3 ml) seguido de hidróxido sódico (2,0 M, 6 ml) y agua (3 ml). El sólido resultante se filtró sobre una pequeña capa de celite, se lavó con Et_2O/DCM (1:1 6 x 50 ml) y se concentró *al vacío* dando el compuesto del título en forma de un sólido amarillo pálido (635 mg, 78 %).

^1H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,88 (d, 2H), 4,02 (t, 2H), 3,80-3,68 (m, 2H), 3,55 (dt, 2H), 2,68 (s, 2H), 2,60 (t, 2H), 2,58-2,42 (m, 6H), 2,18-2,08 (m, 2H), 2,00 (quintuplete, 2H) 1,94-1,86 (m, 2H), 1,84-1,76 (m, 4H), 1,92 (t, 3H). EMAR (IEN$^+$) 347,2693 $(M+H)^+$.

Ejemplo 128: *N*-metil-*N*-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il]metil)etanamina



Una solución de $LiAlH_4$ (1,0 M en dietiléter, 1,20 ml, 0,60 mmol) se añadió gota a gota a 0°C a una solución de *N*-metil-*N*-[4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil]-acetamida (220 mg, 0,60 mmol) en tetrahidrofurano (1 ml) en una atmósfera de nitrógeno. La mezcla de reacción se dejó calentar a temperatura ambiente durante una noche. La mezcla de reacción se enfrió a 0°C, se añadió gota a gota agua (1 ml) seguido de hidróxido sódico (2,0 M, 3 ml) y agua (1 ml). El sólido resultante se filtró sobre una pequeña capa de celite, se lavó con DCM (150 ml) y se concentró *al vacío*. El compuesto se purificó por cromatografía en columna sobre gel de sílice Biotage®, eluyendo con diclorometano:metanol:amoniaco, 97,5:2,5:0,25 a 95,5:4,5:0,45 dando el compuesto del título en forma de un aceite amarillo pálido (114 mg, 88%).

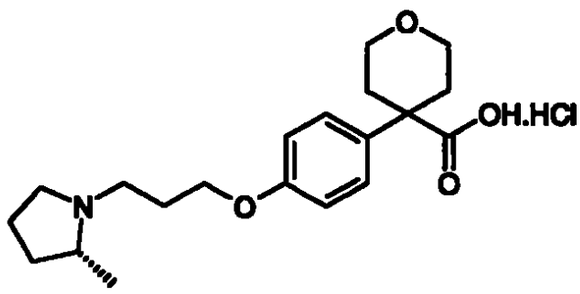
^{1}H RMN (400 MHz, $CDCl_3$) δ 7,18 (d, 2H), 6,86 (d, 2H), 4,04 (t, 2H), 3,78-3,70 (m, 2H), 3,52 (dt, 2H), 2,66 (t, 2H), 2,52-2,66 (m, 4H), 2,38 (s, 2H), 2,18 (cuadruplete, 2H), 2,00-2,12 (m, 4H), 1,92-1,86 (m, 5H), 1,82-1,76 (m, 4H), 0,86 (t, 3H); EMAR (IEN$^+$) 361,2850 $(M+H)^+$.

Intermedio 47: 4-(4-[3-[(2*S*)-2-metilpirrolidinil]propoxi]fenil)-tetrahidro-2*H*-piran-4-carbonitrilo

Una solución de 4-(4-hidroxi-fenil)-tetrahidro-piran-4-carbonitrilo (203 mg, 1,0 mmol) y tri-*n*-butilfosfina (299 µl, 1,20 mmol) en tolueno (6 ml) se añadió a

una solución de 3-[(2*R*)-2-metilpirrolidin-1-il]propan-1-ol (172 mg, 1,20 mmol) en tolueno (6 ml) y tetrahidrofurano (2 ml) a temperatura ambiente. Se añadió 1'1-azobis(*N*,*N*-dimetilformamida) (206 mg, 1,20 mmol) y la reacción se calentó a 85ºC durante una noche. La mezcla de reacción se concentró *al vacío* seguido de adición de diclorometano (30 ml). La solución orgánica se lavó con NaOH (2,0 M, 2 x 20 ml), se secó con Na_2SO_4 y se concentró *al vacío*. El compuesto se purificó por cromatografía en columna sobre gel de sílice Biotage®, eluyendo con diclorometano:metanol:amoniaco, 98:2:0,2 a 96:4:0,4 dando el compuesto del título en forma de un aceite amarillo pálido (70 mg, 21%). EMAR (IEN$^+$) 329,2224 $(M+H)^+$.

Ejemplo 129: Ácido 4-(4-{3-[(2R)-2-metilpirrolidin-1-il]propoxi}fenil)-tetra-hidro-2*H*-piran-4-carboxílico



Una solución de 4-(4-{3-[(2*S*)-2-metilpirrolidinil]propoxi}fenil)tetrahidro-2*H*-piran-4-carbonitrilo (70 mg, 0,21 mmol) en ácido clorhídrico concentrado (1 ml) se calentó a reflujo durante 3 días. Se añadieron 2 ml más de ácido clorhídrico concentrado y la reacción se calentó a reflujo durante 2 días más. La solución se evaporó a sequedad *al vacío*, se trituró usando acetona y formó un azeótropo con tolueno dando un sólido pardo pálido (51 mg, 73 %).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,36 (d, 2H), 6,94 (d, 2H), 4,12 (t, 2H), 3,92-3,84 (m, 2H), 3,76-3,46 (m, 6H), 2,54-2,44 (m, 2H), 2,20-2,02 (m, 1H), (m, 8H), (m,

A36
435

3H); EMAR (IEN$^+$) 348,2170 $(M+H)^+$.

Intermedio 48: 4-[4-(4-cianotetrahidro-2*H*-piran-4-il)fenoxi]-1-piperidincarboxilato de *terc*-butilo

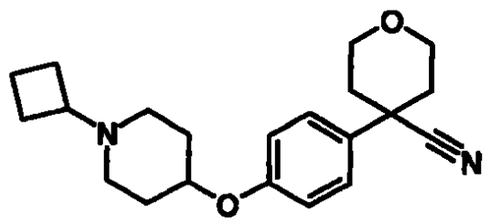
4-[(metilsulfonil)oxi]-1-piperidincarboxilato de *terc*-butilo (1,35 g, 4,93 mmol), 4-(4-hidroxifenil)tetrahidro-2*H*-piran-4-carbonitrilo (1,00 g, 4,93 mmol) y carbonato potásico (1,36 g, 9,85 mmol) se agitaron en 10 ml de DMF a 56ºC durante 28 horas. La mezcla de reacción se dividió entre acetato de etilo (50 ml) y agua (50 ml). El acetato de etilo se secó sobre Na_2SO_4 y se concentró a presión reducida. Después, el producto en bruto se purificó por cromatografía en columna sobre gel de sílice eluyendo con dietilamina al 2% en acetato de etilo. Esto solo produjo una separación pobre, de forma que el material impuro se trituró con diisopropiléter (20 ml) dando un polvo blanco (1,5 g). Este sólido se disolvió en dietiléter (100 ml) y se lavó con NaOH 2 M (50 ml) y después con agua (50 ml). El dietiléter se secó sobre Na_2SO_4 y se evaporó dando 4-[4-(4-cianotetrahidro-2*H*-piran-4-il)fenoxi]-1-piperidinacarboxilato de *terc*-butilo en forma de cristales blancos (740 mg, 39%).

Intermedio 49: 4-[4-(4-piperidiniloxi)fenil]tetrahidro-2*H*-piran-4-carbonitrilo

Se disolvió 4-[4-(4-cianotetrahidro-2*H*-piran-4-il)fenoxi]-1-piperidinacarboxilato de *terc*-butilo (720 mg) en diclorometano (50 ml) a 0ºC. Se añadió TFA (10 ml) y la mezcla se agitó calentando a temperatura ambiente durante 2 horas. La mezcla de reacción se concentró *al vacío* y se dividió entre diclorometano (80 ml) y NaOH 0,5 M (50 ml). La solución de diclorometano se secó sobre Na_2SO_4 y se evaporó dando 4-[4-(4-piperidiniloxi)fenil]tetrahidro-2*H*-piran-4-carbonitrilo en forma de aceite incoloro que cristalizó en reposo (500 mg, 94%).

427
436

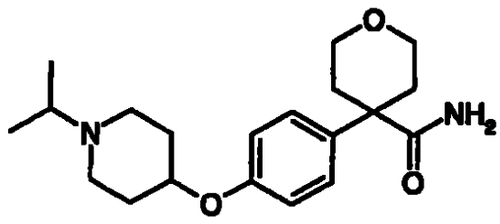
Ejemplo 130: 4-[4-[(1-ciclobutil-4-piperidinil)oxi]fenil]tetrahidro-2*H*-piran-4-carbonitrilo



4-[4-(4-Piperidiniloxi)fenil]tetrahidro-2*H*-piran-4-carbonitrilo (130 mg, 0,45 mmol) y ciclobutanona (140 µl, 1,9 mmol) se agitó en THF (2 ml) y ácido acético (26 µl, 0,45 mmol) a temperatura ambiente durante 15 minutos. Se añadió triacetoxiborohidruro sódico (340 mg, 1,6 mmol) y la mezcla se agitó durante 18 horas. La reacción se inactivó añadiendo Na_2CO_3 acuoso al 10% (5 ml) y después se dividió entre acetato de etilo (50 ml) y agua (30 ml). Los extractos orgánicos se secaron sobre Na_2SO_4 y se evaporaron dando un sólido que se purificó por cromatografía en columna sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco, 98:2:0,2 a 94:6:0,6 dando el producto que se cristalizó en diisopropiléter (5 ml) dando 4-[4-[(1-ciclobutil-4-piperidinil)oxi]fenil]tetrahidro-2*H*-piran-4-carbonitrilo en forma de un polvo blanco (50 mg, 33%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,38 (d, 2H), 6,93 (d, 2H), 4,33 (m, 1H), 4,08 (m, 2H), 3,89 (m, 2H), 2,75 (quintuplete, 1H), 2,62 (m, 2H), 2,20-1,58 (m, 16H)

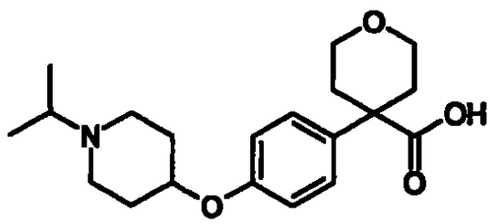
Ejemplo 131: 4-[4-[(1-isopropilpiperidin-4-il)oxi]fenil]tetrahidro-2*H*-piran-4-carboxamida



4-[4-(1-isopropilpiperidin-4-iloxi)fenil]tetrahidropiran-4-carbonitrilo (50 mg, 0,152 mmol) se combinó con complejo de trifluoruro de boro-ácido acético (500 µl, 3,6 mmol) y se agitó a temperatura ambiente durante 18 horas, seguido de 65°C durante 3 horas. La mezcla de reacción se dejó enfriar y después se basificó con una solución de $NaHCO_3$ saturado (15 ml). El producto se extrajo con diclorometano (2 x 35 ml). Los extractos orgánicos combinados se secaron usando Na_2SO_4, se filtraron y se concentraron *al vacío*. El compuesto se purificó por cromatografía en columna sobre gel de sílice (15 g), eluyendo con diclorometano:metanol:amoniaco, (96:4:0,4) a diclorometano:metanol:amoniaco, (90:10:1) dando el compuesto del título en forma de un sólido blanco (22 mg, 42%).

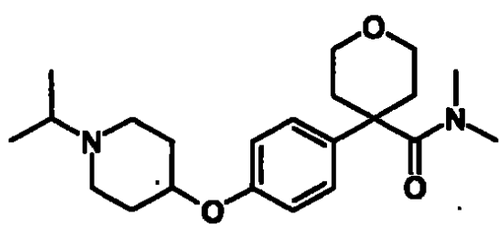
^{1}H RMN (400 MHz, CD_3OD) δ 7,3 (d, 2H), 6,9 (d, 2H), 4,4 (m, 1H), 3,8 (m, 2H), 3,65 (m, 2H), 2,78-2,85 (m, 3H), 2,5 (m, 2H), 2,4 (d, 2H), 1,95-2,08 (m, 4H), 1,8 (m, 2H), 1,1 (d, 6H)

Ejemplo 132: ácido 4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-carboxílico



Se combinó 4-[4-(1-isopropilpiperidin-4-iloxi)fenil]tetrahidropiran-4-carbonitrilo (1 g, 3 mmol) y ácido clorhídrico concentrado (10 ml) y se calentó a reflujo durante 44 horas. La mezcla de reacción se concentró *al vacío* y el sólido gris resultante se trituró con acetona (20 ml) dando un sólido de color crema. El compuesto se purificó usando una columna SCX de isoelución lavada con metanol (60 ml) *y* después con NH_3 2 M en metanol (150 ml). El compuesto del título se aisló en forma de sólido de color crema (550 mg, 52%).^{1}H RMN (400 MHz, CD_3OD) δ 7,4 (d, 2H), 6,9 (d, 2H), 4,4 (m, 1H), 3,85 (m, 2H), 3,65 (m, 2H), 3,4 (1H), 3,2 (m, 2H), 3,03 (m, 2H), 2,5 (m, 2H), 2,0- 1,8 (m, 6H), 1,3 (d, 6H)

Ejemplo 133: 4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}-*N,N*-dimetiltetrahidro-2*H*-piran-4-carboxamida



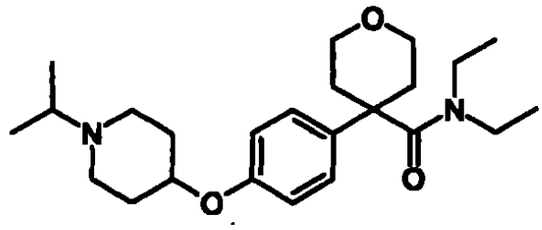
Se combinó ácido 4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-carboxílico (150 mg, 3,9 mmol), hexafluorofosfato de O-(1*H*-benzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (222 mg, 5,8 mmol), clorhidrato de dimetilamina (96 mg, 1,1 mmol), piridina (126 µl, 1,56 mmol) y se disolvió en dimetilformamida (2 ml). La mezcla de reacción se agitó a temperatura ambiente durante 18 horas. Se añadió más hexafluorofosfato de O-(1*H*-benzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (222 mg, 5,8 mmol) y clorhidrato de dimetilamina en etanol (33%) (500 µl) y la mezcla de reacción se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se diluyó con

440
439

agua (20 ml) y después se extrajo con acetato de etilo (2 x 40 ml). Los extractos orgánicos combinados se secaron usando Na_2SO_4, se filtraron y se concentraron *al vacío*. El compuesto se purificó por cromatografía en columna sobre gel de sílice, eluyendo con diclorometano:metanol:amoniaco (97:3:0,3) a diclorometano:metanol:amoniaco (90:10:1) dando un compuesto en forma de aceite transparente. Este aceite se disolvió en acetato de etilo (70 ml) y se lavó con una solución de $NaHCO_3$ saturado (2 x 10 ml). El extracto orgánica se secó usando Na_2SO_4, se filtró y se concentró al vacío dando el compuesto del título en forma de sólido cristalino transparente (72 mg, 50%).

^{1}H RMN (400 MHz, CD_3OD) δ 7,2 (d, 2H), 6,95 (d, 2H), 4,4 (m, 1H), 3,85 (m, 2H), 3,7 (m, 2H), 2,9-2,5 (m, 11 H), 2,28 (m, 2H), 2,0 (m, 4H), 1,8 (m, 2H), 1,1 (d, 6H)

Ejemplo 134: 4-[4-[(1-isopropilpiperidin-4-il)oxi]fenil]-*N,N*-dietiltetrahidro-2*H*-piran-4-carboxamida



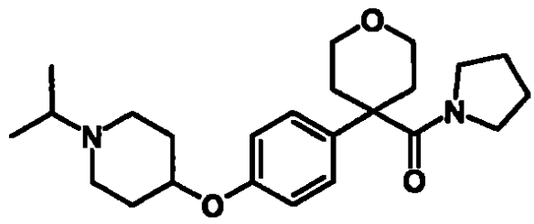
Se combinaron ácido 4-[4-[(1-isopropilpiperidin-4-il)oxi]fenil]tetrahidro-2*H*-piran-4-carboxílico (86 mg, 0,2 mol), dietilamina (27 µl, 0,26 mmol), hexafluorofosfato de O-(1*H*-benzotiazol-1-il)-*N,N,N',N'*-tetrametiluronio (108 mg, 0,29 mmol), piridina (53 µl, 0,66 mmol) y se disolvió en dimetilformamida (1,5 ml). La mezcla de reacción se agitó a 60°C durante 5 horas. Se añadió más dietilamina (500 µl). La mezcla de reacción se agitó a temperatura ambiente durante 60 horas. La mezcla de reacción se diluyó con agua (25 ml) y se

441
640

extrajo con acetato de etilo (2 x 35 ml). Los extractos orgánicos combinados se secaron usando Na_2SO_4, se filtraron y se concentraron *al vacío*. El compuesto se purificó por cromatografía en columna usando 15 g de gel de sílice, eluyendo con diclorometano:metanol:amoniaco (96:4:0,4) a diclorometano:metanol:amoniaco (90:10:1) dando el compuesto del título en forma de un aceite amarillo transparente (10 mg, 11%).

^{1}H RMN (400 MHz, CD_3OD) δ 7,2 (d, 2H), 6,95 (d, 21-1), 4,4 (m, 1H), 3,85-3,7 (m, 41-1), 3,3 (m, 21-1), 3,05-2,9 (m, 5H), 2,6 (m, 21-1), 2,25 (d, 2H), 2,0 (m, 41-11), 1,8 (m, 21-11), 1,1 (m, 9H), 0,63(m, 3H)

Ejemplo 135: 4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il]carbonil}pirrolidina



Se suspendió ácido 4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-carboxílico (93 mg, 0,27 mmol) en dimetilformamida (3 ml), se añadió hexafluorofosfato de O-(1*H*-benzotiazol-1-il)-*N,N,N',N'*-tetrametiluronio (203 mg, 0,53 mmol) y trietilamina (112 µl, 0,8 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora. Se añadió pirrolidina (300 µl) y la mezcla de reacción se agitó a temperatura ambiente durante 2,5 horas. La mezcla de reacción se concentró *al vacío*, después se dividió entre una solución de $NaHCO_3$ saturado (50 ml) y diclorometano (2 x 75 ml). Los extractos orgánicos combinados se secaron usando Na_2SO_4, se filtraron y se concentraron *al vacío*. El compuesto se purificó por cromatografía en columna usando 20 g de gel de

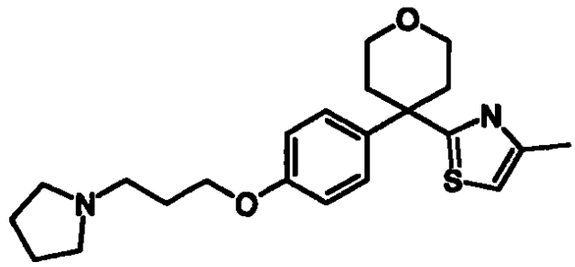
sílice, eluyendo con diclorometano:metanol:amoniaco (96:4:0,4) a diclorometano:metanol:amoniaco (94:6:0,6) dando el compuesto del título en forma de un aceite transparente (34 mg, 32%).

^{1}H RMN (400 MHz, CD_3OD) δ 7,2 (d, 21-1), 6,9 (d, 21-1), 4,4 (m, 1 H), 3,85-3,7 (m, 4H), 3,45 (m, 21-1), 2,95 (m, 21-1), 2,8-2,7 (m, 31-1), 2,5 (m, 2H), 2,3 (m, 21-1), 2,0 (m, 4H), 1,8-1,7 (m, 41-1), 1,6 (m, 21-11), 1,1 (d, 61-1).

Intermedio 50: 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbotioamida

Se combinó 4-[4-(3-pirrolidin-1-il-propoxi)-fenil)-tetrahidro-piran-4-carbonitrilo (2 g, 6,4 mmol), ditiofosfato de dietilo (15 ml, 8,9 mmol) y agua (1,5 ml) y se agitó a temperatura ambiente durante 5 horas, a 55 °C durante 2 horas y después a 70°C durante 2 horas. La mezcla de reacción se diluyó con diclorometano (100 ml) y se basificó a pH 8 con una solución saturada de $NaHCO_3$ en agua y $NaHCO_3$ sólido. Las fases se separaron y se usó más diclorometano (100 ml) para extraer el producto. Los extractos orgánicos combinados se secaron usando Na_2SO_4, se filtraron y se concentraron *al vacío* dejando un aceite amarillo. El compuesto se purificó con cromatografía en columna sobre 50 g de sílice, eluyendo con diclorometano:metanol:amoniaco (96:4:0,4) a diclorometano:metanol:amoniaco (90:10:1) dando un aceite transparente. El aceite transparente se disolvió en acetato de etilo (150 ml) y se lavó con una solución de Na_2CO_3 al 10%. La fase orgánica se secó usando Na_2SO_4, se filtró y se concentró *al vacío* dando el compuesto del título en forma de un sólido blanco (0,61 g, 28%).

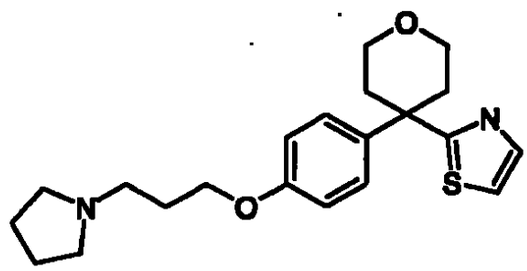
Ejemplo 136: 4-metil-2-[4-(4-(3-pirrolidin-1-ilpropoxi)fenil)tetrahidro-2*H*-piran-4-il]-1,3-tiazol



Se combinó 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbotioamida (100 mg, 0,29 mmol), cloroacetona (46 µl, 0,57 mmol) y etanol (5 ml) y se calentó a reflujo durante 18 horas. La mezcla de reacción se concentró *al vacío* dando un sólido de color crema. Esto se disolvió en diclorometano (100 ml) y se lavó con una solución de $NaHCO_3$ saturado (50 ml). El extracto orgánico se secó usando Na_2SO_4, se filtró y se concentró *al vacío*. El compuesto se purificó por cromatografía en columna usando 15 g de gel de sílice, eluyendo con diclorometano:metanol:amoniaco (97:3:0,3) a diclorometano:metanol:amoniaco (94:6:0,6) dando el compuesto del título en forma de un sólido blanco (68 mg, 61 %).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,3 (d, 21-1), 6,9 (d, 211), 6,75 (s, 1H), 4,0 (t, 2H), 3,83 (m, 2H), 3,7 (m, 211), 2,75-2,58 (m, 8H), 2,4 (s, 3H), 2,35 (m, 2H), 2,03 (m, 2H), 1,8 (m, 4H)

Ejemplo 137: 2-[4-(4-(3-pirrolidin-1-ilpropoxi)fenil)tetrahidro-2*H*-piran-4-il]-1,3-tiazol



Se combinó 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbotioamida (150 mg, 0,43 mmol), bromoacetaldehído dietilacetal (67 µl, 0,43 mmol), ácido clorhídrico concentrado (5 gotas) y etanol y se calentó a reflujo durante 5 horas. La mezcla de reacción se concentró *al vacío* y se dividió entre Na_2CO_3 al 10% (20 ml) y diclorometano (2 x 35 ml). Los extractos orgánicos combinados se secaron usando Na_2SO_4, se filtraron y se concentraron *al vacío*. El compuesto se purificó usando cromatografía en columna usando 15 g de gel de sílice, eluyendo con diclorometano:metanol:amoniaco (95:5:0,5) dando un sólido de color crema. Esto se trituró con 3 ml de éter dietílico dando el compuesto del título en forma de un sólido de color crema (25 mg, 16%).

^{1}H RMN (400 MHz, CD_3OD) δ 7,7 (s, 1 H), 7,45 (s, 1 H), 7,3 (d, 2H), 6,9 (d, 2H), 4,0 (t, 2H), 3,8 (m, 2H), 3,7 (m, 2H), 2,85-2,75 (m, 6H), 2,6 (m, 2H), 2,4 (m, 2H), 2,03 (m, 2H), 1,9 (m, 4H)

Intermedio 51: (4-[4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metilamina

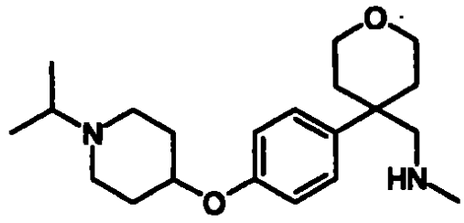
A una solución agitada 4-[4-(1-isopropilpiperidin-4-iloxi)fenil]tetrahidropiran-4-carbonitrilo (2,5 g, 7,62 mmol) en éter dietílico anhidro (15 ml) a 0ºC se le añadió gota a gota una solución de LiAlH4 (solución 1,0 M en Et_2O, 22,87 ml, 22,9 mmol). La reacción se agitó a 0ºC durante 30 minutos, después se calentó a temperatura ambiente durante una noche en una atmósfera de nitrógeno hasta que se completó. La reacción se enfrió a 0ºC, se le añadió agua (0,9 ml) gota a gota seguido de hidróxido sódico (2,0 M, 0,9 ml) y agua (2,7 ml). Se añadieron diclorometano (25 ml) y metanol (1 ml) y la mezcla se filtró a través de una capa corta de arbocel, eluyendo con metanol al 2% en diclorometano (200 ml). Los lavados orgánicos se secaron sobre

Na_2SO_4 y se concentraron *al vacío* dando el compuesto del título en forma de un aceite naranja (2,59 g, 100%).

Intermedio 52: (4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metilcarbamato de *terc*-butilo

A una solución agitada de (4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metilamina (600 mg, 1,81 mmol) y trietilamina (578 0,5.42 mmol) en diclorometano (2,5 ml) a 0ºC, se le añadió gota a gota una solución de di-*terc*-butildicarbonato (540 µl, 2,35 mmol) en diclorometano (2,5 ml). La solución se agitó a 0ºC durante 2 horas y después se dejó calentar hasta temperatura ambiente y se agitó hasta que se completó la reacción. La mezcla de reacción se diluyó con diclorometano (10 ml), se lavó con agua (3 x 10 ml) y después con salmuera (2 x 10 ml). Los lavados orgánicos se secaron sobre Na_2SO_4 y se concentraron *al vacío*. El compuesto se purificó por cromatografía en columna sobre gel de sílice, eluyendo con diclorometano:metanol:amoniaco, 100:0:0 a 96:4:0:0,4 dando el compuesto del título en forma de una espuma (532 mg, 68%).

Ejemplo 138: *N*-[(4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]-*N*-metilamina

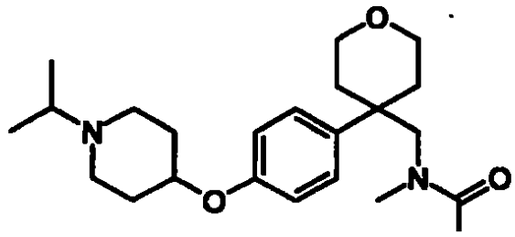


A una solución agitada de [4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il]metilcarbamato de *terc*-butilo (532 mg, 1,23 mmol) en THF (3,5 ml) a 0ºC se le añadió gota a gota una solución de $LiAlH_4$

(solución 1,0 M en Et_2O, 3,69 ml, 3,69 mmol). La reacción se agitó durante 60 horas a temperatura ambiente antes de la adición gota a gota de $LiAlH_4$ (solución 1,0 M en Et_2O, 0,6 ml, 0,6 mmol). Se calentó a 40°C hasta que se completó la reacción. La reacción se enfrió después a 0°C, se añadió gota a gota agua (0,2 ml) seguido de hidróxido sódico (2,0 M, 0,2 ml) y agua (0,6 ml). Se añadió metanol al 1% en diclorometano (10 ml) y la mezcla se filtró a través de una capa corta de arbocel, eluyendo con metanol al 1% en diclorometano (25 ml). Los lavados orgánicos se secaron sobre Na_2SO_4 y se concentraron *al vacío* dando el compuesto del título en forma de un sólido (399 mg, 94%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 7,88 (d, 2H), 4,22-4,34 (m, 1H), 3,70-3,80 (m, 2H), 3,60-4,01 (d, 2H), 2,70-2,88 (m, 3H), 2,64 (s, 2H), 2,32-2,44 (m, 2H) 2,24 (s, 3H), 2,10-2,18 (M, 2H), 1,99-2,08 (m, 2H), 1,79-1,96 (m, 4H), 1,03 (d, 6H).

Ejemplo 139: *N*-[[4-[4-[(1-isopropilpiperidin-4-il)oxi]fenil]tetrahidro-2*H*-piran-4-il]metil]-*N*-metilacetamida

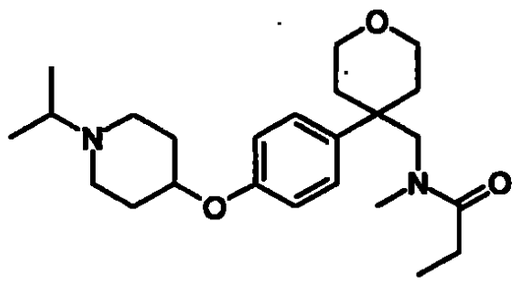


A una solución agitada de *N*-[(4-[4-[(1-isopropilpiperidin-4-il)oxi]fenil]tetrahidro-2*H*-piran-4-il)metil]-*N*-metilamina (120 mg, 0,347 mmol) y trietilamina (121 µl, 0,867 mmol) en diclorometano (1 ml) a 0°C se le añadió gota a gota anhídrido acético (36 µl, 0,382 mmol). La mezcla de reacción se calentó a temperatura ambiente hasta que se completó la reacción. Se añadió agua (1 ml) y diclorometano (15 ml) a la reacción, se extrajo con $NaHCO_3$

saturado (2 x 10 ml). Los lavados orgánicos se secaron sobre Na_2SO_4 y se concentraron *al vacío* dando el compuesto del título en forma de un aceite (113 mg, 83%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,10-7,22 (2 dobletes debido a rotámeros, 2H), 6,80 (d, 2H), 4,24-4,38 (m, 1H), 3,79-3,80 (m, 2H), 3,42-3,60 (m, 2H), 2,70-2,90 (m, 3H), 2,39-2,48 (m, 2H), 3,20-3,35 (singlete y doblete debido a rotámeros, 3H), 1,75-2,10 (m, 11 H), 1,10 (d, 6H).

Ejemplo 140: *N*-[[4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il]metil)-*N*-metilpropanamida

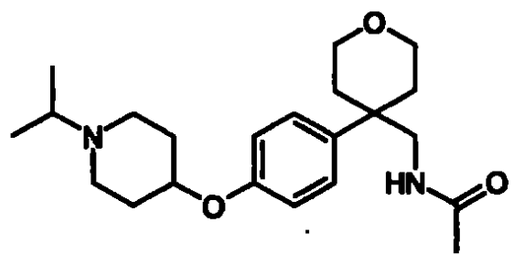


A una solución agitada de *N*-[(4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]-*N*-metilamina (120 mg, 0,347 mmol) y trietilamina (121 µl, 0,867 mmol) en diclorometano (1 ml) a 0ºC se le añadió gota a gota anhídrido propiónico (44 µl, 0,382 mmol). La reacción se dejó calentar hasta temperatura ambiente hasta que se completó la reacción. Se añadió agua (0,5 ml) y diclorometano (15 ml) a la reacción. La fase orgánica se separó y se extrajo con $NaHCO_3$ saturado (3 x 10 ml). Los lavados orgánicos se secaron sobre Na_2SO_4 y se concentraron *al vacío* dando el compuesto del título en forma de un aceite (153 mg, 82%).

^{1}H RMN (400 MHz, CD_3OD) δ 7,20-7,32 (2 dobletes debido a rotámeros, 2H), 7,95 (d, 2H), 3,95-4,05 (m, 1 H), 3,76-3,85 (m, 2H), 3,40-3,60 (múltiples picos

debido a rotámeros, 4H), 2,70-2,88 (múltiples picos debido a rotámeros, 4H), 2,42-2,58 (m, 2H), 2,40 (s, 2H), 2,20-2,38 (m, 2H), 1,52-2,58 (varios multipletes, 8H), 1,10 (d, 6H), 0,70-1,08 (dos tripletes debido a rotámeros, 3H).

Ejemplo 141: *N*-[[4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il]metil]-acetamida

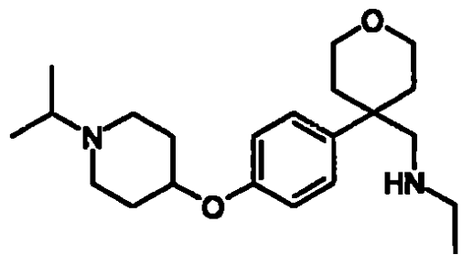


A una solución agitada de (4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metilamina (250 mg, 0,753 mmol) y trietilamina (200 µl, 1,88 mmol) en diclorometano (2 ml) se le añadió gota a gota anhídrido acético (78 0, 0,828 mmol). La reacción se dejó a temperatura ambiente hasta que se completó la reacción. A la reacción se le añadió diclorometano (10 ml), la fase orgánica se extrajo con $NaHCO_3$ saturado (3 x 10 ml). Los lavados orgánicos se secaron sobre Na_2SO_4 y se concentraron *al vacío* dando el compuesto del título en forma de un aceite (203 mg, 72%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,19 (d, 2H), 6,94 (d, 2H), 4,95-5,02 (ancha, 1H), 4,24-4,38 (m, 1H), 3,79-3,88 (m, 2H), 3,52-3,64 (m, 2H), 3,45 (d, 2H), 2,70-2,88 (m, 3H), 2,36-2,45 (m, 2H), 1,98-2,10 (m, 4H), 1,78-1,90 (m, 7H), 1,05 (d, 6H).

Ejemplo 142: *N*-[(4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]-*N*-etilamina

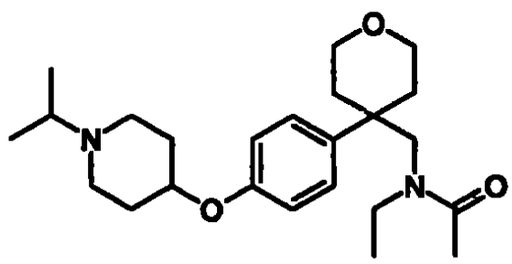
444
448



A una solución agitada de *N*-[[4-(4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il]metil}acetamida (192 mg, 0,513 mmol) en THF (1,5 ml) a 0°C se le añadió gota a gota una solución de $LiAlH_4$ (solución 1,0 M en Et_2O, 1,54 ml, 1,54 mmol). La reacción se calentó a 40°C durante 24 horas, después aumentó a 50°C. Se requirió adición gota a gota posterior de $LiAlH_4$ (solución 1,0 M en Et_2O, 2 ml, 2 mmol) y más calentamiento a 50°C durante 24 horas para completar la reacción. Después, la reacción se enfrió a 0°C, se le añadió gota a gota agua (0,15 ml) seguido de hidróxido sódico (2,0 M, 0,15 ml) y agua (0,45 ml). Se añadió metanol al 1% en diclorometano (15 ml) y la mezcla se filtró a través de una capa corta de Arbocel®, eluyendo con metanol al 1% en diclorometano (25 ml). Los lavados orgánicos se secaron sobre Na_2SO_4 y se concentraron *al vacío* (185 mg en bruto, 82%). El compuesto se purificó por cromatografía en columna sobre gel de sílice, eluyendo con diclorometano:metanol:amoniaco, 98:2:0,2, dando el compuesto del título en forma de un sólido blanco (9,9 mg, 4,4%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 7,88 (d, 2H), 4,24-4,56 (m, 1H), 3,71-3,82 (m, 2H), 3,52-3,63 (m, 2H), 2,72-2,88 (m, 3H), 2,70 (s, 2H), 2,46-2,52 (cuadruplete, 2H), 2,34-2,42 (m, 2H), 1,78-2,18 (varios multipletes, 8H), 1,08 (d, 6H), 0,96 (t, 3H).

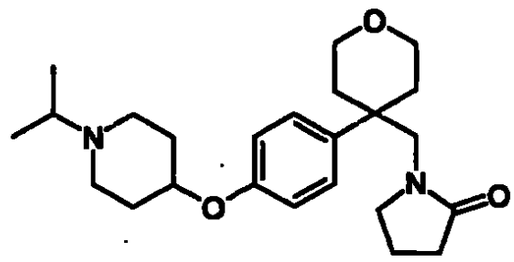
Ejemplo 143: *N*-[[4-(4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il]metil}-*N*-etilacetamida



A una solución agitada de *N*-[(4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]-*N*-etilamina (102 mg, 0,283 mmol) y trietilamina (99 µl, 0,708 mmol) en diclorometano (1 ml) se le añadió gota a gota anhídrido acético (29 µl, 0,312 mmol). La reacción se dejó a temperatura ambiente durante 4 horas hasta que se completó la reacción. Se añadió agua (1 ml) y diclorometano (10 ml) a la reacción, después se extrajo con $NaHCO_3$ saturado (2 x 10 ml). Los lavados orgánicos se secaron sobre Na_2SO_4 y se concentraron *al vacío* dando el compuesto del título en forma de un aceite (107 mg, 94%).

^{1}H RMN (400 MHz, CD_3OD) δ 7,20-7,31 (multiplete debido a rotámeros, 2H), 6,92-7,00 (multiplete debido a rotámeros, 2H), 4,36-4,46 (m, 1 H), 3,70-3,88 (m, 2H), 3,20-3,55 (varios picos debido a rotámeros, 4H), 2,78-2,90 (m, 3H), 2,60, (q, 2H), 2,25-2,52 (múltiples picos debido a rotámeros, 2H), 1,70-2,10 (múltiples picos, 11 H), 1,10 (d, 6H), 0,80-1,00 (dos tripletes debido a rotámeros, 3H).

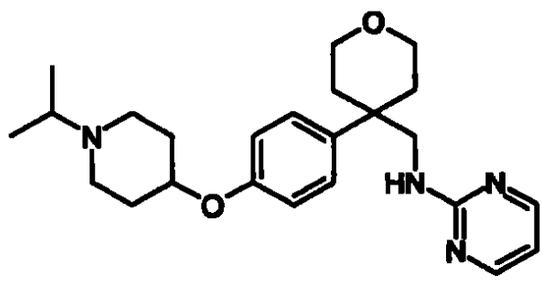
Ejemplo 144: 1-[(4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]pirrolidin-2-ona



A una solución de (4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metilamina (100 mg, 0,301 mmol) en tolueno (2 ml) se le añadió etil-4-bromobutirato (43 µl, 0,301 mmol), *N,N*-diisopropiletilamina (157 µl, 0,904 mmol) y yoduro potásico (5 mg, 0,030 mmol). La mezcla de reacción se calentó a 80°C durante 48 horas, después se aumentó a reflujo. Se añadió carbonato potásico (83 mg, 0,602 mmol) y la reacción se dejó a reflujo durante 24 horas más hasta que se completó la reacción. La mezcla de reacción se dividió entre acetato de etilo (20 ml) y $NaHCO_3$ saturado (10 ml). Los lavados orgánicos se secaron sobre Na_2SO_4 y se concentraron *al vacío dando* un aceite pardo (101 mg en bruto, 84%). El compuesto se purificó por cromatografía en columna sobre gel de sílice, eluyendo con diclorometano:metanol:amoniaco, 100:0:0 a 98:2:0,2, dando el compuesto del título en forma de un aceite (7 mg, 6%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 7,90 (d, 2H), 4,22-4,36 (m, 1H), 4,80-4,90 (m, 2H), 3,52-3,67 (m, 2H), 3,40 (s, 2H), 2,72-3,88 (varios multipletes, 3H), 2,50 (t, 2H), 2,34-2,44 (m, 2H), 2,21-2,30 (t, 2H), 1,60-2,10 (varios multipletes, 10H), 1,08 (d, 6H).

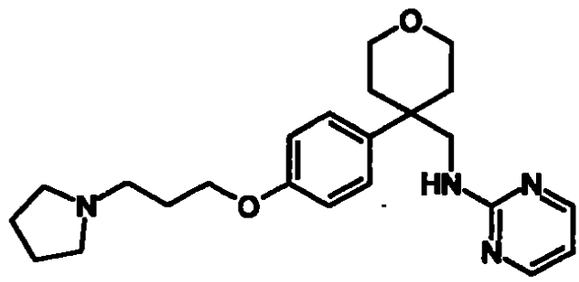
Ejemplo 145: *N*-[(4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]pirimidin-2-amina



Una mezcla de (4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metilamina (150 mg, 0,422 mmol), 2-cloropirimidina (52 mg, 0,422 mmol) y *N*,*N*-diisopropiletilamina (161 µl, 0,904 mmol) en *N*-metil pirrolidinona (0,5 ml) se calentó a 150ºC en el microondas (Smith Personal Synthesiser) durante 900 segundos. La mezcla de reacción se dividió entre acetato de etilo (10 ml) y $NaHCO_3$ saturado (10 ml). Los lavados orgánicos se secaron sobre Na_2SO_4 y se concentraron *al vacío* dando un aceite naranja. El compuesto se purificó por cromatografía en columna sobre gel de sílice, eluyendo con diclorometano:metanol:amoniaco, 100:0:0 a 96:4:0,4, dando el compuesto del título en forma de un sólido (87 mg, 47%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 8,20 (d, 2H), 7,21 (d, 2H), 6,90 (d, 2H), 6,48 (t, 2H), 4,71 (m, 1H), 4,20-4,35 (ancha, 1H), 3,80-3,90 (m, 2H), 3,55-3,70 (múltiples picos, 4H), 2,70-2,90 (m, 3H), 2,32-2,49 (m, 2H), 1,78-2,19 (varios multipletes, 8H), 1,10 (d, 6H).

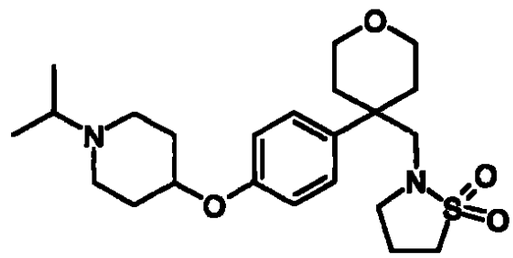
Ejemplo 146: *N*-{4-[4-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metilpirimidin-2-amina



Una mezcla de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il} metilamina (100 mg, 0,314 mmol), 2-cloropirimidina (50 mg, 0,346 mmol) y *N*,*N*-diisopropiletilamina (112 µl, 0,629 mmol) en *N*-metil pirrolidinona (0,5 ml) se calentó a 180ºC en el microondas (Smith Personal Synthesiser) durante 600 segundos. La mezcla de reacción se dividió entre acetato de etilo (10 ml) y $NaHCO_3$ saturado (10 ml). Los lavados orgánicos se secaron sobre Na_2SO_4 y se concentraron *al vacío* dando un aceite. El compuesto se purificó por cromatografía en columna sobre gel de sílice, eluyendo con diclorometano:metanol:amoniaco, 100:0:0 a 88:12:1,2. El compuesto todavía contenía impurezas de forma que se purificó adicionalmente en el sistema LC automatizado Fraction Lynx dando el compuesto del título en forma de un sólido (22 mg, 17%)

^{1}H RMN (400 MHz, $CDCl_3$) δ 8,30 (sa, 2H), 7,34 (d, 2H), 6,92 (d, 2H), 6,70 (t, 1H), 4,10 (t, 2H), 3,78-3,84 (m, 2H), 3,62-3,72 (múltiples picos, 4H), 3,44-3,55 (m, 2H), 3,40 (m, 2H), 3,04-3,18 (m, 2H), 1,85-2,25 (múltiples picos, 10H).

Ejemplo 147: 1,1-dióxido de 2-{[4-(4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il]metil}isotiazolidina



Una solución de (4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metilamina (100 mg, 0,30 mmol), cloruro de 3-cloropropanosulfonilo (51 µl, 0,40 mmol) y *N,N*-diisopropiletilamina (520, 0,30 mmol) en diclorometano (2 ml) se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se concentró *al vacío* y después se dividió entre diclorometano (10 ml) y una solución de bicarbonato sódico (10 ml). La fase acuosa se extrajo con 10 ml más de diclorometano y Los extractos orgánicos combinados se secaron sobre sulfato sódico y se concentraron *al vacío* dando un aceite. Este aceite se disolvió en tetrahidrofurano (2 ml). A la solución se le añadió *terc*-butóxido potásico (65 mg, 0,60 mmol) y la mezcla de reacción se agitó a 40ºC durante 18 horas. Esto se concentró después *al vacío* y se dividió entre éter dietílico (10 ml) y agua (10 ml). La fase acuosa se extrajo con 10 ml más de éter dietílico y los extractos orgánicos combinados se secaron sobre sulfato sódico y se concentraron *al vacío* dando un aceite amarillo pálido. El compuesto se purificó por cromatografía en columna sobre gel de sílice Biotage®, eluyendo con diclorometano:metanol:amoniaco, 96:4:0,4 dando el compuesto del título en forma de un aceite amarillo pálido (19 mg, 15%).

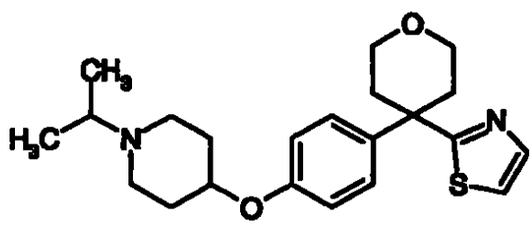
^{1}H RMN (400 MHz, $CDCl_3$) δ 7,20 (d, 2H), 6,90 (d, 2H), 4,26 (m, 2H), 3,80 (m, 2H), 3,58 (m, 2H), 3,15 (s, 2H), 2,99 (t, 2H), 2,80 (m, 2H), 2,75(m, 2H), 2,40 (t, 2H), 2,38 (m, 2H), 2,16 (m, 2H), 2,02 (m, 4H), 1,90 (m, 2H) 1,81 (m, 2H), 1,03 (d, 6H); EMAR (IEN$^+$) 437,2457 $(M+H)^+$.

Intermedio 53: 4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-carbotioamida

El compuesto del título (320 mg, 74%) se preparó a partir de 4-[4-(1-isopropilpiperidin-4-iloxi)fenil]tetrahidropiran-4-carbonitrilo y ditiofosfato de dietilo de forma similar al procedimiento usado para el Intermedio 50.

EMBR APCI$^+$ m/z 363 $[MH]^+$.

Ejemplo 148: 1-isopropil-4-{4-[4-(1,3-tiazol-2-il)tetrahidro-2*H*-piran-4-il]fenoxi}piperidina



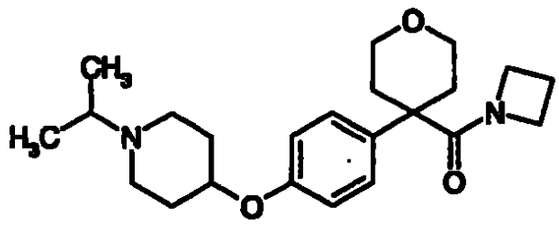
El compuesto del título (320 mg, 74%) se preparó a partir de 4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-carbotioamida y bromoacetaldehído dietilacetal de forma similar al procedimiento usado para el ejemplo 137.

^{1}H RMN (400 MHz, CD_3OD) δ 1,10 (d, 6H), 1,75-1,80 (m, 2H), 1,98-2,02 (m, 2H), 2,37-2,44 (m, 2H), 2,47-2,51 (m, 2H), 2,61-2,65 (m, 2H), 2,75-2,84 (m, 3H), 3,66-3,70 (m, 2H), 3,78-3,83 (m, 2H), 4,37 (m, 1H), 6,89 (d, 2H), 7,28 (d, 2H), 7,46 (d, 1H), 7,70 (d, 1H).

EMAR IEN$^+$ m/z 387,2090 $[MH]^+$.

Microanálisis: Encontrado: C, 67,42; H, 7,83; N, 7,08%. $C_{22}H_{30}N_2O_2S$. $0,2H_2O$ requiere C, 67,73; H, 7,85; N, 7,18%.

Ejemplo 149: 4-{4-[4-(azetidin-1-ilcarbonil)tetrahidro-2*H*-piran-4-il]fenoxi}-1-isopropilpiperidina

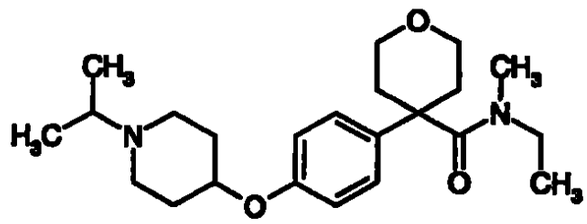


Se agitó ácido 4-(4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-carboxílico (200 mg, 0,58 mmol), clorhidrato de azetidina (81 mg, 0,87 mmol), clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (121 mg, 0,63 mmol), hidrato de 1-hidroxibenzotriazol (97 mg, 0,63 mmol) y trietilamina (210 µl, 1,51 mmol) en diclorometano (8 ml) a temperatura ambiente durante 18 horas. La reacción se diluyó con diclorometano (60 ml) y se lavó con bicarbonato sódico acuoso. La fase acuosa se extrajo otra vez con diclorometano. Los extractos orgánicos se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron a presión reducida. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (96:4:0,5, en volumen) proporcionando el compuesto del título (97 mg, 43%) en forma de un sólido blanco.

^{1}H RMN (400 MHz, CD_3OD) δ 1,11 (d, 6H), 1,77-1,82 (m, 2H), 1,88-1,95 (m, 2H), 2,01-2,08 (m, 4H), 2,26-2,29 (m, 2H), 2,47-2,52 (m, 2H), 2,76-2,86 (m, 3H), 3,66-3,74 (m, 4H), 3,79-3,82 (m, 2H), 3,92-3,96 (m, 2H), 4,40 (m, 1 H), 6,95 (d, 2H), 7,22 (d, 2H).

EMAR IEN$^+$ m/z 387,2634 $[MH]^+$.

Ejemplo 150: *N*-etil-4-[4-[(1-isopropilpiperidin-4-il)oxi]fenil]-*N*-metiltetrahidro-2*H*-piran-4-carboxamida

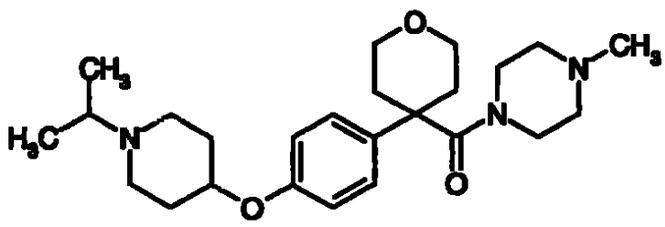


Se añadió hexafluorofosfato de O-(1*H*-Benzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (286 mg, 0,75 mmol) a una solución de ácido 4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-carboxílico (200 mg, 0,58 mmol) en *N,N*-dimetilformamida (6 ml). Después se añadió trietilamina (243 µl, 1,74 mmol). La mezcla se agitó a temperatura ambiente durante 15 minutos. Se añadió etilmetilamina (500 µl, 5,8 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 18 horas. La reacción se concentró *al vacío.* El residuo se dividió entre una solución de bicarbonato sódico acuoso (30 ml) y acetato de etilo (2x75 ml). Los extractos orgánicos se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron a presión reducida. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (96:4:0,5, en volumen) proporcionando el compuesto del título (80 mg, 35%).

^{1}H RMN (400 MHz, CD_3OD) δ 1,06-1,25 (m, 9H), 1,90-2,02 (m, 4H), 2,08-2,12 (m, 2H), 2,25-2,28 (m, 2H), 2,58 (m, 2H), 2,87 (m, 3H), 2,95 (m, 2H), 3,09-3,12 (m, 3H), 3,71-3,76 (m, 2H), 3,82-3,86 (m, 2H), 4,53 (m, 1 H), 6,98 (d, 2H), 7,20 (d, 2H).

EMAR IEN$^+$ m/z 389,2791 $[MH]^+$.

Ejemplo 151: 1-[(4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)carbonil]-4-metilpiperazina

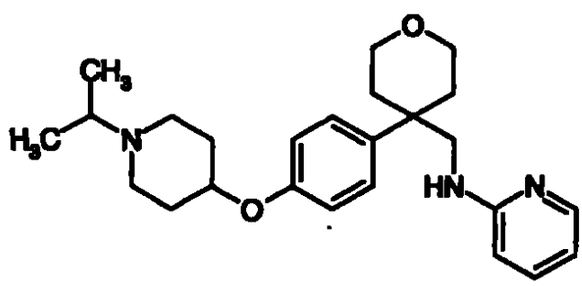


El compuesto del título (60 mg, 48%) se preparó a partir de ácido 4-[4-[(1-isopropilpiperidin-4-il)oxi]fenil]tetrahidro-2*H*-piran-4-carboxílico y *N*-metil piperazina de forma similar al procedimiento usado para el ejemplo 150.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,05 (d, 6H), 1,79-1,81 (m, 2H), 2,00-2,03 (m, 7H), 2,15 (s, 3H), 2,18-2,22 (m, 2H), 2,37-2,42 (m, 2H), 2,77-2,79 (m, 3H), 2,99 (m, 1H), 3,27-3,56 (m, 4H), 3,78 (t, 2H), 3,87-3,89 (m, 2H), 4,28 (m, 1 H), 6,88 (d, 2H), 7,14 (d, 2H).

EMAR IEN$^+$ m/z 430,3062 $[MH]^+$.

Ejemplo 152: *N*-[(4-[4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]piridin-2-amina



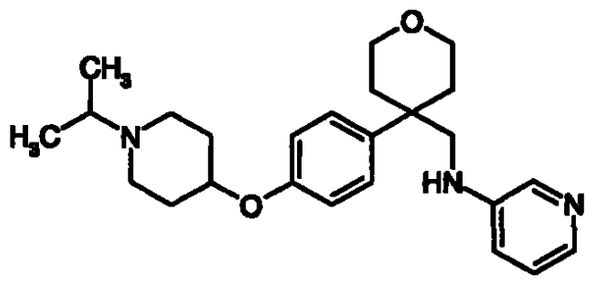
Se calentó (4-[4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metilamina (300 mg, 0,9 mmol), 2-bromopiridina (50 µl, 0,75 mmol), tris(dibencilidenacetona)dipaladio (0) (15 mg, 0,018 mmol), 2,2'-bis(difenilfosfino)-1,1'-binaftilo (19 mg, 0,036 mmol) y *terc*-butóxido sódico (100 mg, 1 mmol) a 70ºC en tolueno (6 ml) durante 24 horas en una atmósfera de nitrógeno. La reacción se dividió entre bicarbonato sódico acuoso (302 ml) y

diclorometano (2x75 ml). Los extractos orgánicos se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron a presión reducida. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (96:4:0,4, a 94:6:0,6 en volumen) proporcionando el compuesto del título (81 mg, 22%) en forma de un sólido blanco después de trituración en éter dietílico.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,11 (d, 6H), 1,86-1,95 (m, 4H), 2,07-2,16 (m, 4H), 2,46-2,51 (m, 2H), 2,82-2,86 (m, 3H), 3,49 (d, 2H), 3,56-3,61 (m, 2H), 3,80-3,85 (m, 2H), 4,03 (m, 1H), 4,33 (m, 1H), 6,22 (d, 1H), 6,51 (t, 1H), 6,91 (d, 2H), 7,24 (d, 2H), 7,32 (t, 1H), 8,01 (d, 1H).

EMAR IEN$^+$ m/z 410,2793 $[MH]^+$.

Ejemplo 153: *N*-[(4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]piridin-3-amina



El compuesto del título (20 mg, 5%) se preparó a partir de (4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metilamina y 3-yodopiridina de forma similar al procedimiento usado para el ejemplo 152.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,12 (d, 6H), 1,88-1,95 (m, 4H), 2,10-2,21 (m, 4H), 2,51 (m, 2H), 2,83-2,88 (m, 3H), 3,22-3,27 (m, 3H), 3,55-3,59 (m, 2H), 3,77-3,82 (m, 2H), 4,35 (m, 1H), 6,73 (d, 1H), 6,93 (d, 2H), 7,00 (t, 1 H), 7,24 (d, 2H), 7,87-7,90 (m, 2H).

460
459

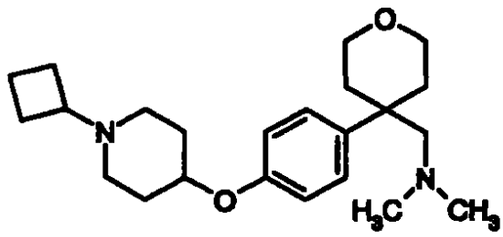
EMAR IEN$^+$ m/z 410,2791 $[MH]^+$.

Intermedio 54: 1-ciclobutilpiperidin-4-ol

Se agitó 4-hidroxipiperidina (2,41 g, 23,8 mmol), ciclobutanona (5 g, 71,4 mmol) y ácido acético (1,36 ml, 23,8 mmol) en tetrahidrofurano (35 ml) a 0ºC durante 1,5 horas. Después se añadió triacetoxiborohidruro sódico (10,1 g, 47,7 mmol) a 0ºC y la mezcla de reacción se agitó a 0ºC durante 1 hora. La mezcla se calentó a temperatura ambiente y se agitó durante 1 hora, después se calentó a 40ºC durante 18 horas. La reacción se concentró *al vacío*. El residuo se recogió en agua (30 ml). La fase acuosa se basificó a pH 9 con amoniaco y se extrajo con éter dietílico (3x50 ml). Los extractos orgánicos se combinaron, se secaron sobre sulfato de magnesio, se filtraron y se concentraron *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (100:0:0 a 93:7:0,7 en volumen) proporcionando el compuesto del título (2,47 g, 67%) en forma de un aceite.

EMBR APCI m/z 156 $[MH]^+$.

Ejemplo 154: 1-(4-[4-[(1-ciclobutilpiperidin-4-il)oxi]fenil]tetrahidro-2*H*-piran-4-il)-*N*,*N*-dimetilmetanamina



Se hizo reaccionar de forma conjunta 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (0,75 g, 3,19 mmol), 1-ciclobutilpiperidin-4-ol (0,45 g, 2,90

mmol), PPh_3 (0,84 g, 3,19 mmol), THF (10 ml) y DIAD (0,66 ml, 3,19 mmol) de forma similar al procedimiento general C. El material en bruto se sometió a cromatografía sobre sílice gel eluyendo con diclorometano:metanol:amoniaco (98:2:0,2) proporcionando el compuesto del título (114 mg, 11%) en forma de un sólido blanquecino.

^{1}H RMN (400 MHz, CD_3OD) δ 1,71-1,77 (m, 4H), 1,85-1,90 (m, 4H), 1,94 (s, 6H), 1,99-2,06 (m, 4H), 2,12-2,16 (m, 2H), 2,20-2,28 (m, 2H), 2,45 (s, 2H), 2,58-2,70 (m, 2H), 2,79 (m, 1H), 3,46-3,53 (m, 2H), 3,72-3,75 (m, 2H), 4,39 (m, 1H), 6,91 (d, 2H), 7,26 (d, 2H).

EMAR IEN$^+$ m/z 373,2846 $[MH]^+$.

Intermedio 55: {4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}acetato de etilo

Se añadió gota a gota DIAD (9,8 ml, 47,3 mmol) durante 10 minutos a una solución de etil-4-hidroxifenilacetato (7,7 g, 42,7 mmol), 1-ciclobutilpiperidin-4-ol (6,58 g, 42,5 mmol) y PPh_3 (12,3 g, 47 mmol) en THF (150 ml) a 0ºC. La mezcla de reacción se agitó después a temperatura ambiente durante 18 horas. La reacción se concentró *al vacío*. El residuo se recogió en acetato de etilo (150 ml). La fase orgánica se lavó con agua (150 ml) y ácido clorhídrico acuoso 2 N (50 ml) dos veces. Las fases ácidas se basificaron con carbonato sódico y se extrajeron con diclorometano (2x80 ml). Estos extractos orgánicos se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con acetato de etilo:pentano:dietilamina (70:30:2 en volumen) proporcionando el compuesto del título (2,0 g, 15%) en forma de un aceite incoloro.

EMBR APCI$^+$ m/z 318 $[MH]^+$.

Intermedio 56: 4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-carboxilato de etilo

Se añadió NaH (dispersión al 60% en aceite, 800 mg, 20 mmol) a 0ºC a una solución de {4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}acetato de etilo (2 g, 6,3 mmol) en THF (25 ml) y *N*-metilpirrolidinona (2 ml) en una atmósfera de nitrógeno. La reacción se agitó a 0ºC durante 15 minutos. Se añadieron bis(2-bromoetil)éter (1,2 ml, 9,54 mmol) y yoduro potásico (500 mg, 3 mmol) y la mezcla se agitó a 0ºC durante 45 minutos. La reacción se calentó después a temperatura ambiente y se agitó durante 18 horas. La reacción se enfrió a 0ºC, se inactivó con hielo y dióxido de carbono sólido. La mezcla se diluyó con agua y se extrajo con acetato de etilo (100 ml y 20 ml). Los extractos orgánicos combinados se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con acetato de etilo:dietilamina (99:1 en volumen) proporcionando el compuesto del título (870 mg, 36%) en forma de un aceite amarillo pálido.

EMBR APCI$^+$ m/z 388 $[MH]^+$.

Intermedio 57: Ácido 4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-carboxílico

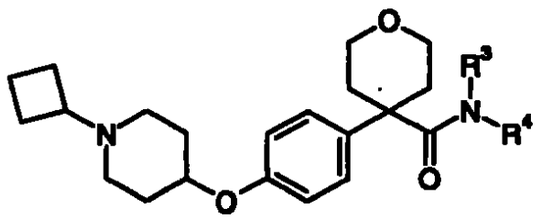
Se añadió hidróxido sódico (200 mg, 5 mmol) a una solución de 4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-carboxilato de etilo (870 mg, 2,25 mmol) en dioxano (10 ml) y agua (2 ml). La mezcla de reacción se calentó a reflujo durante 16 horas en una atmósfera de nitrógeno. La reacción no se completó. Se añadió más hidróxido sódico (190 mg, 4,75 mmol) en agua (4 ml) y la reacción se calentó a reflujo durante 18 horas. Se añadió ácido

clorhídrico 2 N (5 ml, 9,75 mmol) y la mezcla se concentró *al vacío* a un polvo blanco (2,0 g) que contenía el compuesto del título y cloruro sódico.

EMBR APCI$^+$ m/z 360 $[MH]^+$.

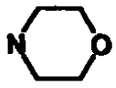
Ejemplos 155-160

Los compuestos de los siguientes Ejemplos tabulados de fórmula general



se prepararon usando ácido 4-[4-[(1-ciclobutilpiperidin-4-il)oxi]fenil]tetrahidro-2*H*-piran-4-carboxílico y las aminas apropiadas de forma similar al procedimiento usado para el ejemplo 149.

Nº Ej	NR^3R^4	Datos analíticos
155	NMe_2	4-[4-[(1-ciclobutilpiperidin-4-il)oxi]fenil]-*N*,*N*-dimetiltetrahidro-2*H*-piran-4-carboxamida ^{1}H RMN (400 MHz, CD_3OD) δ 1,70-1,79 (m, 4H), 1,89-2,02 (m, 6H), 2,07-2 10 (m, 2H), 2,25 (d, 4H), 2,63-2,87 (m, 9H), 3,73 (t, 2H), 3,82-3,85 (m, 2H), 4,41 (m, 1 H), 6,94 (d, 2H), 7,16 (d, 2H). EMAR IEN$^+$ m/z 387,2637 $[MH]^+$ Rendimiento del 25%.

156	NHMe	4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}-*N*-metiltetrahidro-2*H*-piran-4-carboxamida ^{1}H RMN (400 MHz, CD_3OD) δ 1,70-1,76 (m, 4H), 1,88-2,08 (m, 8H), 2,22- 2,25 (m, 2H), 2,38-2,42 (m, 2H), 2,59-2,63 (m, 2H), 2,66 (s, 3H), 2,80 (m, 1H), 3,61 (t, 2H), 3,75-3,80 (m, 2H), 4,39 (m, 1H), 6,90 (d, 2H), 7,27 (d, 2H). EMAR IEN$^+$ m/z 373,2480 $[MH]^+$. 10% rendimiento
157		4-[(4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)carbonil]morfolina ^{1}H RMN (400 MHz, CD_3OD) δ 1,70-1,76 (m, 4H), 1,85-2,09 (m, 8H), 2,20- 2,24 (m, 4H), 2,63-2,67 (m, 2H), 2,81 (m, 1H), 3,25-3,31 (m, 6H), 3,33- 3,39 (m, 2H), 3,73 (t, 2H), 3,82-3,87 (m, 2H), 4,41 (m, 1H), 6,96 (d, 2H), 7,20 (d, 2H). EMAR IEN$^+$ m/z 429,2740 $[MH]^+$. Rendimiento del 20%
158	NH_2	4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-carboxamida ^{1}H RMN (400 MHz, CD_3OD) δ 1,76-1,82 (m, 2H), 1,94-2,00 (m, 4H), 2,06- 2,10 (m, 4H), 2,20-2,22 (m, 2H), 2,42 (d, 2H), 2,65-2,79 (m, 2H), 2,89- 2,99 (m, 2H), 3,26 (m, 1H), 3,66 (t, 2H), 3,78-3,82 (m, 2H), 4,55 (m, 1H), 6,95 (d, 2H), 7,34 (d, 2H). EMAR IEN$^+$ m/z 359,2322 $[MH]^+$. Rendimiento del 13%

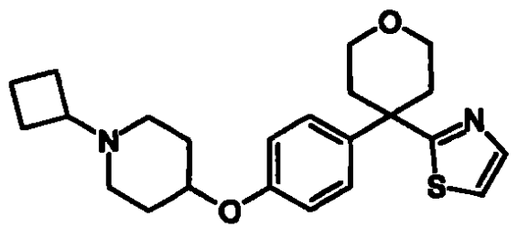
159	NHiPr	4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}-*N*-isopropiltetrahidro-2*H*-piran-4-carboxamida ^{1}H RMN (400 MHz, CD_3OD) δ 1,04 (d, 6H), 1,70-1,77 (m, 4H), 1,88-2,00 (m, 6H), 2,05-2,08 (m, 2H), 2,20-2,26 (m, 2H), 2,42 (d, 2H), 2,60-2,68 (m, 2H), 2,81 (m, 1H), 3,62 (t, 2H), 3,77-3,82 (m, 2H), 3,99 (m, 1H), 4,39 (m, 1 H), 6,90 (d, 2H), 7,28 (d, 2H). EMAR IEN$^+$ m/z 401,2789 $[MH]^+$. Rendimiento del 13%
160	NHEt	4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}-*N*-etiltetrahidro-2*H*-piran-4- carboxamida ^{1}H RMN (400 MHz, CD_3OD) δ 1,01 (t, 3H), 1,69-1,75 (m, 4H), 1,88-2,01 (m, 6H), 2,04-2,07 (m, 2H), 2,16-2,28 (m, 2H), 2,41 (d, 2H), 2,56-2,68 (m, 2H), 2,79 (m, 1H), 3,15 (q, 2H), 3,62 (t, 2H), 3,76-3,80 (m, 2H), 4,38 (m, 1 H), 6,89 (d, 2H), 7,28 (d, 2H). EMAR IEN$^+$ m/z 387,2636 $[MH]^+$. Rendimiento del 22%

Intermedio 58: 4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-carbotioamida

El compuesto del título (223 mg, 50%) se preparó a partir de 4-{4-[(1-ciclobutil-4-piperidinil)oxi]fenil}tetrahidro-2*H*-piran-4-carbonitrilo y ditiofosfato de dietilo de forma similar al procedimiento usado para el Intermedio 50.

EMBR APCI$^+$ m/z 375 $[MH]^+$.

Ejemplo 161: 1-ciclobutil-4-{4-[4-(1,3-tiazol-2-il)tetrahidro-2*H*-piran-4-il]fenoxi}piperidina

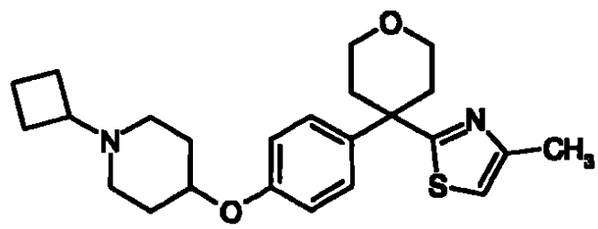


El compuesto del título (92 mg, 39%) se preparó a partir de 4-(4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-carbotioamida y bromoacetaldehído dietilacetal de forma similar al procedimiento usado para el ejemplo 137.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,66-1,72 (m, 2H), 1,77-1,89 (m, 5H), 1,95-2,04 (m, 4H), 2,11 (m, 1H), 2,36-2,43 (m, 2H), 2,58-2,72 (m, 5H), 3,71 (t, 2H), 3,84-3,88 (m, 2H), 4,27 (m, 1H), 6,84 (d, 2H), 7,23-7,26 (m, 3H), 7,70 (s, 1H).

EMBR APCI$^+$ m/z 399 $[MH]^+$.

Ejemplo 162: 1-ciclobutil-4-{4-[4-(4-metil-1,3-tiazol-2-il)tetrahidro-2*H*-piran-4-il]fenoxi}piperidina



El compuesto del título (155 mg, 83%) se preparó a partir de 4-(4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-carbotioamida y cloroacetona de forma similar al procedimiento usado para el ejemplo 136.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,64-1,71 (m, 2H), 1,78-1,81 (m, 2H), 1,88-2,04

(m, 6H), 2,10-2,20 (m, 2H), 2,31-2,38 (m, 2H), 2,42 (s, 3H), 2,61-2,64 (m, 4H), 2,74 (m, 1H), 3,71 (t, 2H), 3,81-3,85 (m, 2H), 4,28 (m, 1H), 6,75 (s, 1H), 6,83 (d, 2H), 7,23 (d, 2H).

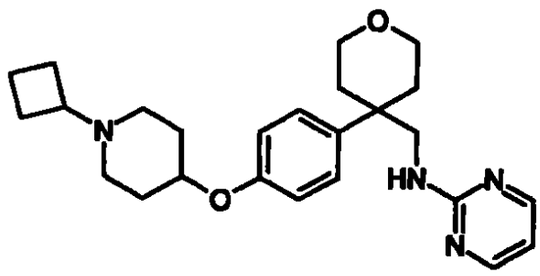
EMAR IEN$^+$ m/z 413,2257 $[MH]^+$.

Intermedio 59: 1-{4-[4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metanamina

El compuesto del título (1,05 g, 100%) se preparó a partir de 4-{4-[(1-ciclobutil-4-piperidinil)oxi]fenil}tetrahidro-2*H*-piran-4-carbonitrilo e hidruro de aluminio litio de forma similar al procedimiento usado para el Intermedio 51.

EMBR APCI$^+$ m/z 345 $[MH]^+$.

Ejemplo 163: *N*-[(4-{4-[4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]pirimidin-2-amina

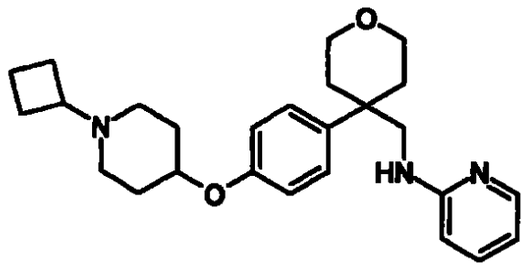


El compuesto del título (31 mg, 25%) se preparó a partir de 1-{4-[4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metanamina y 2-cloropirimidina de forma similar al procedimiento usado para el ejemplo 145.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,66-1,73 (m, 2H), 1,83-1,95 (m, 6H), 1,98-2,15 (m, 8H), 2,60-2,66 (m, 2H), 2,75 (m, 1H), 3,57-3,62 (m, 2H), 3,66 (d, 2H), 3,81-3,85 (m, 2H), 4,31 (m, 1H), 4,68 (t, 1H), 6,47 (t, 1H), 6,90 (d, 2H), 7,23 (d, 2H), 8,20 (d, 2H).

EMBR APCI m/z 423 $[MH]^+$.

Ejemplo 164: *N*-[(4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]piridin-2-amina

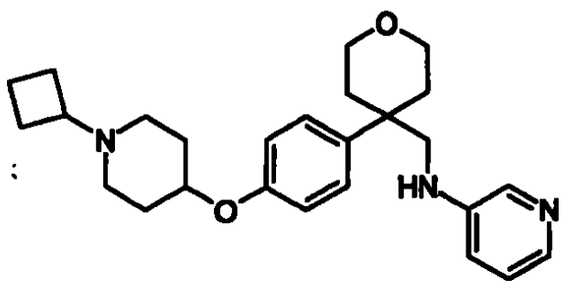


El compuesto del título (25 mg, 31%) se preparó a partir de 1-(4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metanamina y 2-bromopiridina de forma similar al procedimiento usado para el ejemplo 152.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,68-1,72 (m, 2H), 1,84-1,94 (m, 6H), 2,00-2,16 (m, 8H), 2,63-2,67 (m, 2H), 2,74 (m, 1H), 3,49 (d, 2H), 3,56-3,62 (m, 2H), 3,80-3,85 (m, 2H), 4,02 (m, 1H), 4,31 (m, 1H), 6,22 (d, 1H), 6,51 (t, 1H), 6,91 (d, 2H), 7,24 (d, 2H), 7,32 (t, 1H), 8,01 (d, 1H).

EMAR IEN$^+$ m/z 422,2792 $[MH]^+$.

Ejemplo 165: *N*-[(4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]piridin-3-amina

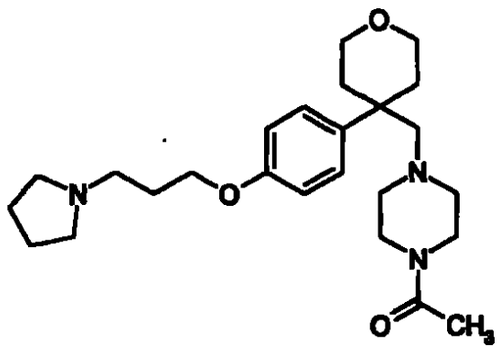


El compuesto del título (28 mg, 18%) se preparó a partir de 1-(4-{4-[(1-ciclobutilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metanamina y 3-yodopiridina de forma similar al procedimiento usado para el ejemplo 153.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,66-1,94 (m, 8H), 2,01-2,06 (m, 4H), 2,17-2,20 (m, 4H), 2,60-2,68 (m, 2H), 2,76 (m, 1H), 3,22-3,27 (m, 3H), 3,57 (t, 2H), 3,77-3,81 (m, 2H), 4,32 (m, 1H), 6,73 (d, 1H), 6,92 (d, 2H), 6,99 (m, 1 H), 7,23 (d, 2H), 7,88 (m, 2H).

EMAR IEN$^+$ m/z 422,2789 $[MH]^+$.

Ejemplo 166: 1-acetil-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piperazina



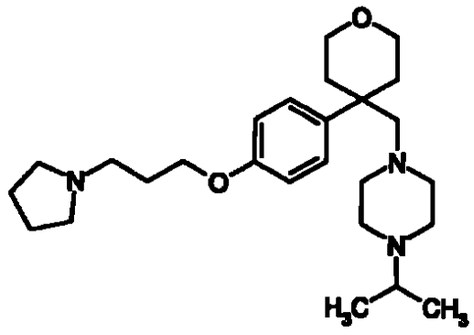
A una solución agitada de 1-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil}piperazina (160 mg, 0,41 mmol) y *N,N*-diisopropiletilamina (180 µl, 1,03 mmol) en diclorometano (2 ml) a 0ºC se le añadió gota a gota anhídrido acético (47111, 0,49 mmol). La reacción se dejó calentar a temperatura ambiente y se agitó durante 18 horas. La mezcla de reacción se concentró a presión reducida y el residuo se dividió entre diclorometano (20 ml) y una solución de carbonato sódico acuoso (20 ml). Las fases se separaron y la fase acuosa se extrajo otra vez con diclorometano (20 ml). Los extractos orgánicos se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (96:4:0,4 a 90:10:1 en volumen)

proporcionando el compuesto del título (34 mg, 19%) en forma de un aceite transparente.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,78-1,81 (m, 4H), 1,83-1,89 (m, 2H), 1,99 (s, 3H), 2,01-2,03 (m, 2H), 2,06-2,11 (m, 3H), 2,15-2,18 (m, 3H), 2,40 (s, 2H), 2,51-2,53 (m, 4H), 2,63 (t, 2H), 3,22 (t, 2H), 3,42-3,44 (m, 2H), 3,52 (t, 2H), 3,73-3,76 (m, 2H), 4,02 (t, 2H), 6,86 (d, 2H), 7,21 (d, 2H).

EMAR IEN$^+$ m/z 430,3052 $[MH]^+$.

Ejemplo 167: 1-isopropil-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piperazina

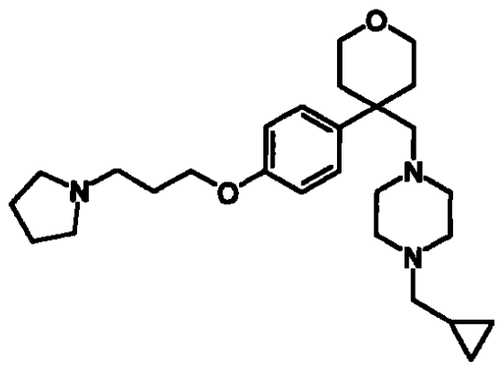


El compuesto del título (78 mg, 44%) se preparó a partir de 1-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil)piperazina y acetona de forma similar al procedimiento usado para el ejemplo 54.

^{1}H RMN (400 MHz, $CDCl_3$) δ 0,98 (d, 6H), 1,77-1,80 (m, 4H), 1,86-1,93 (m, 2H), 1,98-2,02 (m, 2H), 2,06-2,09 (m, 2H), 2,20-2,22 (m, 4H), 2,34-2,38 (m, 6H), 2,50-2,54 (m, 5H), 2,62 (t, 2H), 3,52 (t, 2H), 3,71-3,75 (m, 2H), 4,02 (t, 2H), 6,85 (d, 2H), 7,21 (d, 2H).

EMAR IEN$^+$ m/z 430,3417 $[MH]^+$.

Ejemplo 168: 1-(ciclopropilmetil)-4-({4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-2*H*-piran-4-il}metil)-piperazina

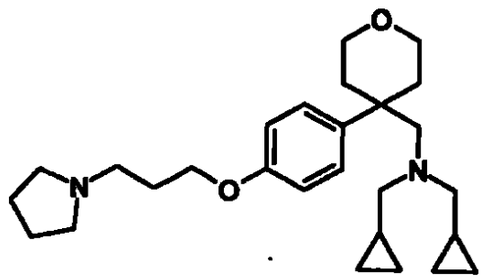


El compuesto del título (26 mg, 14%) se preparó a partir de 1-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-ilmetil}piperazina y ciclopropano carboxaldehído de forma similar al procedimiento usado para el ejemplo 54.

^{1}H RMN (400 MHz, $CDCl_3$) δ 0,02 (q, 2H), 0,43 (q, 2H), 0,76 (m, 1H), 1,74-1,76 (m, 4H), 1,83-1,89 (m, 2H), 1,95-1,99 (m, 2H), 2,03-2,06 (m, 3H), 2,13 (d, 2H), 2,19-2,21 (m, 4H), 2,26-2,40 (m, 5H), 2,47-2,51 (m, 4H), 2,59 (t, 2H), 3,49 (t, 2H), 3,68-3,72 (m, 2H), 3,98 (t, 2H), 6,82 (d, 2H), 7,17 (d, 2H).

EMAR IEN$^+$ m/z 442,3412 $[MH]^+$.

Ejemplo 169: 1-ciclopropil-*N*-(ciclopropilmetil)-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]-tetrahidro-2*H*-piran-4-il}metil)metanamina.



El compuesto del título (169 mg, 51%) se preparó a partir de la base libre de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il}metilamina y

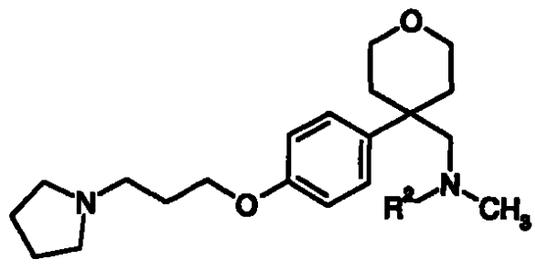
ciclopropano carboxaldehído de forma similar al procedimiento usado para el ejemplo 54. Se necesitaron 3 equivalentes de ciclopropano carboxaldehído para la síntesis de este ejemplo.

^{1}H RMN (400 MHz, $CDCl_3$) δ -0,04 (q, 4H), 0,39 (q, 4H), 0,71-0,76 (m, 2H), 1,80-1,86 (m, 4H), 1,94-2,12 (m, 6H), 2,16 (d, 4H), 2,55-2,72 (m, 8H), 3,51 (t, 2H), 3,75-3,79 (m, 2H), 4,04 (t, 2H), 6,88 (d, 2H), 7,21 (d, 2H).

EMAR IEN$^+$ m/z 427,3306 [MH]$^+$.

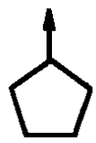
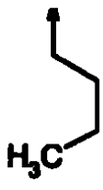
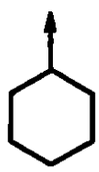
Ejemplos 170-178

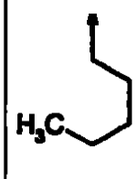
Los compuestos de los siguientes Ejemplos tabulados de fórmula general

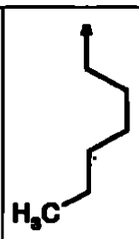
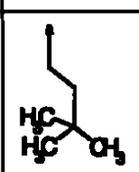
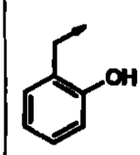


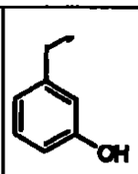
se prepararon usando metil-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]-tetrahidropiran-4-ilmetil]amina y los aldehídos o cetonas apropiados de forma similar al procedimiento usado para el ejemplo 54.

Nº Ej	R^2	Datos Analíticos

170		*N*-metil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)ciclopentanamina ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,21-1,28 (m, 2H), 1,39-1,43 (m, 2H), 1,53- 1,60 (m, 4H), 1,83-1,94 (m, 9H), 2,07-2,12 (m, 4H), 2,41 (s, 2H), 2,61- 2,72 (m, 7H), 3,49 (t, 2H), 3,73-3,79 (m, 2H), 4,02 (t, 2H), 6,89 (d, 2H), 7,20 (d, 2H). EMAR IEN$^+$ m/z 401,3162 $[MH]^+$. Rendimiento del 53%
171		*N*-metil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)butan-1-amina ^{1}H RMN (400 MHz, $CDCl_3$) δ 0,83 (t, 3H), 1,15-1,20 (m, 2H), 1,23-1,29 (m, 2H), 1,85-1,92 (m, 9H), 2,07-2,15 (m, 8H), 2,40 (s, 2H), 2,69-2,77 (m, 6H), 3,51 (t, 2H), 3,73-3,78 (m, 2H), 4,03 (t, 2H), 6,86 (d, 2H), 7,20 (d, 2H). EMAR IEN$^+$ m/z 389,3153 $[MH]^+$. Rendimiento del 57%
172		*N*-metil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)ciclohexanamina ^{1}H RMN (400 MHz, CD_3OD) δ 1,02-1,14 (m, 6H), 1,53 (m, 1H), 1,60 (d, 2H), 1,69 (d, 2H), 1,81-1,87 (m, 6H), 1,91 (s, 3H), 1,99-2,03 (m, 2H), 2,14 (d, 2H), 2,49 (s, 2H), 2,61 (t, 4H), 2,69 (t, 2H), 3,48 (t, 2H), 3,72-3,76 (m, 2H), 4,03 (t, 2H), 6,89 (d, 2H), 7,24 (d, 2H). EMAR IEN$^+$ m/z 415,3314 $[MH]^+$. Rendimiento del 61%

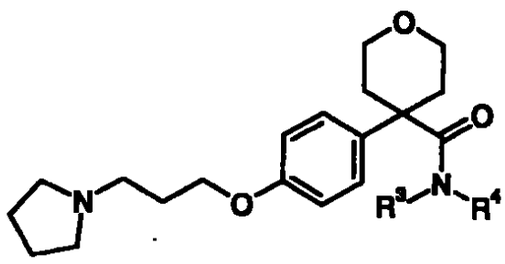
173		1-ciclopentil-*N*-metil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)metanamina ^{1}H RMN (400 MHz, CD_3OD) δ 1,07-1,12 (m, 2H), 1,46-1,50 (m, 4H), 1,60- 1,64 (m, 2H), 1,82-1,85 (m, 5H), 1,87-1,91 (m, 5H), 1,99-2,01 (m, 2H), 2,04 (d, 2H), 2,14 (d, 2H), 2,43 (s, 2H), 2,59-2,62 (m, 4H), 2,69 (t, 2H), 3,49 (t, 2H), 3,71-3,76 (m, 2H), 4,02 (t, 2H), 6,88 (d, 2H), 7,24 (d, 2H). EMAR IEN$^+$ m/z 415,3313 $[MH]^+$. Rendimiento del 44%
174		*N*-metil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)pentan-1-amina ^{1}H RMN (400 MHz, CD_3OD) δ 0,86 (t, 3H), 1,08-1,13 (m, 2H), 1,20-1,28 (m, 4H), 1,82-1,88 (m, 6H), 1,92 (s, 3H), 1,97-2,01 (m, 2H), 2,08 (t, 2H), 2,14 (d, 2H), 2,44 (s, 2H), 2,60-2,64 (m, 4H), 2,70 (t, 2H), 3,49 (t, 2H), 3,71-3,76 (m, 2H), 4,02 (t, 2H), 6,89 (d, 2H), 7,25 (d, 2H). EMAR IEN$^+$ m/z 403,3313 $[MH]^+$. Rendimiento del 30%

175		*N*-metil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)hexan-1-amina ^{1}H RMN (400 MHz, $CDCl_3$) δ 0,87 (t, 3H), 1,13-1,20 (m, 4H), 1,23-1,29 (m, 4H), 1,83-1,91 (m, 9H), 2,06-2,13 (m, 6H), 2,40 (s, 2H), 2,58-2,72 (m, 6H), 3,51 (t, 2H), 3,73-3,77 (m, 2H), 4,02 (t, 2H), 6,85 (d, 2H), 7,19 (d, 2H). EMAR IEN$^+$ m/z 417,3469 $[MH]^+$. Rendimiento del 74%
176		*N*,3,3-trimetil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)butan-1-amina ^{1}H RMN (400 MHz, $CDCl_3$) δ 0,77 (s, 9H), 1,17 (t, 2H), 1,84-1,90 (m, 6H), 1,92 (s, 3H), 2,08-2,12 (m, 6H), 2,41 (s, 2H), 2,57-2,70 (m, 6H), 3,52 (t, 2H), 3,73-3,78 (m, 2H), 4,01 (t, 2H), 6,86 (d, 2H), 7,20 (d, 2H). EMAR IEN$^+$ m/z 417,3457 $[MH]^+$. Rendimiento del 59%
177		2-{[metil({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)amino]metil}fenol ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,78 (s, 3H), 1,79-1,85 (m, 6H), 2,06-2,09 (m, 2H), 2,21 (d, 2H), 2,67-2,75 (m, 8H), 3,48-3,54 (m, 4H), 3,70-3,75 (m, 2H), 4,03 (t, 2H), 6,73 (t, 1H), 6,77 (d, 1H), 6,86 (d, 1H), 6,90 (d, 2H), 7,13 (t, 1H), 7,25 (d, 2H). EMAR IEN$^+$ m/z 439,2943 $[MH]^+$. Rendimiento del 30%

178		3-[[metil({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)amino]metil]fenol ^{1}H RMN (400 MHz, CD_3OD) δ 1,83 (sa, 7H), 1,88-1,91 (m, 2H), 1,95-2,01 (m, 2H), 2,11-2,15 (d, 2H), 2,55 (s, 2H), 2,58-2,62 (m, 4H), 2,69 (t, 2H), 3,17 (s, 2H), 3,49 (t, 2H), 3,63-3,67 (m, 2H), 4,02 (t, 2H), 6,62 (d, 1 H), 6,67 (d, 1H), 6,72 (s, 1H), 6,89 (d, 2H), 7,05 (t, 1H), 7,29 (d, 2H). EMAR IEN$^+$ m/z 439,2941 $[MH]^+$. Rendimiento del 68%

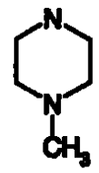
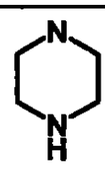
Ejemplos 179-191

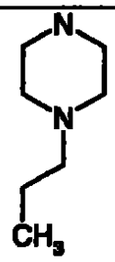
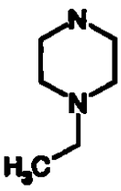
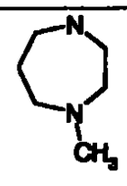
Los compuestos de los siguientes Ejemplos tabulados de fórmula general

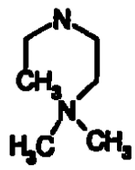
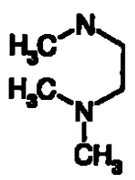
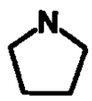


se prepararon usando ácido 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxílico, las amidas apropiadas y hexafluorofosfato de O-(1*H*-benzotriazol-1-il)-*N*,*N*,*N*',*N*'-tetrametiluronio (HBTU), tetrafluoroborato de O-(1*H*-benzotriazol-1-il)-*N*,*N*,*N*',*N*'-tetrametiluronio (TBTU) o clorhidrato de 1-[3-(Dimetilamino)propil]-3-etilcarbodiimida (WSCDI) de forma similar al procedimiento usado para el ejemplo 150.

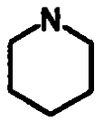
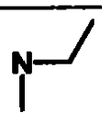
Nº	NR^3R^4	Datos Analíticos

Ej		
179		*N,N*-dietil-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxamida ^{1}H RMN (400 MHz, $CDCl_3$) δ 0,64-0,74 (m, 3H), 1,04-1,12 (m, 3H), 1,79- 1,82 (m, 4H), 1,91-2,03 (m, 4H), 2,23 (d, 2H), 2,54-2,58 (m, 4H), 2,65 (t, 2H), 2,86-2,94 (m, 2H), 3,27-3,35 (m, 2H), 3,77-3,89 (m, 4H), 4,01 (t, 2H), 6,86 (d, 2H), 7,15 (d, 2H). EMAR IEN$^+$ m/z 389,2789 $[MH]^+$. Microanálisis: Encontrado: C, 69,16; H, 9,18; N, 7,05%. $C_{23}H_{36}N_2O_3$. 0,5H_2O requiere C, 69,49; H, 9,38; N, 7,05%. Rendimiento del 68%
180		1-metil-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}carbonil)piperazina ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,76-1,81 (m, 4H), 1,97-2,03 (m, 8H), 2,15 (s, 3H), 2,19-2,22 (m, 2H), 2,50-2,54 (m, 4H), 2,62 (t, 2H), 3,26-3,44 (m, 4H), 3,78 (t, 2H), 3,87-3,90 (m, 2H), 4,02 (t, 2H), 6,88 (d, 2H), 7,15 (d, 2H). EMAR IEN$^+$ m/z 416,2908 $[MH]^+$. Rendimiento del 9%
181		1-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}carbonil)piperazina ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,77-1,80 (m, 6H), 1,97-2,02 (m, 4H), 2,20 (d, 2H), 2,50-2,54 (m, 6H), 2,61 (t, 2H), 3,24-3,38 (m, 4H), 3,78 (t, 2H), 3,86- 3,90 (m, 2H), 4,00 (t, 2H), 6,87 (d,

		2H), 7,15 (d, 2H). EMAR IEN$^+$ m/z 402,2746 [MH]$^+$. Rendimiento del 43%
182		1-propil-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}carbonil)piperazina ^{1}H RMN (400 MHz, $CDCl_3$) δ 0,84 (t, 3H), 1,37-1,43 (m, 2H), 1,1.69-1,77 (m, 2H), 1,84-1,88 (m, 4H), 1,98-2,07 (m, 6H), 2,14-2,19 (m, 4H), 2,65- 2,69 (m, 4H), 2,74 (t, 2H), 3,26-3,40 (m, 4H), 3,78 (t, 2H), 3,87-3,89 (m, 2H), 4,02 (t, 2H), 6,86 (d, 2H), 7,15 (d, 2H). EMAR IEN$^+$ m/z 444,3196 [MH]$^+$. Rendimiento del 71%
183		1-etil-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}carbonil)piperazina ^{1}H RMN (400 MHz, $CDCl_3$) δ 0,97 (t, 3H), 1,76-1,83 (m, 4H), 1,98-2,01 (m, 8H), 2,18 (d, 2H), 2,25 (d, 2H), 2,51-2,55 (m, 4H), 2,62 (t, 2H), 3,20-3,40 (m, 4H), 3,77 (t, 2H), 3,85-3,88 (m, 2H), 3,98-4,03 (m, 2H), 6,85 (d, 2H), 7,13 (d, 2H). EMAR IEN$^+$ m/z 430,3047 [MH]$^+$. Rendimiento del 81%
184		1-metil-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4- il}carbonil)-1,4-diazepan ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,75-1,81 (m, 8H), 1,98-2,03 (m, 4H), 2,14- 2,29 (m, 7H), 2,51-2,54 (m, 4H), 2,62 (t, 2H), 3,12-3,24 (m, 2H), 3,54-3,65 (m, 2H), 3,77-3,88 (m, 4H), 4,01 (t,

		2H), 6,88 (d, 2H), 7,16 (d, 2H). EMAR IEN$^+$ m/z 430,3057 [MH]$^+$. Rendimiento del 68%
185		*N*-[2-(dimetilamino)etil]-*N*-etil-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxamida ^{1}H RMN (400 MHz, $CDCl_3$) δ 0,66-0,72 (m, 3H), 1,76-1,81 (m, 4H), 1,98- 2,02 (m, 6H), 2,23-2,26 (m, 6H), 2,40-2,45 (m, 2H), 2,50-2,55 (m, 4H), 2,61 (t, 2H), 2,93-3,00 (m, 2H), 3,30-3,39 (m, 2H), 3,80 (t, 2H), 3,86-3,89 (m, 2H), 4,01 (t, 2H), 6,88 (d, 2H), 7,16 (d, 2H). EMAR IEN$^+$ m/z 432,3215 [MH]$^+$. Rendimiento del 62%
186		*N*-[2-(dimetilamino)etil]-*N*-metil-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxamida ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,77-1,80 (m, 4H), 1,96-2,01 (m, 6H), 2,18- 2,27 (m, 6H), 2,35-2,42 (m, 3H), 2,50-2,53 (m, 4H), 2,62 (t, 2H), 3,03 (s, 2H), 3,35-3,45 (m, 2H), 3,79 (t, 2H), 3,86-3,88 (m, 21-1), 4,01 (t, 2H), 6,87 (d, 2H), 7,15 (d, 2H). EMAR IEN$^+$ m/z 418,3052 [MH]$^+$. Rendimiento del 61%
187		1-(3-{4-[4-(pirrolidin-1-ilcarbonil)tetrahidro-2*H*-piran-4-il]fenoxi}propil)pirrolidina ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,40-1,52 (m, 3H), 1,52-1,80 (m, 3H), 1,82-2,10 (m, 6H), 2,10-2,30 (m, 2H), 2,30-2,38 (m, 2H), 2,60-3,05 (m, 6H), 3,40-3,60 (m, 2H), 3,75-3,90 (m, 4H), 4,05

480
479

		(t, 2H), 6,84 (d, 2H), 7,18 (d, 2H). EMBR APCI$^+$ m/z 387 [MH]$^+$. EMAR IEN$^+$ m/z 387,2634[MH]$^+$.
188		1-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}carbonil)piperidina ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,18-1,38 (m, 2H), 1,40-1,50 (m, 2H), 1,50- 1,80 (m, 6H), 1,84-2,05 (m, 2H), 2,10-2,30 (m, 8H), 2,30-2,48 (m, 2H), 3,10-3,40 (m, 4H), 3,75-3,90 (m, 4H), 4,10 (t, 2H), 6,88 (d, 2H), 7,20 (d, 2H). EMBR APCI$^+$ m/z 401 [MH]$^+$. EMAR IEN$^+$ m/z 401,2670 [MH]$^+$.
189		^{1}H RMN (400 MHz, $CDCl_3$) δ 1,80-2,00 (m, 6H), 2,00-2,20 (m, 4H), 2,20- 2,30 (m, 2H), 2,60-2,82 (m, 6H), 3,50-3,65(m, 2H), 3,72-3,90(m, 4H), 3,90-4,05(m, 2H), 4,08 (t, 2H), 6,90 (d, 2H), 7,20 (d, 2H). EMBR APCI$^+$ m/z 373 [MH]$^+$. EMAR IEN$^+$ m/z 373,2477 [MH]$^+$
190		*N*-etil-*N*-metil-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxamida ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,00-1,20(m, 3H), 1,78-1,86(m, 4H), 1,92- 2,08(m, 4H), 2,18-2,30(m, 2H), 2,45-2,60(m, 6H), 2,60-2,70(t, 3H), 3,22- 3,50(m, 2H), 3,70-3,94 (m, 4H), 4,00 (t, 2H), 6,88 (d, 2H), 7,15 (d, 2H). EMBR APCI$^+$ m/z 375 [MH]$^+$. EMAR IEN$^+$ m/z 375,2634 [MH]$^+$.

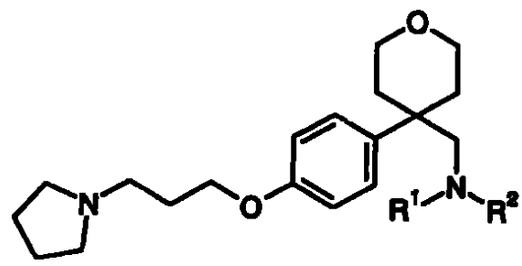
191		*N,N*-dimetil-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxamida ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,70-1,90(m, 4H), 1,92-2,10(m, 4H), 2,20- 2,30(m, 2H), 2,50-2,90(m, 12H), 3,70-3,82(m, 2H), 2,82-2,92(m, 2H), 4,00 (t, 2H), 6,88 (d, 2H), 7,15 (d, 2H). EMBR APCI$^+$ m/z 361 $[MH]^+$. EMAR IEN$^+$ m/z 361,2478$[MH]^+$.

Intermedio 60: 1-(Metoxiacetil)-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}carbonil)piperazina

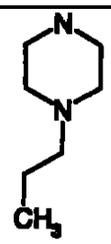
Se añadió gota a gota cloruro de metoxiacetilo (550, 0,6 mmol) a 0ºC a una solución de 1-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il]carbonil)piperazina del ejemplo 181 (200 mg, 0,5 mmol) y *N,N*-diisopropiletilamina (1000, 0,6 mmol) en diclorometano (3 ml). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se diluyó con diclorometano (20 ml) y se lavó con hidróxido sódico 2 N (20 ml). Las fases se separaron y la fase acuosa se extrajo posteriormente con diclorometano (20 ml). Los extractos orgánicos se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (97:3:0,3 a 90:10:1 en volumen) proporcionando el compuesto del título (160 mg, 67%).

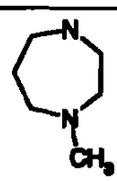
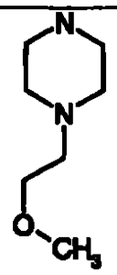
EMAR IEN$^+$ m/z 474,2952 $[MH]^+$.

Ejemplos 192-195



Los compuestos de los siguientes ejemplos tabulados de fórmula general 145 se prepararon usando hidruro de aluminio litio, las amidas de los ejemplos 182, 183, 184 e Intermedio 60 de forma similar al procedimiento usado para el ejemplo 142.

Nº Ej	NR^1R^2	Datos Analíticos
192 (del Ej 182)		1-propil-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piperazina ^{1}H RMN (400 MHz, $CDCl_3$) δ 0,85 (t, 3H), 1,40-1,46 (m, 2H), 1,77-1,80 (m, 4H), 1,84-1,91 (m, 2H), 1,98-2,03 (m, 2H), 2,08 (d, 2H), 2,18-2,22 (m, 6H), 2,24-2,28 (m, 4H), 2,36 (s, 2H), 2,51-2,54 (m, 4H), 2,63 (t, 2H), 3,51 (t, 2H), 3,72-3,75 (m, 2H), 4,01 (t, 2H), 6,84 (d, 2H), 7,20 (d, 2H). EMAR IEN$^+$ m/z 430,3410 $[MH]^+$. Rendimiento del 96%
193 (del Ej 183)		1-etil-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4- il}metil)piperazina ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,02 (t, 3H), 1,77-1,81 (m, 4H), 1,86-1,91 (m, 2H), 1,99-2,02 (m, 2H), 2,08 (d, 2H), 2,19-2,23 (m, 4H), 2,27-2,35 (m, 6H), 2,38 (s, 2H), 2,51-2,54 (m, 4H), 2,63 (t, 2H), 3,52 (t, 2H), 3,73- 3,76 (m, 2H), 4,02 (t, 2H), 6,85

		(d, 2H), 7,21 (d, 2H). EMAR IEN$^+$ m/z 416,3267 [MH]$^+$. Rendimiento del 54%
194 (del Ej 184)		1-metil-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)-1,4-diazepan ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,60 (p, 2H), 1,77-1,80 (m, 4H), 1,86-1,92 (m, 4H), 1,98-2,02 (m, 2H), 2,08 (d, 2H), 2,28 (s, 3H), 2,38-2,40 (m, 2H), 2,47-2,53 (m, 8H), 2,57 (s, 2H), 2,62 (t, 2H), 3,50 (t, 2H), 3,73-3,77 (m, 2H), 4,01 (t, 2H), 6,85 (d, 2H), 7,19 (d, 2H). EMAR IEN$^+$ m/z 416,3265 [MH]$^+$. Rendimiento del 13%
195 (del Int 60)		1-(2-metoxietil)-4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro- 2*H*-piran-4-il}metil)piperazina ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,76-1,79 (m, 4H), 1,84-1,89 (m, 2H), 1,97- 2,01 (m, 2H), 2,06 (d, 2H), 2,19-2,21 (m, 4H), 2,28-2,33 (m, 4H), 2,35 (s, 2H), 2,47 (t, 2H), 2,50-2,53 (m, 4H), 2,61 (t, 2H), 3,29 (s, 3H), 3,43 (t, 2H), 3,50 (t, 2H), 3,71-3,74 (m, 2H), 4,00 (t, 2H), 6,83 (d, 2H), 7,19 (d, 2H). EMAR IEN$^+$ m/z 446,3374 [MH]$^+$. Rendimiento del 31%

Intermedio 61: 2-nitro-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)anilina

Se agitó {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il}metilamina

(300 mg, 0,94 mmol), 2-fluoronitrobenceno (100 µl, 0,95 mmol) y carbonato potásico (150 mg, 1,08 mmol) a temperatura ambiente en *N,N*-dimetilformamida (1 ml) durante 2 días. La mezcla de reacción se concentró *al vacío* y el residuo se dividió entre agua (30 ml) y acetato de etilo (100 ml). Las fases se separaron y la fase orgánica se lavó con agua (2x20 ml), se secó sobre sulfato sódico, se filtró y se concentró *al vacío* dando el compuesto del título en forma de una goma amarilla (570 mg, 100%).

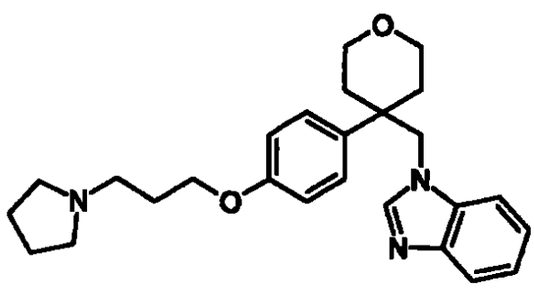
EMAR IEN$^+$ m/z 440,2537 $[MH]^+$.

Intermedio 62: *N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)benceno-1,2-diamina

Una solución de 2-nitro-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)anilina (570 mg, 1,3 mmol) en etanol (40 ml) se hidrogenó durante 5 horas a temperatura ambiente a 50 psi en presencia de Pd al 10%/C (60 mg, 10%p/p). La mezcla de reacción se filtró sobre Arbocel® y se aclaró con etanol. El filtrado se concentró *al vacío* dando el compuesto del título en forma de una goma, se usó sin purificación adicional (500 mg, 94%).

EMAR IEN$^+$ m/z 410,2791 $[MH]^+$.

Ejemplo 196: 2-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}-1*H*-bencimidazol



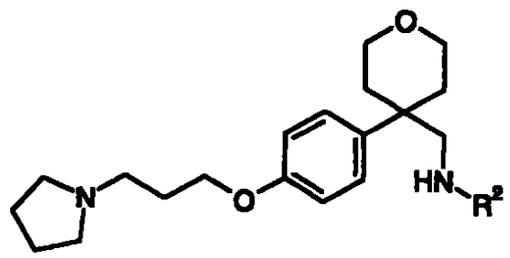
Se agitó *N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-

il]metil)benceno-1,2-diamina (500 mg, 1,22 mmol), trimetilortoformiato (5 ml) y ácido fórmico (0,5 ml) a temperatura ambiente durante 18 horas. La mezcla de reacción se concentró *al vacío* y el residuo se dividió entre carbonato sódico acuoso (50 ml) y acetato de etilo (100 ml). Las fases se separaron y la fase orgánica se lavó con agua (50 ml), se secó sobre sulfato sódico, se filtró y se concentró *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (98:2:0,2 a 92:8:1 en volumen). Las fracciones relevantes se evaporaron y el residuo se recogió en éter dietílico (20 ml). El material insoluble se retiró por filtración y el filtrado se concentró *al vacío* proporcionando el compuesto del título (150 mg, 29%).

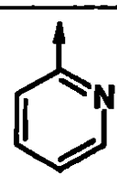
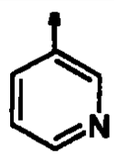
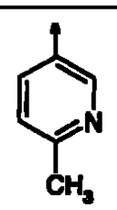
^{1}H RMN (400 MHz, CD_3OD) δ 1,83-1,85 (m, 4H), 1,98-2,06 (m, 4H), 2,23 (d, 2H), 2,62 (s, 4H), 2,69 (t, 2H), 3,42 (t, 2H), 3,82 (d, 2H), 4,00 (t, 2H), 4,33 (s, 2H), 6,84 (d, 2H), 7,08 (d, 2H), 7,14-7,18 (m, 3H), 7,26 (s, 1 H), 7,55 (d, 1 H).

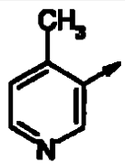
EMAR IEN$^+$ m/z 420,2637 $[MH]^+$.

Ejemplos 197-200

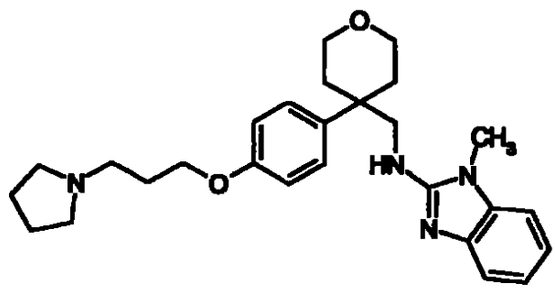


Los compuestos de los siguientes Ejemplos tabulados se prepararon usando {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il}metilamina y las bromo o yodo-piridinas apropiadas de forma similar al procedimiento de acoplamiento con paladio usado para el ejemplo 152.

Nº Ej	R^2	Datos Analíticos
197		*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piridin-2-amina ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,81-1,86 (m, 4H), 1,90-1,96 (m, 2H), 2,05- 2,17 (m, 4H), 2,58-2,75 (m, 6H), 3,50 (d, 2H), 3,59 (t, 2H), 3,81-3,85 (m, 2H), 4,00 (t, 1H), 4,05 (t, 2H), 6,23 (d, 1H), 6,51 (t, 1H), 6,92 (d, 2H), 7,25 (d, 2H), 7,32 (t, 1H), 8,02 (d, 1H). EMAR IEN$^+$ m/z 396,2633 $[MH]^+$. Rendimiento del 14%
198		*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piridin-3-amina ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,80-1,84 (m, 4H), 1,88-1,94 (m, 2H), 2,03- 2,07 (m, 2H), 2,19 (d, 2H), 2,56-2,63 (m, 4H), 2,66-2,70 (m, 2H), 3,24 (s, 3H), 3,57 (t, 2H), 3,77-3,82 (m, 2H), 4,05 (t, 2H), 6,74 (d, 1H), 6,93 (d, 2H), 7,01 (t, 1H), 7,24 (d, 2H), 7,88-7,91 (m, 2H). EMAR IEN$^+$ m/z 396,2640 $[MH]^+$. Rendimiento del 13%
199		6-metil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4- il}metil)piridin-3-amina ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,83 (d, 7H), 1,94-2,01 (m, 2H), 2,04 (t, 2H), 2,24 (d, 2H), 2,2.58-2,62 (m, 4H), 2,68 (t, 2H), 2,98 (t, 1H), 3,29 (d, 2H), 3,59 (t, 2H), 3,79-3,83 (m, 2H), 4,04

		(t, 2H), 6,85 (d, 1H), 6,94 (d, 2H), 7,27 (d, 2H), 7,86 (d, 1H), 7,92 (s, 1H). EMAR IEN$^+$ m/z 410,2793 $[MH]^+$. Rendimiento del 11%
200		~~4-metil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piridin-3-amina~~ ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,81-1,83 (m, 4H), 1,87-1,94 (m, 2H), 2,05 (t, 2H), 2,18 (d, 2H), 2,38 (s, 3H), 2,58-2,61 (m, 4H), 2,69 (t, 2H), 3,10 (t, 1H), 3,20 (d, 2H), 3,56 (t, 2H), 3,77-3,82 (m, 2H), 4,05 (t, 2H), 6,69 (dd, 1 H), 6,87 (d, 1 H), 6,93 (d, 2H), 7,24 (d, 2H), 7,78 (s, 1 H). EMAR IEN$^+$ m/z 410,2793 $[MH]^+$. Rendimiento del 13%

Ejemplo 201: 1-metil-*N*-({4-[4(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)-1*H*-bencimidazol-2-amina



Una mezcla de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il} metilamina (150 mg, 0,47 mmol), ácido 1-metilbencimidazol-2-sulfónico (83,4 mg, 0,39 mmol) y *N,N*-diisopropiletilamina (175 µl, 0,98 mmol) en acetonitrilo (1,5 ml) se calentó a 155ºC en el Smith Personal Synthesiser durante 2400 segundos y después 900 segundos más. La mezcla de reacción se dividió entre diclorometano (10 ml) y bicarbonato sódico acuoso saturado solución (10 ml). La fase orgánica se secó sobre sulfato sódico, se filtró y se concentró *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (100:0:0 a 95:5:0,5 en volumen) proporcionando el compuesto del título (29 mg, 14%). ^{1}H RMN (400 MHz, CD_3OD) δ 1,83-1,86 (m, 4H), 1,96-2,02 (m, 4H), 2,19 (d, 2H), 2,63-2,66 (m, 4H), 2,70 (t, 2H), 3,41 (s, 3H), 3,50 (t, 2H), 3,57 (s, 2H), 3,79-3,82 (m, 2H), 3,97 (t, 2H), 6,91 (d, 2H), 6,97-7,02 (m, 2H), 7,08 (d, 1H), 7,22 (d, 1H), 7,36 (d. 2H).

EMBR APCI$^+$ m/z 449 $[MH]^+$.

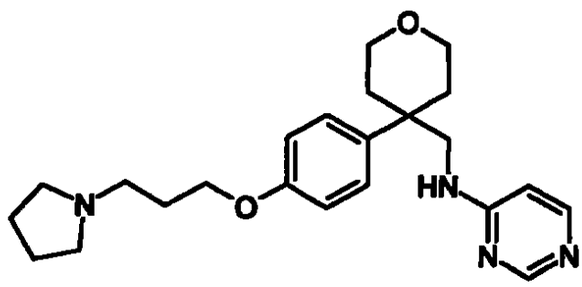
Intermedio 63: 6-cloro-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)pirimidin-4-amina

Una mezcla de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il)

metilamina (100 mg, 0,31 mmol), 4,6-dicloropirimidina (46,8 mg, 0,31 mmol) y *N,N*-diisopropiletilamina (137 µl, 0,78 mmol) en isopropanol (1 ml) se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se dividió entre acetato de etilo (3x10 ml) y bicarbonato sódico acuoso saturado (10 ml). Las fases orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (100:0:0 a 92:8:0,8 en volumen) proporcionando el compuesto del título (50 mg, 37%).

EMBR APCI$^+$ m/z 431 $[MH]^+$.

Ejemplo 202: *N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)pirimidin-4-amina



Una solución de 6-cloro-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)pirimidin-4-amina (50 mg, 0,12 mmol) y trietilamina (48,6 µl, 0,35 mmol) en etanol (2 ml) se hidrogenó durante 16 horas a temperatura ambiente a 50 psi en presencia de Pd al 10%/C (5 mg, 10% p/p). La mezcla de reacción se filtró a través de Arbocel® y se aclaró con etanol y agua. El filtrado se concentró *al vacío*. El residuo se dividió entre acetato de etilo (20 ml) y carbonato sódico acuoso saturado (20 ml). La fase orgánica se secó sobre sulfato sódico, se filtró y se concentró *al vacío*. El producto en bruto se purificó

488
489

por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (100:0:0 a 95:5:0,5 en volumen) proporcionando el compuesto del título (9 mg, 20%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,78-1,81 (m, 4H), 1,85-1,90 (m, 2H), 2,00-2,05 (m, 2H), 2,09-2,16 (m, 2H), 2,53-2,60 (m, 4H), 2,66 (t, 2H), 3,54-3,58 (m, 4H), 3,79-3,83 (m, 2H), 4,02 (t, 2H), 4,44 (sa, 1H), 6,12 (d, 1H), 6,92 (d, 2H), 7,20 (d, 2H), 8,05 (d, 1H), 8,47 (s, 1H).

EMAR IEN$^+$ m/z 397,2596 $[MH]^+$.

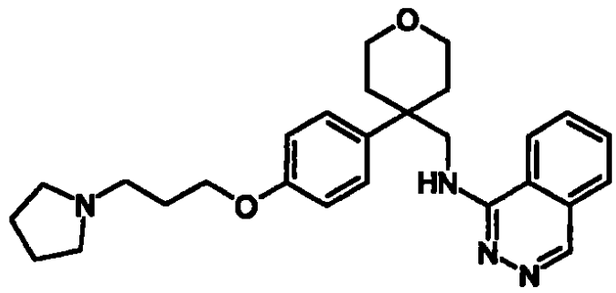
Intermedio 64: 4-cloro-*N*-({4-[4(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)ftalazin-1-amina

Una mezcla de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il) metilamina (300 mg, 0,94 mmol), 1,4-dicloroftalazina (188 mg, 0,94 mmol) y *N,N*-diisopropiletilamina (4101.l, 2,36 mmol) en *N,N*-dimetilformamida (1 ml) se agitó a temperatura ambiente durante 18 horas. Se añadió más 1,4-dicloroftalazina (188 mg, 0,94 mmol) y la reacción se agitó a temperatura ambiente durante 36 horas, después se calentó a 55ºC durante 18 horas. La mezcla de reacción se dividió entre acetato de etilo (20 ml) y una solución de bicarbonato sódico acuoso saturado (20 ml). La fase orgánica se lavó con más bicarbonato sódico acuoso, salmuera, se secó sobre sulfato sódico, se filtró y se concentró *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (100:0:0 a 92:8:0,8 en volumen) proporcionando el compuesto del título (183 mg, 61%).

EMBR APCI$^+$ m/z 481 $[M+H]^+$

Ejemplo 203: *N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-

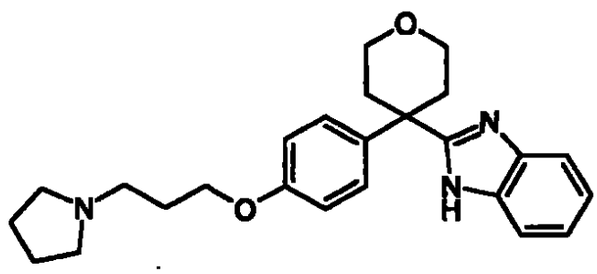
piran-4-il]metil)ftalazin-1-amina



El compuesto del título (86 mg, 51%) se preparó a partir de 4-cloro-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)ftalazin-1-amina por hidrogenación de forma similar al procedimiento usado para el ejemplo 202. ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,80-1,84 (m, 4H), 2,01-2,08 (m, 4H), 2,15-2,20 (m, 2H), 2,55-2,60 (m, 4H), 2,68 (t, 2H), 3,61-3,66 (m, 2H), 3,86-3,92 (m, 2H), 3,98 (d, 2H), 4,07 (t, 2H), 4,62 (t, 1H), 7,00 (d, 2H), 7,32-7,36 (m, 3H), 7,68-7,77 (m, 3H), 8,89 (s, 1 H).

EMAR IEN$^+$ m/z 447,2746 $[MH]^+$.

Ejemplo 204: 2-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}-1*H*-bencimidazol



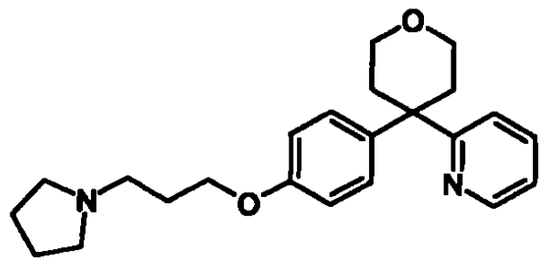
Una mezcla de ácido 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxílico (400 mg, 1,20 mmol), 1,2-diaminobenceno (129 mg, 1,20 mmol) y ácido polifosfórico (2 g) se calentó a 130°C durante 2 días. La mezcla

de reacción enfriada se dividió entre diclorometano (20 ml) y amoníaco acuoso (20 ml). La fase acuosa se extrajo posteriormente con diclorometano (2x50 ml). La fase orgánicas se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío*. El producto en bruto se purificó por HPLC preparativa en Fraction-Lynx@ eluyendo con agua:acetonitrilo:TFA (95:5:0,1) proporcionando el compuesto del título (3,5 mg, 1%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,92-1,96 (m, 2H), 2,06-2,21 (m, 4H), 2,40-2,48 (m, 2H), 2,96-3,00 (m, 4H), 3,05-3,09 (m, 2H), 3,16-3,20 (m, 2H), 3,57-3,65 (m, 4H), 3,93 (d, 2H), 5,45 (d, 2H), 7,06 (d, 2H), 7,45 (d, 2H), 7,71-7,74 (m, 2H).

LCEM IEN$^+$ m/z 406 $[MH]^+$.

Ejemplo 205: 2-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}-piridina



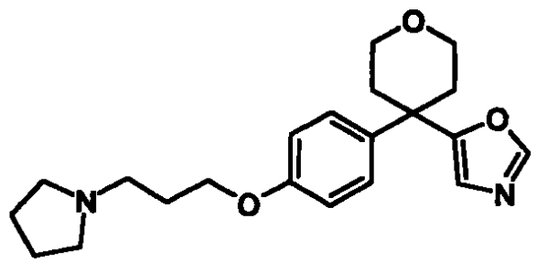
Se añadió trimetilsililacetileno (0,9 ml, 6 mmol) a temperatura ambiente a una solución de 4-[3-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-carbonitrilo (200 mg, 0,6 mmol) y dicarbonilciclopentadienilo cobalto (12 mg, 0,07 mmol) en tolueno (3 ml). Se añadió fluoruro tetrabutilamónico (1,54 g, 6 mmol) en porciones durante 10 minutos. Después, la mezcla de reacción se agitó a temperatura ambiente en luz visible en una atmósfera de nitrógeno durante 12 días. La mezcla de reacción se concentró *al vacío*. El residuo se dividió entre diclorometano (50 ml) y una solución de hidróxido sódico acuoso (50 ml). La

fase acuosa se extrajo otra vez con diclorometano (50 ml). Las fases orgánicas se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío*. El producto en bruto se purificó por HPLC preparativa en Fraction-Lynx® eluyendo con agua:acetonitrilo:TFA (95:5:0,1) proporcionando el compuesto del título (4 mg, 2%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,78-1,81 (m, 4H), 1,95-2,02 (m, 2H), 2,32-2,39 (m, 2H), 2,51-2,56 (m, 4H), 2,61-2,70 (m, 4H), 3,67 (t, 2H), 3,78-3,84 (m, 2H), 3,98 (d, 2H), 6,81 (d, 2H), 7,06 (t, 1H), 7,13 (d, 1H), 7,21 (d, 2H), 7,55 (t, 1H), 8,58 (d, 1H).

EMAR IEN$^+$ m/z 367,2375 $[MH]^+$.

Ejemplo 206: 5-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}-1,3-oxazol

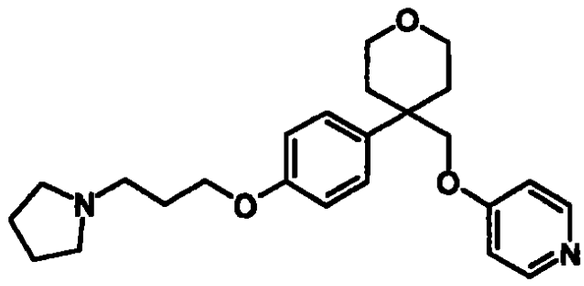


Se añadió isocianuro de tosilmetilo (370 mg, 1,89 mmol) a una solución de 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbaldehído (500 mg, 1,58 mmol) y carbonato potásico (652 mg, 4,73 mmol) en metanol (7 ml). La mezcla de reacción se calentó a reflujo durante 3 horas. La mezcla de reacción se dividió entre acetato de etilo (2x75 ml) y agua (20 ml). La fase orgánicas se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío*. El producto en bruto se recogió en ácido clorhídrico 2 N (3 ml) y se agitó a temperatura ambiente durante 1,5 horas. La mezcla se

dividió entre carbonato sódico acuoso y diclorometano (2x75 ml). Las fases orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:5:0,5 en volumen) proporcionando el compuesto del título (12 mg, 2%).

^{1}H RMN (400 MHz, CD_3OD) δ 1,81-1,85 (m, 4H), 1,97-2,02 (m, 2H), 2,25-2,31 (m, 2H), 2,38-2,43 (m, 2H), 2,60-2,63 (m, 4H), 2,69 (t, 2H), 3,61 (t, 2H), 3,78-3,83 (m, 2H), 4,01 (t, 2H), 6,87 (d, 2H), 6,98 (s, 1H), 7,22 (d, 2H), 8,09 (s, 1H). EMBR APCI$^+$ *m/z* 357 $[MH]^+$.

Ejemplo 207: 4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metoxi)piridina



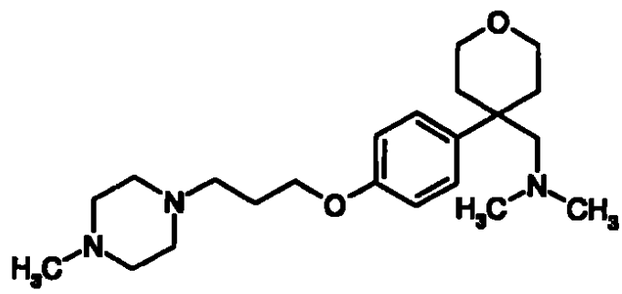
El compuesto del título (75 mg, 60%) se preparó a partir de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metanol y 4-bromopiridina de forma similar al procedimiento usado para el ejemplo 152.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,76-1,82 (m, 4H), 1,98-2,04 (m, 2H), 2,12-2,17 (m, 4H), 2,49-2,58 (m, 4H), 2,61-2,66 (m, 2H), 3,54-3,60 (m, 2H), 3,81-3,85 (m, 2H), 3,87 (s, 2H), 4,03 (t, 2H), 6,71 (d, 2H), 6,91 (d, 2H), 7,29 (d, 2H), 8,36 (d, 2H). EMAR IEN$^+$ m/z 397,2479 $[MH]^+$.

Intermedio 65: 1-{4-[4-(3-cloropropoxi)fenil]tetrahidro-2*H*-piran-4-il}-*N*,*N*-dimetilmetanamina

Se añadió 1-bromo-3-cloropropano (0,42 ml, 4,25 mmol) a una solución de 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (1,0 g, 4,25 mmol) y carbonato potásico (1,5 g, 10,8 mmol) en *N,N*-dimetilformamida (10 ml). La mezcla de reacción se agitó a 45ºC durante 18 horas. La mezcla de reacción se concentró *al vacío*. El residuo se dividió entre acetato de etilo (100 ml) y agua (50 ml). La fase orgánica se separó, se secó sobre sulfato sódico, se filtró y se concentró *al vacío*. proporcionando el compuesto del título (800 mg, 60%). EMBR APCI$^+$ m/z 412 [MH]$^+$.

Ejemplo 208: *N,N*-dimetil-1-{4-[4-[3-(4-metilpiperazin-1-il)propoxi]fenil}tetrahidro-2*H*-piran-4-il)metanamina

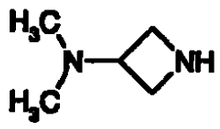


Una mezcla de 1-[4-[4-(3-cloropropoxi)fenil]tetrahidro-2*H*-piran-4-il)-*N,N*-dimetilmetanamina (200 mg, 0,7 mmol), *N*-metil piperazina (87 µl, 0,79 mmol), bicarbonato sódico sólido (66 mg, 0,79 mmol) y una cantidad catalítica de yoduro potásico se calentó a 50ºC en *N,N*-dimetilformamida (2 ml) durante 18 horas. La mezcla de reacción se concentró *al vacío*. El residuo se dividió entre acetato de etilo (2x75 ml) y agua (20 ml). La fase orgánicas se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (96:4:0,4 en volumen) proporcionando el compuesto del título (102 mg, 39%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,84-1,91 (m, 2H), 1,95-1,99 (m, 8H), 2,07-2,11 (m, 2H), 2,30 (s, 3H), 2,40 (s, 2H), 2,42-2,59 (m, 10H), 3,54 (t, 2H), 3,72-3,78 (m, 2H), 4,00 (t, 2H), 6,86 (d, 2H), 7,20 (d, 2H).

EMAR IEN$^+$ m/z 376,2951 $[MH]^+$.

Intermedio 66: Ditrifluoroacetato de *N,N*-dimetilazetidin-3-amina

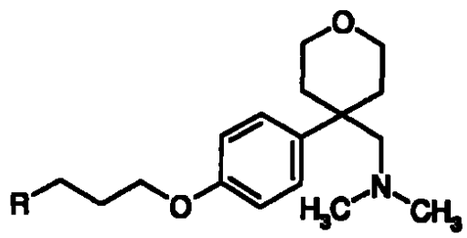


. 2TFA

Esta amina se ha descrito en la patente WO 2004096810 (prep 170, p240).

Ejemplos 208-211

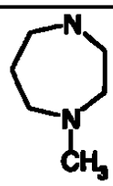
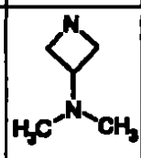
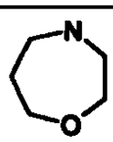
Los compuestos de los siguientes ejemplos tabulados de fórmula general



se prepararon usando 1-[4-[4-(3-cloropropoxi)fenil]tetrahidro-2*H*-piran-4-il)-*N,N*-dimetilmetanamina y las amidas apropiadas de forma similar al procedimiento usado para el ejemplo 208.

Ej Nº	R	Datos Analíticos

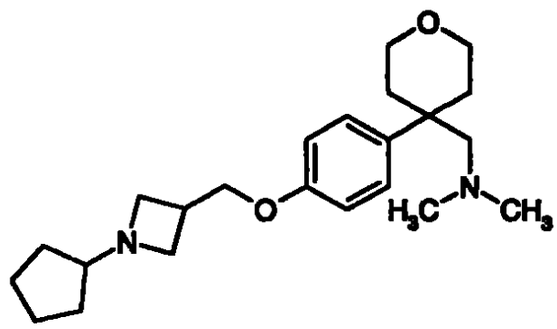
APT 496

209		*N,N*-dimetil-1-(4-{4-[3-(4-metil-1,4-diazepan-1-il)propoxi]fenil}tetrahidro-2*H*-piran-4-il)metanamina ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,77-1,91 (m, 6H), 1,94 (s, 6H), 2,04-2,08 (m, 2H), 2,33 (s, 3H), 2,38 (s, 2H), 2,57-2,65 (m, 6H), 2,70-2,73 (m, 4H), 3,52 (t, 2H), 3,70-3,75 (m, 2H), 3,98 (t, 2H), 6,84 (d, 2H), 7,18 (d, 2H). EMBR APCI$^+$ m/z 390 $[MH]^+$. Rendimiento del 30%
210		1-[3-(4-{4-[(dimetilamino)metil]tetrahidro-2*H*-piran-4-il}fenoxi)propil]-*N,N*-dimetilazetidin-3-amina ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,62-1,90 (m, 6H), 1,96 (s, 6H), 2,11 (s, 6H), 2,40 (s, 2H), 2,63 (t, 3H), 2,80-2,86 (m, 3H), 3,52-3,56 (m, 4H), 3,72- 3,76 (m, 2H), 3,96-3,99 (m, 2H), 6,85 (d, 2H), 7,20 (d, 2H). EMAR IEN$^+$ m/z 376,2959 $[MH]^+$. Rendimiento del 53%
211		Dimetil-[4-(4-(3-[1,4]oxazepan-4-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil]-amina ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,85-2,04 (m, 12H), 2,11 (M, 2H), 2,42 (s, 2H), 2,7-2,8 (m, 6H), 3,55 (t, 2H), 3,72-3,82 (m, 6H), 4,02 (t, 2H), 6,87 (d, 2H), 7,22 (d, 2H) EMAR IEN$^+$ m/z 377,2792 $[MH]^+$ Rendimiento del 35%

Intermedio 67: Clorhidrato de 1-benzhidril-3-clorometil-azetidina

Se disolvió (1-Benzhidril-azetidin-3-il)-metanol (3,07 g, 12,1 mmol) en diclorometano (60 ml). La reacción se enfrió a 0-5°C y se añadió lentamente cloruro de tionilo (1,07 ml, 14,6 mmol). La reacción se dejó calentar a temperatura ambiente y se agitó durante 18 horas. La reacción se concentró *al vacío* y formó un azeótropo con tolueno (3x20 ml) dando el compuesto del título (3,8 g, 100%) en forma de un sólido pardo pálido.

Ejemplo 212: 1-(4-[4-[(1-ciclopentilazetidin-3-il)metoxi]fenil)tetrahidro-2*H*-piran-4-il)-*N*,*N*-dimetilmetanamina



Etapa 1:

Se hizo reaccionar de forma conjunta 4-(4-dimetilaminometil-tetrahidro-piran-4-il)-fenol (1,15 g, 5,65 mmol), clorhidrato de 1-benzhidril-3-clorometil-azetidina (1,58 g, 5,13 mmol), *N*,*N*-dimetilformamida (32 ml) y carbonato potásico (2,84 g, 20,52 mmol) de acuerdo con el procedimiento general B. La mezcla de reacción se diluyó con acetato de etilo. La fase orgánica se lavó con hidróxido sódico 2 M (3x50 ml), salmuera (3x50 ml), se secó sobre sulfato de magnesio, se filtró y se concentró *al vacío* proporcionando 1-[4-[4-([1-benzhidrilazetidin-3-il]metoxi)fenil)tetrahidro-2*H*-piran-4-il]-*N*,*N*-dimetilmetanamina (1,82 g, 81%) en forma de un sólido blanquecino.

Etapa 2:

Este intermedio se hidrogenó en etanol (20 ml) durante 4 horas a 60°C a presión atmosférica en presencia de Pd al 10%/C (300 mg). La mezcla de reacción se filtró a través de Arbocel y se aclaró con etanol y agua. El filtrado se concentró *al vacío*. El residuo se recogió en ácido clorhídrico 2 N (50 ml) y se extrajo con éter de *terc*-butilmetilo (3x50 ml). La fase acuosa se basificó a pH14 con hidróxido sódico 2 M y se extrajo con diclorometano (3x50 ml). Estas fases orgánicas se combinaron, se secaron sobre sulfato de magnesio, se filtraron y se concentraron *al vacío* proporcionando 1-[4-[4-(azetidin-3-ilmetoxi)fenil]tetrahidro-2*H*-piran-4-il]-*N*,*N*-dimetilmetanamina (850 mg, 85%) en forma de un sólido blanquecino.

Etapa 3:

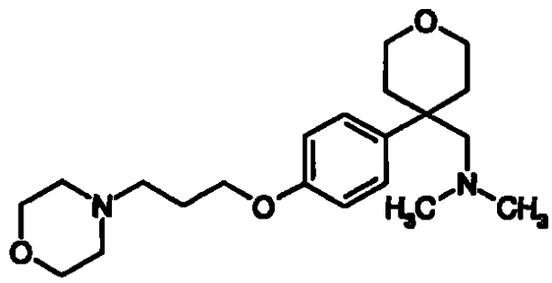
Se añadieron bromuro de ciclopentilo (0,17 ml, 1,54 mmol) e hidróxido sódico acuoso 5 M (0,34 ml, 1,68 mmol) a una solución de 1-[4-[4-(azetidin-3-ilmetoxi)fenil]tetrahidro-2*H*-piran-4-il]-*N*,*N*-dimetilmetanamina (425 mg, 1,4 mmol) en acetona (9 ml). La mezcla de reacción se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se concentró *al vacío*. El residuo se recogió en ácido clorhídrico 2 N alcanzando pH 1 y se extrajo con éter de *terc*-butilmetilo (2x15 ml). La fase acuosa se basificó posteriormente a pH14 con hidróxido sódico 4 M (aproximadamente 40 ml) y se extrajo con diclorometano (3x30 ml). Estas fases orgánicas se combinaron, se secaron sobre sulfato de magnesio, se filtraron y se concentraron *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:4:1 en volumen) proporcionando el compuesto del título (55 mg, 11%) en forma de un sólido amarillo.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,28-1,73 (m, 8H), 1,83-1,93 (m, 2H), 1,96 (s, 6H),

500
499

2,05-2,13 (m, 2H), 2,40 (s, 2H), 2,71 (m, 1 H), 2,90 (m, 1 H), 3,00 (t, 2H), 3,39-3,58 (m, 4H), 3,72-3,78 (m, 2H), 4,05 (d, 2H), 6,87 (d, 2H), 7,21 (d, 2H). EMBR IEN$^+$ m/z 373 [MH]$^+$.

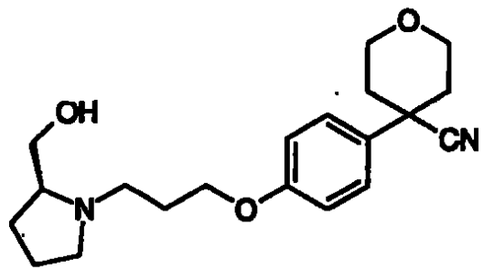
Ejemplo 213: *N,N*-dimetil-1-{4-[4(3-morfolin-4-ilpropoxi)fenil]tetrahidro-2*H*piran-4-il}metanamina



Una mezcla de 1-{4-[4-(3-cloropropoxi)fenil]tetrahidro-2*H*-piran-4-il)-*N,N*-dimetilmetanamina (100 mg, 0,32 mmol), morfolina (100 mg, 1,1 mmol) y carbonato potásico (100 mg, 0,72 mmol) se calentó a reflujo en acetonitrilo (5 ml) durante 8 horas. Se añadió más morfolina (100 mg, 1,1 mmol) y carbonato potásico (100 mg, 0,72 mmol) y la mezcla de reacción se calentó a reflujo durante 6 horas. La mezcla de reacción se concentró *al vacío*. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (90:10:1 en volumen) proporcionando el compuesto del título (61 mg, 52%).

^{1}H RMN (400 MHz, CD_3OD) δ 0,81-0,87 (m, 2H), 1,04-2,01 (m, 8H), 2,13-2,18 (m, 2H), 2,48-2,50 (m, 6H), 2,56 (t, 2H), 3,50 (t, 2H), 3,68-3,77 (m. 6H), 4,03 (t, 2H), 6,90 (d, 2H), 7,27 (d, 2H). EMAR IEN$^+$ m/z 363,2635 [MH]$^+$.

Ejemplo 214: 4-{4-[3-[(2S)-2-(hidroximetil)pirrolidin-1-il]propoxi}fenil)tetrahidro-2*H*-piran-4-carbonitrilo



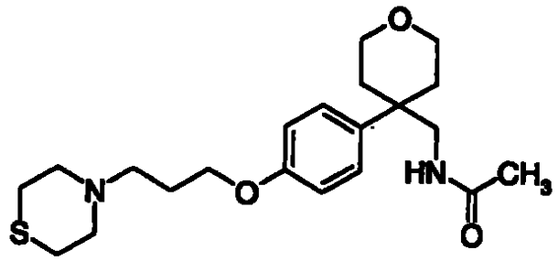
El compuesto del título (30 mg, 12%) se preparó usando 4-[4-(3-cloro-propoxi)-fenil)-tetrahidropiran-4-carbonitrilo y (*S*)-(+)-2-pirrolidina metanol de forma similar al procedimiento usado para el ejemplo 208.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,79-1,85 (m, 3H), 1,94 (m, 1H), 2,01-2,12 (m, 7H), 2,41 (m, 1H), 2,58 (m, 1H), 2,78 (m, 1H), 3,08 (m, 1H), 3,33 (m, 1H), 3,49 (m, 1H), 3,71 (d, 1H), 3,88 (t, 2H), 4,04-4,09 (m, 4H), 6,92 (d, 2H), 7,38 (d, 2H). EMAR IEN$^+$ m/z 345,2167 $[MH]^+$.

Intermedio 68: 1-[4-[4-(3-tiomorfolin-4-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il]metanamina

El compuesto del título (1,58 g, 92%) se preparó usando 4-[4-(3-tiomorfolin-4-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbonitrilo e hidruro de aluminio litio de forma similar al procedimiento usado para el Intermedio 51. EMBR APCI$^+$ m/z 351 $[MH]^+$.

Ejemplo 215: *N*-({4-[4-(3-tiomorfolin-4-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)acetamida

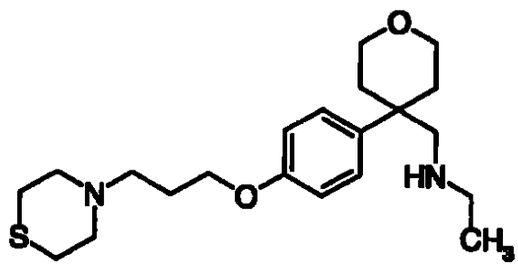


El compuesto del título (1,16 g, 100%) se preparó usando 1-{4-[4-(3-tiomorfolin-4-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metanamina y anhídrido acético de forma similar al procedimiento usado para el ejemplo 140.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,82-1,86 (m, 2H), 1,87 (s, 3H), 2,00-2,04 (m, 4H), 2,58-2,85 (m, 10H), 3,45 (d, 2H), 3,56-3,61 (m, 2H), 3,79-3,84 (m, 2H), 4,02 (t, 2H), 4,97 (sa, 1H), 6,91 (d, 2H), 7,19 (d, 2H).

EMBR APCI$^+$ m/z 393 $[MH]^+$.

Ejemplo 216: *N*-({4-[4-(3-tiomorfolin-4-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)etanamina



El compuesto del título (492 mg, 44%) se preparó usando *N*-({4-[4-(3-tiomorfolin-4-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)acetamida e hidruro de aluminio litio de forma similar al procedimiento usado para el ejemplo 142.

^{1}H RMN (400 MHz, $CDCl_3$) δ 0,96 (t, 3H), 1,88-1,98 (m, 4H), 2,11-2,15 (m, 2H), 2,49 (q, 2H), 2,55 (t, 2H), 2,68-2,74 (m, 10H), 3,55 (t, 2H), 3,74-3,79 (m, 2H), 4,00 (t, 2H), 6,89 (d, 2H), 7,22 (d, 2H).

EMBR APCI$^+$ m/z 379 $[MH]^+$.

Intermedio 69: Ácido 4-(4-metoxifenil)tetrahidro-2*H*-piran-4-carboxílico

Se calentó a reflujo 4-(4-metoxifenil)-tetrahidro-2*H*-piran-4-carbonitrilo (10 g, 46 mmol) durante 18 horas en ácido clorhídrico concentrado (100 ml). La mezcla de reacción se extrajo con diclorometano (2x100 ml). Las fases

orgánicas combinadas se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío* a un sólido gomoso. Este sólido se dividió entre hidróxido sódico 2 M (300 ml) y acetato de etilo (300 ml). Después, la fase acuosa se acidificó con ácido clorhídrico concentrado (se formó un precipitado blanco que se disolvió añadiendo diclorometano (250 ml)). Las fases se separaron y la fase acuosa se extrajo adicionalmente con diclorometano (250 ml). Estas fases orgánicas de diclorometano se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío* proporcionando el compuesto del título (3,4 g, 31%) en forma de un sólido blanco.

EMBR APCI$^-$ m/z 235 [M-H]$^-$.

Intermedio 70: 1-{[4-(4-metoxifenil)tetrahidro-2*H*-piran-4-il]carbonil}-4-metilpiperazina

El compuesto del título (515 mg, 77%) se preparó usando ácido 4-(4-metoxifenil)tetrahidro-2*H*-piran-4-carboxílico, *N*-metil-piperazina y tetrafluoroborato de O-(1*H*-benzotriazol-1-il)-*N*,*N*,*N*',*N*'-tetrametiluronio (TBTU) de forma similar al procedimiento usado para el ejemplo 166.

EMAR IEN$^+$ m/z 319,2009 [MH]$^+$.

Intermedio 71: 1-{[4-(4-metoxifenil)tetrahidro-2*H*-piran-4-il]metil}-4-metilpiperazina

El compuesto del título (428 mg, 93%) se preparó usando 1-{[4-(4-metoxifenil)tetrahidro-2*H*-piran-4-il]carbonil}-4-metilpiperazina e hidruro de aluminio litio de forma similar al procedimiento usado para el ejemplo 142.

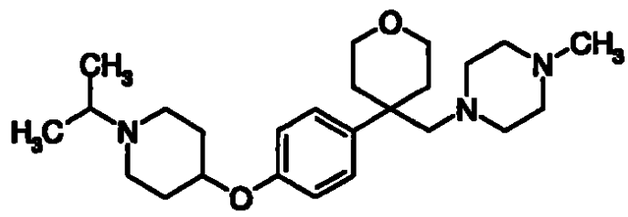
EMAR IEN$^+$ m/z 305,2220 [MH]$^+$.

Intermedio 72: 4-{4-[(4-metilpiperazin-1-il)metil]tetrahidro-2*H*-piran-4-il}fenol

A una suspensión de tiometóxido sódico (660 mg, 9,4 mmol) en *N,N*-dimetilformamida (2 ml) se le añadió 1-([4-(4-metoxifenil)tetrahidro-2*H*-piran-4-il]metil}-4-metilpiperazina (410 mg, 1,3 mmol) en *N,N*-dimetilformamida (3 ml). La mezcla de reacción se calentó a 130ºC en una atmósfera de nitrógeno durante 18 horas. La mezcla se dejó enfriar a temperatura ambiente y se añadió cloruro amónico acuoso saturado. La mezcla se extrajo con acetato de etilo (2x30 ml). Los extractos orgánicos combinados se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío* proporcionando un aceite pardo pálido. Esto formó un azeótropo con tolueno y se secó al vacío proporcionando el compuesto del título (390 mg, 100%) en forma de un sólido blanquecino.

EMAR IEN$^+$ m/z 291,2062 $[MH]^+$.

Ejemplo 217: 1-[(4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]-4-metilpiperazina



El compuesto del título (72 mg, 14%) se preparó usando 4-{4-[(4-metilpiperazin-1-il)metil]tetrahidro-2*H*-piran-4-il}fenol, 1-isopropil-4-hidroxipiperidina (etapa 1 del Intermedio 21), PPh_3 y DIAD de forma similar al procedimiento usado para el Intermedio 55.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,04 (d, 6H), 1,76-1,90 (m, 4H), 1,96-2,08 (m, 4H), 2,17-2,26 (m, 11H), 2,33-2,38 (m, 4H), 2,69-2,80 (m, 3H), 3,51 (t, 2H), 3,69-3,74 (m, 2H), 4,24 (m, 1H), 6,84 (d, 2H), 7,18 (d, 2H),

EMAR IEN$^+$ m/z 416,3268 $[MH]^+$.

Intermedio 73: 4-[[4-(4-metoxifenil)tetrahidro-2*H*-piran-4-il]carbonil]morfolina

El compuesto del título (3,1 g, 87%) se preparó usando ácido 4-(4-metoxifenil)tetrahidro-2*H*-piran-4-carboxílico, morfolina y tetrafluoroborato de O-(1*H*-benzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (TBTU) de forma similar al procedimiento usado para el ejemplo 166.

EMAR IEN$^+$ m/z 306,1696 $[MH]^+$.

Intermedio 74: 4-[[4-(4-metoxifenil)tetrahidro-2*H*-piran-4-il]metil)-morfolina

El compuesto del título (2,48 g, 87%) se preparó usando 4-[[4-(4-metoxifenil)tetrahidro-2*H*-piran-4-il]carbonil]morfolina e hidruro de aluminio litio de forma similar al procedimiento usado para el ejemplo 142.

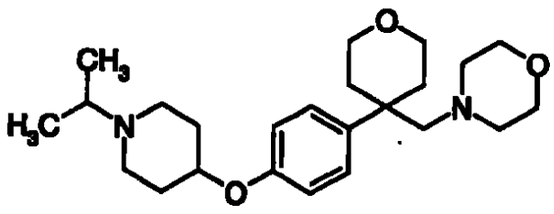
EMAR IEN$^+$ m/z 292,1897 $[MH]^+$.

Intermedio 75: 4-[4-(morfolin-4-ilmetil)tetrahidro-2*H*-piran-4-il]fenol

El compuesto del título (1,70 g, 75%) se preparó usando 4-[[4-(4-metoxifenil)tetrahidro-2*H*-piran-4-il]metil)-morfolina y tiometóxido sódico de forma similar al procedimiento usado para el Intermedio 72.

EMAR IEN$^+$ m/z 278,1740 $[MH]^+$.

Ejemplo 218: 4-[(4-[4-[(1-isopropilpiperidin-4-il)oxi]fenil)tetrahidro-2*H*-piran-4-il)metil]-morfolina



El compuesto del título (52 mg, 12%) se preparó usando 4-[4-(morfolin-4-ilmetil)tetrahidro-2*H*-piran-4-il]fenol, 1-isopropil-4-hidroxipiperidina (etapa 1 del

Intermedio 21), PPh_3 y DIAD de forma similar al procedimiento usado para el Intermedio 55.

^1H RMN (400 MHz, CD_3OD) δ 1,09 (d, 6H), 1,74-1,80 (m, 2H), 1,83-1,90 (m, 2H), 1,98-2,04 (m, 2H), 2,12-2,18 (m, 6H), 2,40 (s, 2H), 2,47 (t, 2H), 2,75 (m, 1H), 2,80-2,85 (m, 2H), 3,47-3,54 (m, 6H), 3,71-3,77 (m, 2H), 4,36 (m, 1H), 6,90 (d, 2H), 7,28 (d, 2H).

EMAR IEN$^+$ m/z 403,2951 $[MH]^+$.

Intermedio 76: 4-[[4-[4-[1-(benzhidril)azetidin-3-il]metoxi]fenil]tetrahidro-2*H*-piran-4-il]metil]-morfolina

El compuesto del título (1,09 g, 66%) se preparó usando 4-[4-(morfolin-4-ilmetil)tetrahidro-2*H*-piran-4-il]fenol, (1-benzhidril-azetidin-3-il)-metanol, PPh_3 y DIAD de forma similar al procedimiento usado para el Intermedio 55.

EMAR IEN$^+$ m/z 513,3103 $[MH]^+$.

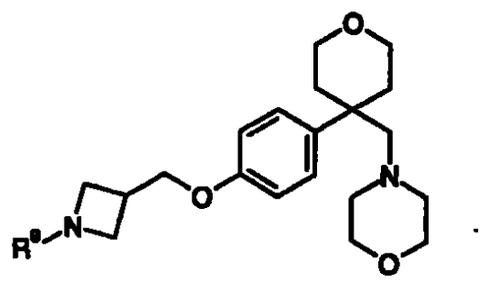
Intermedio 77: 4-[4-[4-(azetidin-3-ilmetoxi)fenil]tetrahidro-2*H*-piran-4-il]metil)-morfolina

Una solución de 4-[[4-(4-[[1-(benzhidril)azetidin-3-il]metoxi]fenil)tetrahidro-2*H*-piran-4-il]metil)-morfolina (1,0 g, 1,95 mmol) en etanol (10 ml) se hidrogenó durante 16 horas a temperatura ambiente a 60 psi en presencia de $Pd(OH)_2/C$ (150 mg, 15% p/p). Se añadió ácido clorhídrico 2 N (unas gotas) y la mezcla de reacción se hidrogenó durante 16 horas a 60ºC a 60 psi. La mezcla de reacción se basificó con carbonato sódico acuoso y la mezcla se filtró sobre Arbocel® y se aclaró con etanol. El filtrado se concentró *al vacío*. El residuo se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (96:4:0,4 a 90:10:1 en volumen) proporcionando el compuesto del título (210 mg, 31%).

EMAR IEN$^+$ m/z 347,2323 $[MH]^+$.

Ejemplos 219-221

Los compuestos de los siguientes ejemplos tabulados de fórmula general



se prepararon usando 4-({4-[4-(azetidin-3-ilmetoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)-morfolina, las cetonas apropiadas y triacetoxiborohidruro sódico de forma similar al procedimiento usado para el ejemplo 54.

Nº Ej	R^9	Datos Analíticos
219	Ciclopentilo	4-[(4-{4-[(1-ciclopentilazetidin-3-il)metoxi]fenil}tetrahidro-2*H*-piran-4-il)metil]morfolina ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,32-1,37 (m, 2H), 1,49-1,53 (m, 2H), 1,58- 1,58- 1,69 (m, 4H), 1,83-1,89 (m, 2H), 2,08-2,15 (m, 6H), 2,38 (s, 2H), 2,74 (m, 1 H), 2,91 (m, 1 H), 3,03 (t, 2H), 3,45 (t, 2H), 3,49-3,54 (m, 6H), 3,72- 3,76 (m, 2H), 4,04 (d, 2H), 6,84 (d, 2H), 7,22 (d, 2H). EMAR IEN$^+$ m/z 415,2946 $[MH]^+$. Rendimiento del 92%
220	isopropilo	4-[(4-{4-[(1-isopropilazetidin-3-il)metoxi]fenil}tetrahidro-2*H*-piran-4-il)metil]morfolina

		^{1}H RMN (400 MHz, $CDCl_3$) δ 0,92 (d, 6H), 1,83-1,90 (m, 2H), 2,09-2,14 (m, 6H), 2,31 (m, 1 H), 2,38 (s, 2H), 2,85 (m, 1 H), 3,03 (t, 2H), 3,41 (t, 2H), 3,49-3,54 (m, 6H), 3,72-3,76 (m, 2H), 4,06 (d, 2H), 6,85 (d, 2H), 7,22 (d, 2H). EMAR IEN$^+$ m/z 389,2791 $[MH]^+$. Rendimiento del 61%
221	Ciclobutilo	4-[(4-[4-[(1-ciclobutilazetidin-3-il)metoxi]fenil]tetrahidro-2*H*-piran-4-il)metil]morfolina ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,62-1,75 (m, 2H), 1,82-1,90 (m, 4H), 1,93-1,99 (m, 2H), 2,09-2,15 (m, 6H), 2,38 (s, 2H), 2,88 (m, 1H), 3,07 (t, 2H), 3,14 (m, 1H), 3,40 (t, 2H), 3,49-3,55 (m, 6H), 3,72-3,77 (m, 2H), 4,07 (d, 2H), 6,85 (d, 2H), 7,22 (d, 2H). EMAR IEN$^+$ m/z 401,2791 $[MH]^+$. Rendimiento del 50%

Intermedio 78: 4-[4-(metiltio)fenil]tetrahidro-2*H*-piran-4-carbonitrilo

El compuesto del título (5,5 g, 77%, sólido después de trituración en pentano) se preparó usando 4-(metiltio)fenilacetonitrilo, bis(2-bromoetil)éter, hidruro sódico y yoduro potásico de forma similar al procedimiento usado para el Intermedio 56. Microanálisis: Encontrado: C, 66,62; H, 6,46; N, 5,97%. $C_{13}H_{15}NOS$ requiere C, 66,92; H, 6,48; N, 6,00%.

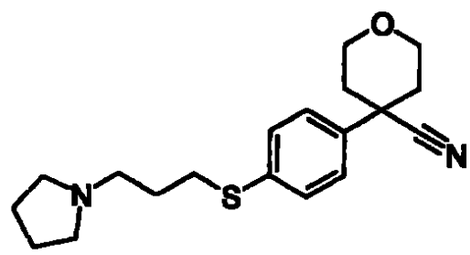
Intermedio 79: 4-[4(metilsulfinil)fenil]tetrahidro-2*H*-piran-4-carbonitrilo

Una solución de ácido meta-cloroperbenzoico (5,08 g, 22,66 mmol) en diclorometano (30 ml) se añadió gota a gota durante 15 minutos a 0ºC a una

solución de 4-[4-(metiltio)fenil]tetrahidro-2*H*-piran-4-carbonitrilo (4,8 g, 20,6 mmol) en diclorometano (40 ml). La mezcla de reacción se calentó a temperatura ambiente durante 4 horas. Después, la mezcla se diluyó con diclorometano (180 ml), se lavó con una solución de sulfito sódico y carbonato sódico acuoso al 10%. La fase orgánica se separó, se secó sobre sulfato sódico y se concentró *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (100:0:0 a 95:5:0,5 en volumen) proporcionando el compuesto del título (4,55 g, 89%) en forma de un sólido blanquecino.

EMBR APCI$^+$ m/z 250 $[MH]^+$.

Ejemplo 222: 4[4-[(3-pirrolidin-1-ilpropil)tio]fenil]tetrahidro-2*H*-piran-4-carbonitrilo



Se añadió 2,6-lutidina (3,33 ml, 28,6 mmol) a una solución de 4-[4-(metilsulfinil)fenil]tetrahidro-2*H*-piran-4-carbonitrilo (2,3 g, 9,23 mmol) en acetonitrilo (70 ml). La mezcla se enfrió en un baño de hielo/acetona y se añadió lentamente anhídrido trifluoroacético (3,87 ml, 27,69 mmol). La solución se agitó a esta temperatura en una atmósfera de nitrógeno durante 3 horas. La mezcla de reacción se concentró posteriormente *al vacío* y el residuo se recogió en metanol (7 ml). Se añadió trietilamina (7 ml) a 0ºC y la mezcla se

agitó a 0ºC durante 30 minutos. Se añadió *N,N*-dimetilformamida (10 ml) a 0ºC, seguido de carbonato potásico (2,8 g, 20,31 mmol) y 1-(3-cloro-propil)-pirrolidina (2,72 g, 18,46 mmol) en *N,N*-dimetilformamida (10 ml). La mezcla se calentó posteriormente a temperatura ambiente y se agitó durante 18 horas. La mezcla de reacción se concentró *al vacío*. El residuo se recogió en agua (50 ml) y se extrajo con acetato de etilo (2x150 ml). La fase orgánicas se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (97:3:0,3 a 95:5:0,5 en volumen) proporcionando el compuesto del título (2,62 g, 86%) en forma de un sólido.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,77-1,80 (m, 4H), 1,84-1,91 (m, 2H), 2,01-2,14 (m, 4H), 2,48-2,52 (m, 4H), 2,58 (t, 2H), 2,99 (t, 2H), 3,89 (t, 2H), 4,06-4,10 (m, 2H), 7,34-7,39 (m, 4H).

EMBR APCI$^+$ m/z 331 $[MH]^+$.

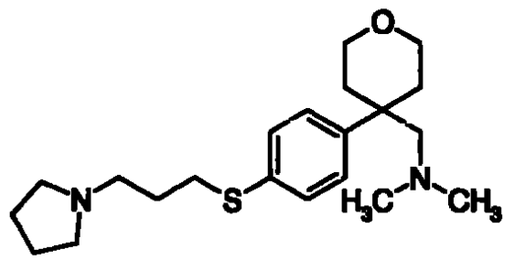
Intermedio 80: 1-(4-{4-[(3-pirrolidin-1-ilpropil)tio]fenil}tetrahidro-2*H*-piran-4-il)metanamina

El compuesto del título (2,42 g, 91%) se preparó usando 4-{4-[(3-pirrolidin-1-ilpropil)tio]fenil}tetrahidro-2*H*-piran-4-carbonitrilo e hidruro de aluminio litio de forma similar al procedimiento usado para el Intermedio 51.

EMBR APCI$^+$ m/z 335 $[MH]^+$.

Microanálisis: Encontrado: C, 64,08; H, 8,79; N, 7,447%. $C_{19}H_{30}N_2OS.0,33DCM$ requiere C, 64,04; H, 8,52; :N, 7,73%.

Ejemplo 223: *N,N*-dimetil-1-(4-{4-[(3-pirrolidin-1-ilpropil)tio]fenil}tetrahidro-2*H*-piran-4-il)metanamina



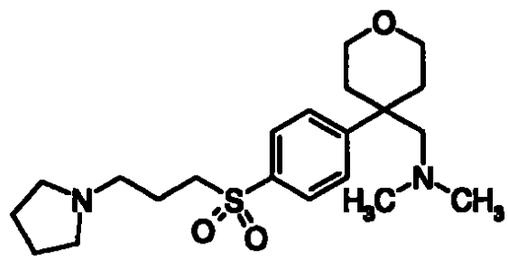
Se añadió formaldehído (solución al 37% p/p en agua, 650 µl, 7,58 mmol) a una solución de 1-(4-{4-[(3-pirrolidin-1-ilpropil)tio]fenil}tetrahidro-2*H*-piran-4-il)metanamina (1,0 g, 3,03 mmol) en tetrahidrofurano (10 ml). Después se añadió ácido acético (173 µl, 3,03 mmol) y la mezcla se agitó a temperatura ambiente durante 10 minutos. La mezcla se enfrió a 0ºC y se añadió triacetoxiborohidruro sódico (1,6 g, 7,57 mmol) en 2 porciones. Después. la mezcla se calentó a temperatura ambiente y se agitó durante 18 horas. La reacción se inactivó con agua y se concentró *al vacío.* El residuo se recogió en bicarbonato sódico hasta que el pH de la fase acuosa alcanzó 8. La fase acuosa se extrajo posteriormente con diclorometano (2x100 ml). Los extractos orgánicos se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío.* El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (97:3:0,3 a 90:10:1 en volumen) proporcionando el compuesto del título (139 mg, 13%) en forma de un aceite que cristalizó en reposo.

^{1}H RMN (400 MHz, CD_3OD) δ 1,77-1,91 (m, 8H), 1,95 (s, 6H), 2,13-2,18 (m, 2H), 2,49 (s, 2H), 2,51-2,54 (m, 4H), 2,60 (t, 2H), 2,96 (t, 2H), 3,50 (t, 2H), 3,73-3,78 (m, 2H), 7,31-7,36 (m, 4H).

EMAR IEN$^+$ m/z 363,2462 $[MH]^+$.

Ejemplo 224: *N,N*-dimetil-1-{4-{4-[(3-pirrolidin-1-

ilpropil)sulfonil]fenil}tetrahidro-2*H*-piran-4-il)metanamina



Se disolvió *N*-dimetil-1-(4-{4-[(3-pirrolidin-1-ilpropil)tio]fenil}tetrahidro-2*H*-piran-4-il)metanamina (70 mg, 0,19 mmol) en acetona (2 ml) y agua (0,5 ml). La mezcla se enfrió a 0ºC y se añadió gota a gota una solución de Oxone® (131 mg, 0,21 mmol) en agua (0,5 ml). La mezcla de reacción se agitó a temperatura ambiente durante 18 horas. Después, la mezcla se diluyó con más agua, se basificó con carbonato sódico acuoso al 10% y se extrajo con diclorometano (2x20 ml). La fase orgánicas se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (96:4:0,4 en volumen) proporcionando el compuesto del título (23 mg, 30%) en forma de un aceite.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,72-1,75 (m, 4H), 1,90-1,99 (m, 10H), 2,10-2,14 (m, 2H), 2,40-2,44 (m, 4H), 2,48-2,52 (m, 4H), 3,20 (t, 2H), 3,52 (t, 2H), 3,75-3,80 (m, 2H), 7,52 (d, 2H), 7,86 (d, 2H).

EMAR IEN$^+$ m/z 395,2363 $[MH]^+$.

Intermedio 81: Ácido 4-{4-[(3-pirrolidin-1-ilpropil)tio]fenil}tetrahidro-2*H*-piran-4-carboxílico

Se calentó a reflujo 4-{4-[(3-Pirrolidin-1-ilpropil)tio]fenil}tetrahidro-2*H*-piran-4-carbonitrilo (1 g, 3,03 mmol) en ácido clorhídrico concentrado (10 ml)

durante 18 horas. Se añadió más ácido clorhídrico (11 ml) y la mezcla se calentó a durante 18 horas más. Después, la mezcla de reacción se concentró al vacío a un sólido. Esto se recogió en diclorometano y se le añadió trietilamina (4 ml). La mezcla de reacción se concentró posteriormente *al vacío*. Esto se repitió dos veces proporcionando el compuesto del título (2,03 g) en forma de un sólido que contenía clorhidrato de trietilamina.

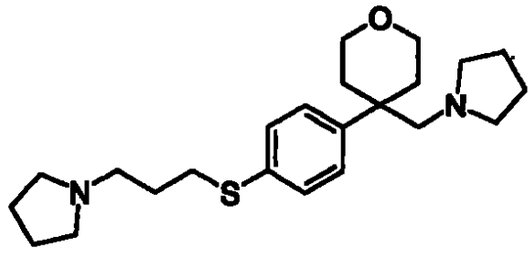
EMBR APCI$^+$ m/z 350 $[MH]^+$.

Intermedio 82: 1-[3-({4[4-(pirrolidin-1-ilcarbonil)tetrahidro-2*H*-piran-4 il]fenil}tio)propil]pirrolidina

El compuesto del título (228 mg, 40%) se preparó usando ácido 4-{4-[(3-pirrolidin-1-ilpropil)tio]fenil}tetrahidro-2*H*-piran-4-carboxílico y pirrolidina de forma similar al procedimiento usado para el ejemplo 149.

EMAR IEN$^+$ m/z 403,2403 $[MH]^+$.

Ejemplo 225: 1-[3-({4-[4-pirrolidin-1-ilmetil)tetrahidro-2*H*-piran-4-il]fenil}tio)propil]pirrolidina



El compuesto del título (58 mg, 27%) se preparó usando 1-[3-({4-[4-(pirrolidin-1-ilcarbonil)tetrahidro-2*H*-piran-4-il]fenil}tio)propil]pirrolidina e hidruro de aluminio litio de forma similar al procedimiento usado para el ejemplo 142.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,54-1,57 (m, 4H), 1,75-1,79 (m, 4H), 1,84-1,94 (m, 4H), 2,06-2,10 (m, 2H), 2,18-2,22 (m, 4H), 2,47-2,50 (m, 4H), 2,57 (t, 2H),

2,63 (s, 2H), 2,96 (t, 2H), 3,54 (t, 2H), 3,73-3,78 (m, 2H), 7,22 (d, 2H), 7,29 (d, 2H).

EMAR IEN$^+$ m/z 389,2615 $[MH]^+$.

Intermedio 83: Ácido 1-[4-[3-pirrolidin-1-ilpropoxi)fenil] ciclohexanocarboxílico

El compuesto del título (contaminado con cloruro amónico) se preparó usando 1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexanocarbonitrilo y ácido clorhídrico concentrado de forma similar al procedimiento usado para el Intermedio 80.

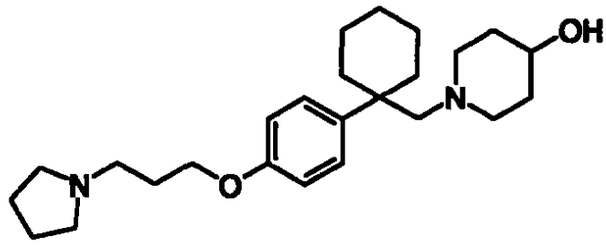
EMBR IEN$^+$ m/z 332 $[MH]^+$.

Intermedio 84: 1-({1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil} carbonil)piperidin-4-ol

El compuesto del título (200 mg, 16%) se preparó usando ácido 1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexanocarboxílico y 4-hidroxipiperidina de forma similar al procedimiento usado para el ejemplo 149.

EMAR IEN$^+$ m/z 415,2943 $[MH]^+$.

Ejemplo 226: 1-({1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil}metil) piperidin-4-ol

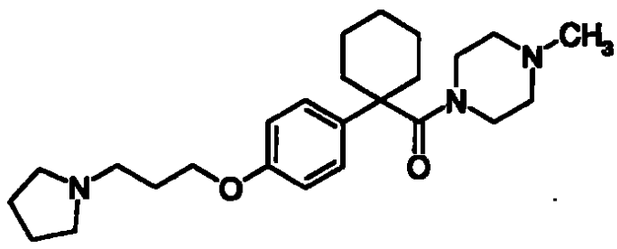


El compuesto del título (90 mg, 46%) se preparó usando 1-({1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil}carbonil)piperidin-4-ol e hidruro de aluminio litio de forma similar al procedimiento usado para el ejemplo 142.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,29-1,55 (m, 10H), 1,64-1,69 (m, 2H), 1,77-1,81 (m, 4H), 1,90-2,06 (m, 4H), 2,10-2,13 (m, 2H), 2,23 (s, 2H), 2,26-2,30 (m, 2H), 2,51-2,54 (m, 4H), 2,62 (t, 2H), 3,51 (m, 1H), 4,01 ~ (t, 2H), 6,83 (d, 2H), 7,25 (d, 2H).

EMAR IEN$^+$ m/z 401,3154 $[MH]^+$.

Ejemplo 227: 1-metil-4-({1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil}carbonil)piperazina



El compuesto del título (10 mg, 8%) se preparó usando ácido 1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexanocarboxílico y 1-metilpiperazina de forma similar al procedimiento usado para el ejemplo 149.

^{1}H RMN (400 MHz, CD_3OD) δ 1,32 (m, 1H), 1,64-1,69 (m, 7H), 1,81-1,85 (m, 4H), 1,98-2,03 (m, 2H), 2,05-2,13 (m, 4H), 2,15 (s, 3H), 2,25-2,28 (m, 2H), 2,59-2,62 (m, 4H), 2,69 (t, 2H), 3,33-3,42 (m, 4H), 4,01 (t, 2H), 6,90 (d, 2H), 7,16 (d, 2H).

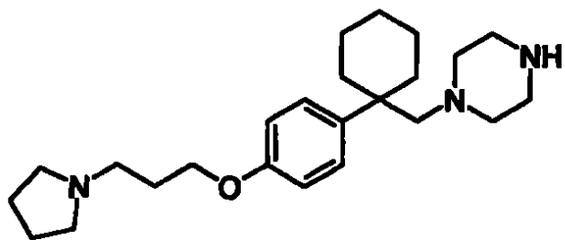
EMAR IEN$^+$ m/z 414,3107 $[MH]^+$.

Intermedio 85: 1-({1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil}carbonil)piperazina

El compuesto del título (351 mg, 19%) se preparó usando ácido 1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexanocarboxílico y piperazina de forma similar al procedimiento usado para el ejemplo 149.

EMBR APCI$^+$ m/z 400 $[MH]^+$.

Ejemplo 228: 1-({1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil}metil)piperazina

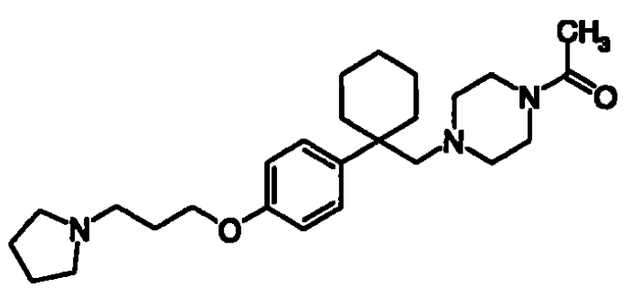


El compuesto del título (187 mg, 59%) se preparó usando 1-({1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil}carbonil)piperazina e hidruro de aluminio litio de forma similar al procedimiento usado para el ejemplo 142.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,30-1,33 (m, 3H), 1,46-1,54 (m, 4H), 1,78-1,81 (m, 4H), 1,98-2,05 (m, 4H), 2,09-2,12 (m, 6H), 2,23 (s, 2H), 2,53-2,57 (m, 4H), 2,62-2,71 (m, 6H), 4,01 (t, 2H), 6,83 (d, 2H), 7,26 (d, 2H).

EMBR APCI$^+$ m/z 386 $[MH]^+$.

Ejemplo 229: 1-acetil-4-({1-[4(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil}metil)piperazina

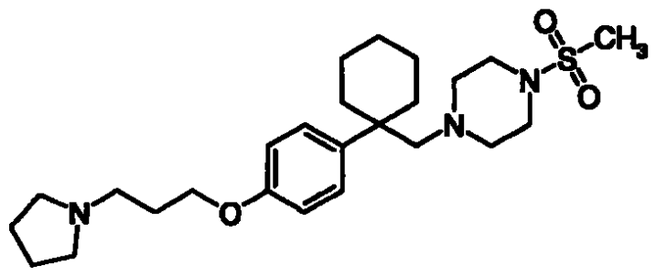


El compuesto del título (73 mg, 73%) se preparó usando 1-({1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil}metil)piperazina y anhídrido acético de forma similar al procedimiento usado para el ejemplo 166.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,31-1,34 (m, 3H), 1,48-1,53 (m, 5H), 1,82-1,85 (m, 4H), 1,99 (s, 3H), 2,02-2,07 (m, 4H), 2,13-2,17 (m, 4H), 2,28 (s, 2H), 2,58-2,64 (m, 4H), 2,70 (t, 2H), 3,20 (t, 2H), 3,41-3,43 (m, 2H), 4,01 (t, 2H), 6,83 (d, 2H), 7,25 (d, 2H).

EMAR IEN$^+$ m/z 428,3264 $[MH]^+$.

Ejemplo 230: 1-(metilsulfonil-4-{1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil}-metil)piperazina



Se añadió anhídrido de ácido metanosulfónico (49 mg, 0,28 mmol) a 0ºC a una solución de 1-({1-[4-(3-pirrolidin-1-ilpropoxi)fenil]ciclohexil}metil) piperazina (90 mg, 0,23 mmol) y piridina (471.l, 0,58 mmol) en diclorometano (1 ml). La reacción se agitó a 0 ºC durante 10 minutos, después se dejó calentar hasta temperatura ambiente y se agitó durante 18 horas. La mezcla de reacción se concentró a presión reducida y se dividió entre diclorometano (20 ml) y carbonato sódico acuoso (20 ml). Las fases se separaron. La fase orgánica se secó sobre sulfato sódico, se filtró y se concentró *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (96:4:0,4 en volumen) proporcionando el compuesto del título (61 mg, 56%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 129-1,36 (m, 3H), 1,45-1,52 (m, 5H), 1,85-1,90 (m, 4H), 2,08-2,15 (m, 4H), 2,22 (t, 4H), 2,32 (s, 2H), 2,67-2,79 (m, 9H), 3,00-

3,03 (m, 4H), 4,02 (t, 2H), 6,83 (d, 2H), 7,24 (d, 2H).

EMAR IEN$^+$ m/z 464,2931 $[MH]^+$.

Intermedio 86: bis(2-cloroetil)carbamato de *terc*-butilo

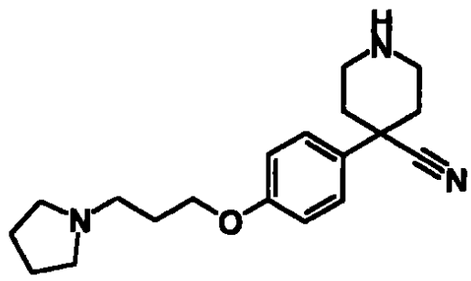
Se agitó enérgicamente clorhidrato de bis-(2-cloroetil)amina (10 g, 56 mmol) en una mezcla de diclorometano (150 ml) e hidróxido sódico acuoso al 10% (50 ml). Después se añadió gota a gota di-*terc*-butildicarbonato (12,2 g, 56 mmol) en forma de una solución en diclorometano (75 ml). La mezcla de reacción se agitó a temperatura ambiente durante 5 horas. El análisis TLC mostró que la reacción no se había completado de forma que se añadió más di-*terc*-butildicarbonato (4 g, 18,3 mmol) añadió. La mezcla se agitó enérgicamente durante 18 horas a temperatura ambiente. Las fases se separaron y la fase acuosa se extrajo con más diclorometano (2x50 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se concentraron a presión reducida. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo (99:1 a 80:20 en volumen) proporcionando el compuesto del título (7,9 g, 58%).

Intermedio 87: 4-ciano-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]piperidin-1-carboxilato de *terc*-butilo

El compuesto del título (1,8 g, 53%) se preparó usando [4-(3-pirrolidin-1-ilpropoxi)fenil]acetonitrilo, bis(2-cloroetil)carbamato de *terc*-butilo, hidruro sódico y yoduro potásico de forma similar al procedimiento usado para el Intermedio 56.

EMBR APCI$^+$ m/z 414 $[MH]^+$ y m/z 245 $[SMH]^+$.

Ejemplo 231: 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]piperidin-4-carbonitrilo

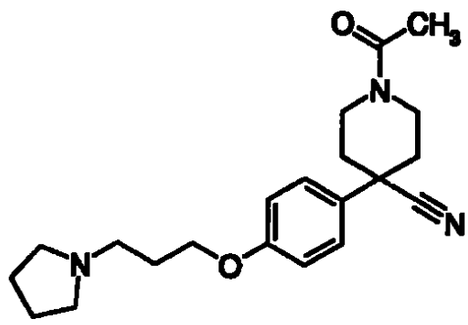


Se agitó 4-ciano-4-[4-(3-pirrolidin-1-ilpropoxi)fenil] piperidin-1-carboxilato de *terc*-butilo (500 mg, 1,24 mmol) durante 1 hora en ácido trifluoroacético (1,91 ml, 24,8 mmol) y diclorometano (30 ml). Se añadió más ácido trifluoroacético (3 ml) y la reacción se agitó a temperatura ambiente durante otra hora. La mezcla de reacción se inactivó con una solución de carbonato sódico acuoso saturado (15 ml) y las fases se separaron. La fase orgánica se secó sobre sulfato sódico y se concentró *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:5:0,5 a 90:10:1 en volumen) proporcionando el compuesto del título (450 mg, 18% en 2 etapas).

^{1}H RMN (400 MHz, CD_3OD) δ 1,81-1,85 (m, 4H), 1,91-2,09 (m, 6H), 2,59-2,62 (m, 4H), 2,69 (t, 2H), 2,99 (t, 2H), 3,12-3,15 (m, 2H), 4,04 (t, 2H), 6,96 (d, 2H), 7,42 (d, 2H).

EMAR IEN$^+$ m/z 314,2227 $[MH]^+$.

Ejemplo 232: 1-acetil-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]piperidin-4-carbonitrilo

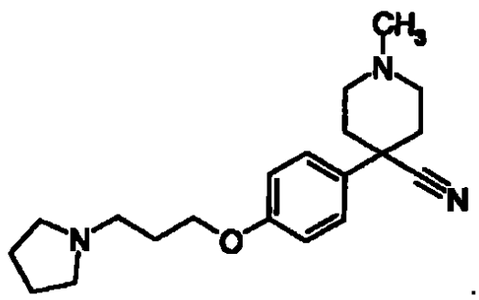


Se añadió gota a gota cloruro de acetilo (270, 0,37 mmol) a una solución de 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]piperidin-4-carbonitrilo (90 mg, 0,28 mmol) y trietilamina (780, 0,56 mmol) en clorometano (3 ml). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se diluyó con diclorometano (15 ml) y se lavó con agua (15 ml). Las fases se separaron y la fase acuosa se extrajo posteriormente con diclorometano (2x10 ml). Los extractos orgánicos se combinaron, se lavaron con salmuera, se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con acetato de etilo:metanol:amoniaco 5:5:0,5 en volumen) proporcionando el compuesto del título (28 mg, 28%).

^{1}H RMN (400 MHz, CD_3OD) δ 1,82-1,85 (m, 4H), 1,89-2,18 (m, 9H), 2,60-2,63 (m, 4H), 2,69 (t, 2H), 3,00 t, 1H), 3,50 (t, 1H), 4,03-4,12 (m, 3H), 4,70 (d, 1H); 6,97 (d, 2H), 7,44 (d, 2H).

EMAR IEN$^+$ m/z 356,2329 $[MH]^+$.

Ejemplo 233: 1-metil-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]piperidin-4-carbonitrilo



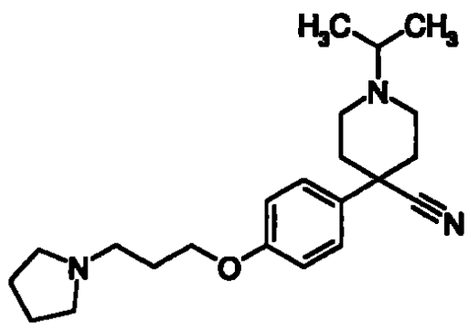
El compuesto del título (80 mg, 76%) se preparó a partir de 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]piperidin-4-carbonitrilo, formaldehído y triacetoxiborohidruro sódico de forma similar al procedimiento usado para el ejemplo 54.

^{1}H RMN (400 MHz, CD_3OD) δ 1,81-1,85 (m, 4H), 1,97-2,15 (m, 6H), 2,37 (s, 3H), 2,45 (t, 2H), 2,58-2,62 (m, 4H), 2,68 (t, 2H), 2,99 (d, 2H), 4,04 (t, 2H), 6,96 (d, 2H), 7,42 (d, 2H).

EMAR APCI$^+$ m/z 328 $[MH]^+$.

Microanálisis: Encontrado: C, 73,01; H, 8,94; N, 12,81%. $C_{20}H_{29}N_3O$ requiere C, 73,36; H, 8,93; N, 12,83%.

Ejemplo 234: 1-isopropil-4-[4(3-pirrolidin-1-ilpropoxi)fenil]piperidin-4-carbonitrilo



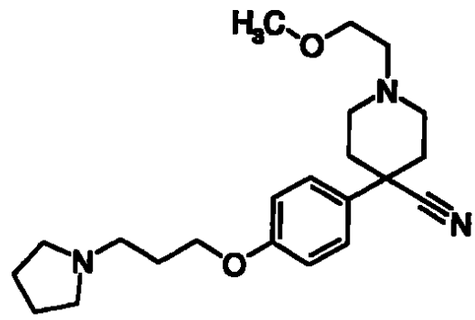
El compuesto del título (45 mg, 58%) se preparó a partir de 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]piperidin-4-carbonitrilo, acetona y triacetoxiborohidruro

sódico de forma similar al procedimiento usado para el ejemplo 54.

^{1}H RMN (400 MHz, CD_3OD) δ 1,12 (d, 6H), 1,81-1,84 (m, 4H), 1,99-2,14 (m, 6H), 2,58-2,69 (m, 8H), 2,82 (m, 1 H), 3,02 (d, 2H), 4,04 (t, 2H), 6,96 (d, 2H), 7,42 (d, 2H).

EMAR IEN$^+$ m/z 356,2691 $[MH]^+$.

Ejemplo 235: 1-(2-metoxietil)-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]piperidin-4-carbonitrilo



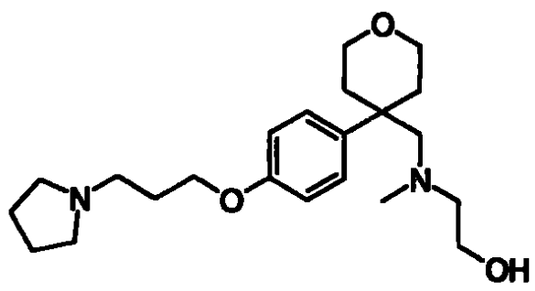
Una mezcla de 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]piperidin-4-carbonitrilo (68 mg, 0,22 mmol), 2-bromoetilmetiléter (21 µl, 0,22 mmol), bicarbonato sódico sólido (84 mg, 1,0 mmol) y yoduro potásico (5 mg, catalítica) se calentó a 50ºC en acetonitrilo (1 ml) durante 18 horas. La mezcla de reacción se concentró *al vacío*. El residuo se dividió entre diclorometano (2x50 ml) y carbonato sódico acuoso al 10% (20 ml). La fase orgánicas se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (97:3:0,3 a 95:5:0,5 en volumen) proporcionando el compuesto del título (46 mg, 61%).

^{1}H RMN (400 MHz, CD_3OD) δ 1,83-1,87 (m, 4H), 2,01-2,10 (m, 6H), 2,45-2,52 (m, 2H), 2,65-2,69 (m, 6H), 2,75 (t, 2H), 3,09 (d, 2H), 3,35 (s, 3H), 3,56 (t, 2H),

4,04 (t, 2H), 6,96 (d, 2H), 7,42 (d, 2H).

EMAR IEN$^+$ m/z 372,2639 $[MH]^+$.

Ejemplo 236: 2-[metil({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)amino]etanol

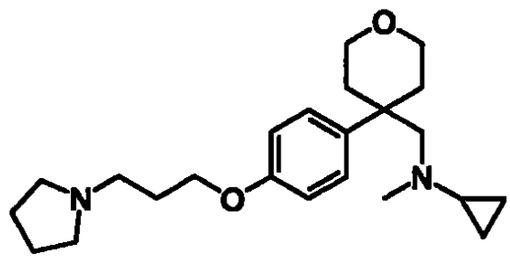


Una solución de metil-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]-tetrahidropiran-4-ilmetil)amina (350 mg, 1,05 mmol), dímero de glicolaldehído (130 mg, 1,05 mmol) y AcOH (0,15 ml, 2,1 mmol) en DCM (5 ml) se agitó a temperatura ambiente durante 18 horas. Se añadió carbonato sódico acuoso saturado (10 ml) y DCM (10 ml) y la mezcla se agitó y se dividió. La fase acuosa se extrajo con DCM (2x10 ml) y los extractos orgánicos combinados se secaron (K_2CO_3), se filtraron y se concentraron *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (92:8:1) proporcionando el compuesto del título en forma de un aceite incoloro transparente (223 mg, 0,59 mmol, 56%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,70-1,90 (m, 6H), 1,96 (s, 3H), 2,00 (quintuplete, 2H), 2,14 (m, 2H), 2,37 (t, 2H), 2,40-2,60 (m, 6H), 2,65 (t, 2H), 3,35 (t, 2H), 3,50 (m, 2H), 3,76 (m, 2H), 4,01 (t, 2H), 6,89 (d, 2H), 7,19 (d, 2H).

EMAR IEN$^+$ m/z 377,2796 $[MH]^+$.

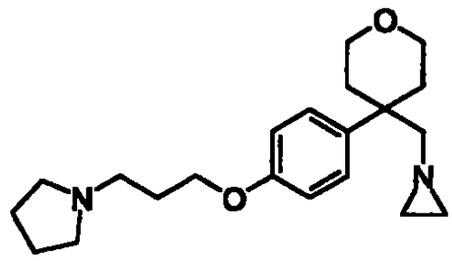
Ejemplo 237: *N*-metil-*N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)ciclopropanamina



Una mezcla de metil-(4-[4-(3-pirrolidin-1-ilpropoxi)fenil]-tetrahidropiran-4-ilmetil)amina (115 mg, 135 mmol), (1-etoxi-ciclopropoxi)-trimetilsilano (360 mg, 2,0 mmol), AcOH (0,2 ml, 3,5 mmol), $NaCNBH_3$ (110 mg, 1,75 mmol) y tamices moleculares 4A (100 mg) en MeOH (5 ml) se calentó a reflujo durante 18 horas. La mezcla se enfrió, se concentró *al vacío* y se dividió entre NaOH 2 M (10 ml) y DCM (10 ml). La fase orgánica se separó y la fase acuosa se extrajo con DCM (2x10 ml). Las fases orgánicas combinadas se concentraron *al vacío* y se purificaron por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (92:8:1) proporcionando el compuesto del título en forma de un aceite incoloro transparente (20 mg, 0,054 mmol, 15%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 0,15 (m, 2H), 0,29 (m, 2H), 1,68 (m, 1H), 1,70-1,90 (m, 6H), 1,85 (s, 3H), 2,00-2,10 (m, 4H), 2,60 (m, 4H), 2,65 (s, 2H), 2,68 (m, 2H), 3,50 (t, 2H), 3,76 (m, 2H), 4,01 (t, 2H), 6,85 (d, 2H), 7,16 (d, 2H). EMAR IEN$^+$ m/z 373,2844 $[MH]^+$.

Ejemplo 238: 1-(3-{4-[4-(aziridin-1-ilmetil)tetrahidro-2*H*-piran-4-il]fenoxi}propil)pirrolidina

524
525

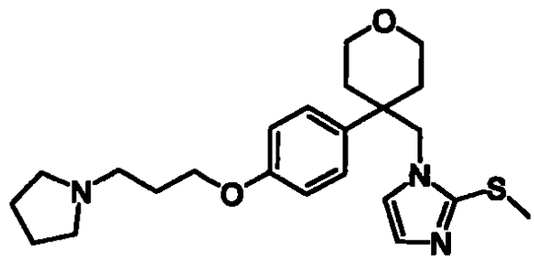


Una mezcla de {4-[4-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il} metilamina (482 mg, 1,50 mmol), 1,2-dibromoetano (0,13 ml, 1,50 mmol) y K_2CO_3 (420 mg, 3,0 mmol) en acetonitrilo (50 ml) se calentó a 70ºC durante 3 días. La mezcla se concentró *al vacío* y se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (93:7:1 a 91:9:1) proporcionando el compuesto del título en forma de un aceite incoloro transparente (51 mg, 0,15 mmol, 10%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 0,71 (m, 2H), 1,48 (m, 2H), 1,78 (m, 4H), 2,00 (m, 4H), 2,19 (m, 2H), 2,30 (s, 2H), 2,54 (m, 4H), 2,63 (t, 2H), 3,54 (m, 2H), 3,78 (m, 2H), 4,01 (t, 2H), 6,86 (d, 2H), 7,21 (d, 2H).

EMAR IEN$^+$ m/z 345,2534 $[MH]^+$.

Ejemplo 239: 2-(metiltio)-1-({4-[4(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)-1*H*-imidazol

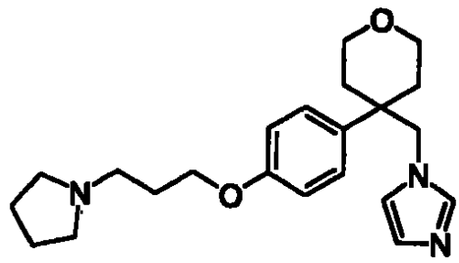


Una solución de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il} metilamina (159 mg, 0,50 mmol) y 2,2-dietoxietilditioimido-carbonato de dimetilo

(120 mg, 0,50 mmol, ARKIVOC 2001, viii, 34-39) en AcOH (5 ml) se calentó a reflujo durante 8 horas. La mezcla se concentró al vacío y se dividió entre bicarbonato sódico acuoso saturado (10 ml) y DCM (10 ml). La fase acuosa se extrajo con DCM (2x10 ml) y los extractos orgánicos combinados se secaron (K_2CO_3), se filtraron y se concentraron al vacío. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (90:10:1) proporcionando el compuesto del título en forma de una goma incolora transparente (90 mg, 0,22 mmol, 43%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,80-2,00 (m, 6H), 2,12 (m, 2H), 2,21 (quintuplete, 2H), 2,48 (s, 3H), 2,80-3,00 (m, 6H), 3,45 (m, 2H), 3,83 (m, 2H), 3,98 (s, 2H), 4,06 (t, 2H), 6,10 (s, 1H), 6,85 (d, 2H), 6,87 (s, 1H), 7,01 (d, 2H).

EMBR APCI$^+$ m/z 416 $[MH]^+$.

Ejemplo 240: 1-{4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil}-1*H*-imidazol



A una solución de 2-(metiltio)-1-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)-1*H*-imidazol (90 mg, 0,22 mmol) en EtOH (4 ml) y agua (1 ml) se le añadió níquel Raney (suspensión al 50% en agua) en alícuotas de 200 mg cada 30 minutos. Después de 3 horas se había consumido todo el material de partida. La mezcla se filtró a través de Arbocel® con EtOH (200 ml) y se concentró al vacío. El producto en bruto se purificó por

cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (90:10:1) proporcionando el compuesto del título en forma de un aceite amarillo (29 mg, 0,078 mmol, 36%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,80-2,00 (m, 6H), 2,10 (m, 4H), 2,70-2,90 (m, 6H), 3,50 (t, 2H), 3,81 (m, 2H), 3,97 (s, 2H), 4,04 (t, 2H), 6,32 (s, 1H), 6,80-6,90 (m, 4H), 6,98 (d, 2H).

EMAR IEN$^+$ m/z 370,2485 $[MH]^+$.

Intermedio 88: 4-(4-{[*terc*-butil(dimetil)silil]oxi}fenil)tetrahidro-2*H*-piran-4-carbonitrilo

Una solución de 4-(4-hidroxi-fenil)-tetrahidro-piran-4-carbonitrilo (5 g, 25 mmol), cloruro de t-butildimetilsililo (4,46 g, 29 mmol) e imidazol (2,34 g, 34 mmol) se agitó en DMF (15 ml) a temperatura ambiente. Después de 30 minutos, se observó una suspensión amarilla. La reacción se dividió entre éter (75 ml) y agua (100 ml). El éter se lavó después con agua (4x50 ml), se secó sobre sulfato sódico, se filtró y se concentró *al vacío*. El compuesto del título se aisló en forma de un sólido ceroso naranja pálido(7 g, 90%).

Intermedio 89: 1-[4-(4-{[*terc*-butil(dimetil)silil)oxi]fenil}tetrahidro-2*H*-piran-4-il]metanamina

A una solución agitada de 4-(4-{[*terc*-butil(dimetil)silil]oxi}fenil)tetrahidro-2*H*-piran-4-carbonitrilo (3,5 g, 11 mmol) en THF (35 ml) a 0ºC se le añadió gota a gota hidruro de aluminio litio (solución 1 M en éter, 44 ml, 44 mmol). La reacción se dejó calentar a temperatura ambiente y se agitó durante 4 horas hasta que se completó. La mezcla de reacción se enfrió a 0ºC, se le añadió agua (1,66 ml) seguido de NaOH (2,0 M, 1,66 ml) y agua (4,97 ml). La mezcla se filtró a través de una capa corta de celite, eluyendo con

diclorometano:metanol (97:3, 150 ml) y se concentró *al vacío*. El sólido obtenido se dividió entre acetato de etilo (50 ml) y bicarbonato sódico (50 ml). La fase orgánica se secó después sobre sulfato sódico, se filtró y se concentró *al vacío* dando el compuesto del título (2,04 g, 58%).

EMBR APCI$^+$ *m/z* 322 $[MH]^+$.

Intermedio 90: *N*-[[4-(4-[(*terc*-butil(dimetil)silil]oxi}fenil)tetrahidro-2*H*-piran-4-il]metil}piridin-2-amina

Se agitó 1-[4-(4-[[*terc*-butil(dimetil)silil]oxi}fenil)tetrahidro-2*H*-piran-4-il]metanamina (3,65 g, 11,4 mmol), 2-bromopiridina (910 µl, 9,48 mmol), tris(dibencilidenacetona)dipaladio (0) (471 mg, 0,455 mmol), 2,2'-bis(difenilfosfino) 1,1'-binaftilo (567 mg, 0,910 mmol) y *terc*-butóxido sódico (1,29 g, 13,0 mmol) en tolueno (50 ml) a 70ºC en una atmósfera de nitrógeno durante 24 horas. El tolueno se retiró *al vacío* y el residuo se dividió entre diclorometano (50 ml) y una solución de bicarbonato sódico saturado (50 ml). La fase orgánica se separó y se secó sobre sulfato sódico, se filtró y se concentró *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con éter:pentano (80:20 en volumen) proporcionando el compuesto del título (2,10 g, 46%) en forma de un sólido amarillo.

EMBR APCI$^+$ *m/z* 399 $[MH]^+$.

Intermedio 91: 4-(4-[(piridin-2-ilamino)metil]tetrahidro-2*H*-piran-4-il}fenol

Se agitó *N*-[[4-(4-[[*terc*-butil(dimetil)silil]oxi}fenil)tetrahidro-2*H*-piran-4-il]metil}piridin-2-amina (2,099 g, 5,27 mmol) y fluoruro tetrabutilamónico (solución 1 M en THF, 5,80 ml, 5,80 mmol) en THF (20 ml) a temperatura ambiente durante 24 horas hasta que se completó. El THF se retiró *al vacío* y el

residuo se dividió entre diclorometano (75 ml) y bicarbonato sódico (50 ml). La fase orgánica se lavó con bicarbonato sódico (2x50 ml), después se separó y se secó sobre sulfato sódico, se filtró y se concentró *al vacío*. El producto en bruto se purificó por cromatografía en columna sobre gel de sílice Biotage® eluyendo con diclorometano:metanol:amoniaco (100:0:0 a 90:10:1 en volumen) dando el compuesto del título (862 mg, 58%) en forma de un sólido.

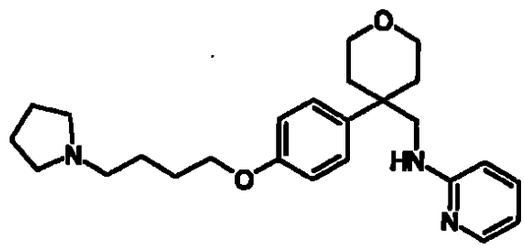
EMBR APCI$^+$ m/z 285 $[MH]^+$.

Intermedio 92: *N*-({4-[4-(4-clorobutoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piridin-2-amina

Se agitó 4-{4-[(piridin-2-ilamino)metil]tetrahidro-2*H*-piran-4-il}fenol (220 mg, 0,775 mmol), 1-bromo-4-clorobutano (146 mg, 0,852 mmol) y carbonato potásico (118 mg, 0,852 mmol) en DMF (1 ml) a 60ºC durante 24 horas hasta que se completó. La reacción se dividió entre acetato de etilo (50 ml) y agua (75 ml). La fase orgánica se separó y se lavó posteriormente con agua (2x30 ml) y después se secó sobre sulfato sódico, se filtró y se concentró *al vacío*. El producto en bruto compuesto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (100:0:0 a 98:2:0,2 en volumen) dando el compuesto del título (184 mg, 63%) en forma de un sólido amarillo.

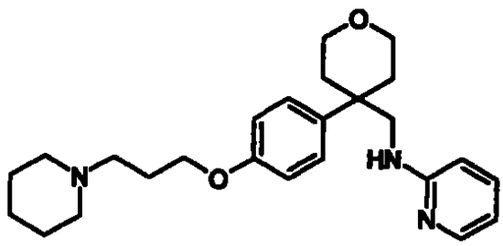
EMBR APCI$^+$ m/z 375 $[MH]^+$.

Ejemplo 241: *N*-({4-[4-(4-pirrolidin-1-ilbutoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piridin-2-amina



Una mezcla de *N*-({4-[4-(4-clorobutoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piridin-2-amina (180 mg, 0,481 mmol), pirrolidina (800, 0,963 mmol), carbonato sódico (102 mg, 0,963 mmol) y yoduro sódico (4 mg, 0,024 mmol) se agitó en butanol (5 ml) a 100°C durante 24 horas hasta que se completó. El butanol se retiró *al vacío* y el residuo se dividió entre acetato de etilo (40 ml) y agua (40 ml). La fase orgánica se secó sobre sulfato sódico, se filtró y se concentró *al vacío* dando un sólido pardo. El sólido se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (98:2:02 a 96:4:0,4 en volumen), seguido de recristalización en éter (1,5 ml) dando el compuesto del título (56,6 mg, 29%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 1,78-2,00 (m, 12H), 2,08-2,20 (m, 2H), 2,54-2,90 (m, 4H), 3,50 (d, 2H), 2,54-2,63 (m, 2H), 3,79-3,88 (m, 2H), 3,96-4,08 (m, 2H), 6,23 (d, 1H), 6,50 (t, 1H), 6,90 (d, 2H), 7,25 (d, 2H), 7,32 (t, 1 H), 8,01 (d, 1 H). EMBR APCI$^+$ m/z 410 $[MH]^+$.

Ejemplo 242: *N*-({4-[4-(3-piperidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)piridin-2-amina

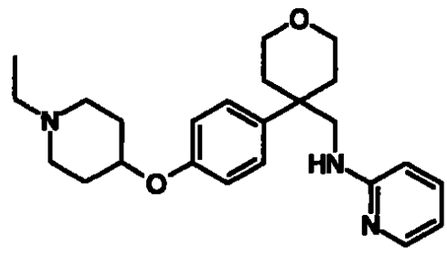


Se agitó 4-{4-[(piridin-2-ilamino)metil]tetrahidro-2*H*-piran-4-il}fenol (200 mg, 0,704 mmol), clorhidrato de 3-cloropropilpiperidina (152 mg, 0,775 mmol) y carbonato potásico (204 mg, 1,48 mmol) en DMF (1 ml) a 45ºC durante 24 horas hasta que se completó. La reacción se dividió posteriormente entre acetato de etilo (40 ml) y agua (40 ml). La fase orgánica se separó, se secó sobre sulfato sódico y se concentró *al vacío* dando un sólido. El sólido se purificó por HPLC preparativa dando el compuesto del título (220 mg, 76%) en forma de un sólido blanco.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,44-1,55 (m, 2H), 1,64-1,78 (m, 4H), 1,85-2,00 (m, 2H), 2,08-2,18 (m, 4H), 2,52-2,70 (m, 6H), 3,48 (d, 2H), 3,52-3,62 (m, 2H), 3,78-3,85 (m, 2H), 4,02 (t, 2H), 6,21 (d, 1H), 6,50. (t, 1H), 6,90 (d, 2H), 7,24 (d, 2H), 7,34 (t, 1H), 8,01 (d, 1H).

EMBR APCI$^+$ m/z 410 $[MH]^+$.

Ejemplo 243: *N*-[(4-{[4-(1-etilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]piridin-2-amina



A una solución de 4-{4-[(piridin-2-ilamino)metil]tetrahidro-2*H*-piran-4-il}fenol (250 mg, 0,881 mmol), 1-etilpiperidin-4-ol (103 mg, 0,8 mmol) y trifenilfosfina (231 mg, 0,881 mmol) en THF (5 ml) a 0°C en una atmósfera de nitrógeno se le añadió gota a gota azodicarboxilato de diisopropilo (solución al 95%, 183 µl, 0,881 mmol). La reacción se agitó durante 10 minutos después se calentó a temperatura ambiente durante 72 horas hasta que se completó. El THF se retiró *al vacío* y el residuo se dividió entre acetato de etilo (50 ml) y una solución de bicarbonato sódico saturado (50 ml). La fase orgánica se separó, se secó sobre sulfato sódico, se filtró y se concentró *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida eluyendo con diclorometano:metanol:amoniaco (100:0:0 a 96:4:0,4 en volumen) dando el compuesto del título (8,2 mg, 23%) en forma de un aceite amarillo.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,05 (t, 3H), 1,80-1,98 (m, 4H), 2,00-2,18 (m, 4H), 2,28-2,42 (m, 2H), 2,44-2,54 (q, 2H), 2,72-2,86 (m, 2H), 3,50 (d, 2H), 3,55-3,62 (m, 2H), 3,78-3,88 (m, 2H), 4,00-4,08 (m, 1H), 4,30-4,39 (m, 1 H), 6,22 (d, 1 H), 6,50 (t, 1 H), 6,90 (d, 2H), 7,23 (d, 2H), 7,30 (t, 1 H), 8,01 (d, 1 H).

EMBR APCI$^+$ m/z 396 $[MH]^+$.

EMAR IEN$^+$ m/z 396,2641 $[MH]^+$.

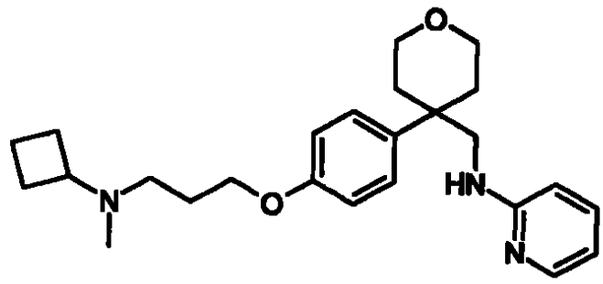
Intermedio 93: *N*-(3-cloropropil)-*N*-metilciclobutanamina

A una solución de *N*-metilciclobutanamina (1 g, 3,89 mmol) y carbonato

potásico (1,18 g, 8,56 mmol) en acetonitrilo (20 ml) a 0ºC se le añadió 1-bromo-3-cloropropano (383 µl, 3,89 mmol). La reacción se calentó a temperatura ambiente y se agitó durante 24 horas. El sólido se retiró por filtración y el filtrado se concentró *al vacío* dando el compuesto del título (241 mg, 38%) en forma de un aceite. No se realizó purificación.

EMBR APCI$^+$ m/z 162 $[MH]^+$.

Ejemplo 244: *N*-[[4-(4-{3-[ciclobutil(metil)amino]propoxi}fenil)tetrahidro-2*H*-piran-4-il]metil}piridin-2-amina



Se agitó 4-(4-[(piridin-2-ilamino)metil]tetrahidro-2*H*-piran-4-il}fenol (386 mg, 1,36 mmol), *N*-(3-cloropropil)-*N*-metilciclobutanamina (241 mg, 1,496 mmol) y carbonato potásico (280 mg, 2,03 mmol) en DMF (2 ml) a 45ºC durante 24 horas hasta que se completó. La reacción se dividió entre acetato de etilo (40 ml) y una solución de bicarbonato sódico saturado (50 ml), después la fase orgánica se lavó con agua (50 ml). La fase orgánica se separó y se secó sobre sulfato sódico, se filtró y se concentró *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (100:0:0 a 90:10:1 en volumen) dando el compuesto del título (165 mg, 30%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,55-1,72 (m, 2H), 1,80-1,99 (m, 6H), 2,00-2,09

(m, 2H), 2,10-2,20 (m, 4H), 2,40 (t, 2H), 2,80 (quintuplete, 1H), 3,50 (d, 2H), 3,54-3,62 (m, 2H), 3,78-3,88 (m, 2H), 4,00 (m, 3H), 6,20 (d, 1H), 6,50 (t, 1H), 6,92 (d, 2H), 7,22 (d, 2H), 7,32 (t, 1H), 8,00 (d, 1H).

EMBR APCI$^+$ m/z 410 $[MH]^+$.

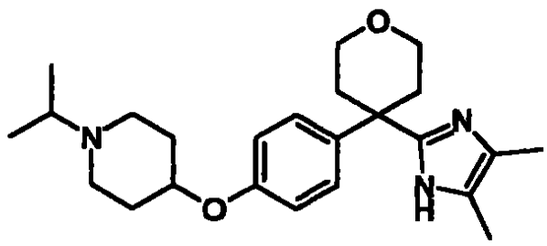
EMAR IEN$^+$ m/z 410,2794 $[MH]^+$.

Intermedio 94: 4-[4-[(1-isopropilpiperidin-4-il)oxi]fenil]tetrahidro-2*H*-piran-4-carbaldehído

A una solución enfriada de 4-[4-[(1-isopropilpiperidin-4-il)oxi]fenil]tetrahidro-2*H*-piran-4-carbonitrilo (1,16 g, 3,53 mmol) en diclorometano (12 ml) a -78ºC en una atmósfera de nitrógeno, se le añadió gota a gota hidruro de diisobutilaluminio (solución 1 M en diclorometano, 12,38 ml, 12 mmol) manteniendo la temperatura por debajo de -60ºC. La reacción se agitó a -78ºC durante 40 minutos, después a -20ºC durante 1 hora antes de dejarla calentar a temperatura ambiente. Después de 1 hora, la reacción se enfrió y se inactivó con HCl 2 M (13,2 ml) y se basificó con carbonato sódico a pH 8, y se filtró a través de una capa corta de celite eluyendo con diclorometano:metanol (99:1 en volumen). La reacción se dividió posteriormente entre diclorometano (50 ml) y agua (50 ml) y la fase orgánica se lavó con otra porción de agua (50 ml) antes de separarse, se secó sobre sulfato sódico, se filtró y se concentró *al vacío*. Se purificó por cromatografía ultrarrápida eluyendo con diclorometano:metanol (99:1 a 92:8 en volumen) dando el compuesto del título (318 mg, 27%).

EMBR APCI$^+$ m/z 332 $[MH]^+$.

Ejemplo 245: 4-[4-[4-(4,5-dimetil-1*H*-imidazol-2-il)tetrahidro-2*H*-piran-4-il]fenoxi]-1-isopropilpiperidina



Se calentó 4-(4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-carbaldehído (50 mg, 0,151 mmol), acetato amónico (116 mg, 1,51 mmol) y 2,3-butanodiona (13 mg, 0,151 mmol) en ácido acético (1 ml) en un microondas Smith Personal Synthesiser durante 900 segundos a 180°C. El ácido acético se retiró *al vacío* y el residuo se dividió entre acetato de etilo (20 ml) y una solución de bicarbonato sódico saturado (20 ml). La fase orgánica se separó, se secó sobre sulfato sódico y se concentró *al vacío*. Se purificó por cromatografía ultrarrápida eluyendo con diclorometano:metanol:amoniaco (100:0:0 a 95:5:0,5 en volumen) dando el compuesto del título (25,5 mg, 43%) en forma de un aceite pardo.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,08 (d, 6H), 1,76-1,88 (m, 2H), 1,96-2,07 (m, 2H), 2,10 (s, 6H), 2,19-2,28 (m, 2H), 2,39-2,50 (m, 4H), 2,72-2,87 (m, 3H), 3,67-3,84 (m, 4H), 4,20-4,34 (m, 1H), 6,83 (d, 2H), 7,14 (d, 2H).

EMBR APCI$^+$ m/z 398 $[MH]^+$.

Intermedio 95: (3-Nitro-piridin-4-il)-{4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil}-amina

A una solución agitada de (4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il}metilamina (390 mg, 1,2 mmol) en acetonitrilo (~5 ml) se le añadió base de Hunig (2304, 1,35 mmol, 1,1 eq.) e hidrógeno cloruro de 4-etoxi-3-nitropiridina (250 mg, 1,2 mmol, 1 eq.) y la mezcla se agitó

a reflujo durante 72 horas. A esto se le añadió una porción adicional de hidrógeno cloruro de 4-etoxi-3-nitropiridina (50 mg, 0,24 mmol, 0,2 eq.) y la mezcla se agitó a reflujo durante 24 horas más. Después, la mezcla de reacción se concentró *al vacío* dando un residuo oleoso amarillo oscuro. Este residuo se dividió entre NaOH 2 M (30 ml) y DCM (2 x 30 ml). Los extractos orgánicos se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío* dando un aceite amarillo oscuro. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (98:2:0,2 a 90:10:1, en volumen) proporcionando el compuesto del título (205 mg, 38%).

EMAR IEN$^+$ m/z 441,2486 $[MH]^+$.

Intermedio 96: (3-Nitro-piridin-2-il)-{4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil}-amina

A una solución agitada de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il}metilamina (320 mg, 1,0 mmol) en acetonitrilo (~5 ml), se añadió Base de Hunig (190 µl, 1,1 mmol, 1,1 eq.) y 2-cloro-3-nitropiridina (175 mg, 1,1 mmol, 1,1 eq.) y la mezcla se agitó a reflujo durante 4 horas. La mezcla de reacción se concentró posteriormente *al vacío* y se dividió entre una solución de $NaHCO_3$ saturado (20 ml) y DCM (2 x 20 ml). Los extractos orgánicos se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío* dando el compuesto del título (475 mg, 100%) en forma de un aceite amarillo.

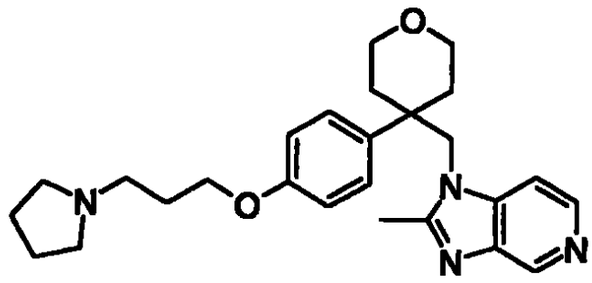
EMBR APCI$^+$ m/z 441 $[MH]^+$.

Intermedio 97: *N4*-{4-[4-(3-Pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil}piridina-3,4-diamina**

Una solución de (3-nitro-piridin-4-il)-[4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil]-amina (200 mg, 0,45 mmol) en etanol (~5 ml) se hidrogenó durante 4 horas a temperatura ambiente a 40 psi en presencia de Pd al 10%/C (20 mg, 10%p/p). La mezcla de reacción se filtró sobre Arbocel® y se aclaró con etanol. El filtrado se concentró *al vacío* dando un residuo pardo oleoso. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (94:6:0,6, en volumen) proporcionando el compuesto del título (68 mg, 36%).

EMAR IEN$^+$ m/z 411,2750 $[MH]^+$.

Ejemplo 246: 2-Metil-1-[4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil]-1*H*-imidazol-[4,5-c]piridina



Se agitó *N**4*-[4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil]-piridina-3,4-diamina (60 mg, 0,15 mmol) y anhídrido acético (~1 ml) a reflujo durante 18 horas. La mezcla de reacción se inactivó con ~1 ml agua, después se basificó con una solución de carbonato sódico diluido y después se extrajo con DCM (2 x 20 ml). Los extractos orgánicos se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío* dando un aceite pardo. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:5:0,5 a 90:10:1 en volumen) proporcionando el compuesto del título en forma de un

aceite pardo (19 mg, 30%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,78-1,82 (m, 6H), 1,97-2,10 (m, 5H), 2,23 (m, 2H), 2,54 (m, 4H), 2,62 (t, 2H), 3,40 (m, 2H), 3,82 (m, 2H), 4,00 (t, 2H), 4,07 (s, 2H), 6,80-6,88 (m, 4H), 7,00 (d, 1H), 8,30 (d, 1H), 8,92 (s, 1H).

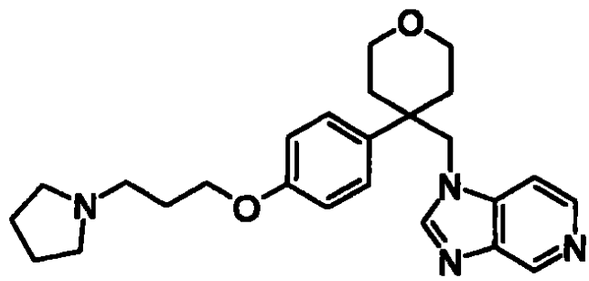
EMBR IEN$^+$ m/z 435 $[MH]^+$.

Intermedio 98: *N2*-{4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil}-piridin-2,3-diamina**

Una solución de (3-nitro-piridin-2-il)-{4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil}-amina (465 mg, 1,06 mmol) en etanol (~10 ml) se hidrogenó durante 4 horas a temperatura ambiente a 40 psi en presencia de Pd al 10%/C (45 mg, 10% p/p). La mezcla de reacción se filtró sobre Arbocel® y se aclaró con etanol (30 ml), HCl 2 M (20 ml) y EtOH (30 ml). El filtrado se concentró *al vacío* dando el compuesto del título (365 mg, 84%).

EMAR IEN$^+$ m/z 411,2750 $[MH]^+$.

Ejemplo 247: 1-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)-1*H*-imidazol[4,5-c]piridina



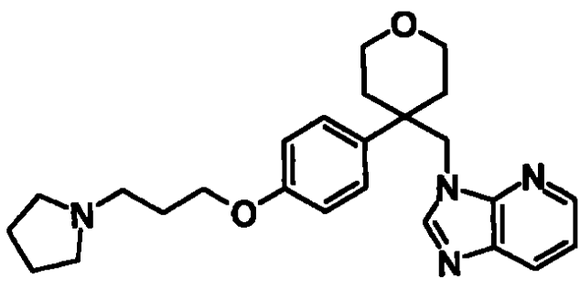
Se agitó *N**4*-[4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil)-piridin-3,4-diamina (280 mg, 0,68 mmol), trimetilortoformiato (5 ml) y ácido fórmico (0,5 ml) a 40ºC durante 18 horas y después a 60ºC durante 24 horas, después a 80ºC durante 24 horas. La mezcla de reacción se concentró

al vacío y el residuo se dividió entre NaOH 2 M (30 ml) y DCM (2 x 30 ml). Los extractos orgánicos se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío* dando un aceite pardo. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:5:0,5 a 90:10:1 en volumen) proporcionando el compuesto del título en forma de un aceite viscoso transparente (185 mg, 65%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,78-1,82 (m, 4H), 1,91-2,03 (m, 4H), 2,15-2,20 (m, 2H), 2,52 (m, 4H), 2,61 (t, 2H), 3,44 (m, 2H), 3,82 (m, 2H), 4,00 (t, 2H), 4,19 (s, 2H), 6,82 (d, 2H), 6,86-6,93 (m, 3H), 7,08 (s, 1H), 8,30 (d, 1H), 9,01 (s, 1H).

EMAR IEN$^+$ m/z 421,2590 $[MH]^+$.

Ejemplo 248: 3-({4-[4-(3-pirrolidin-1-il]propoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)-3*H*-imidazo[4,5-b]piridina



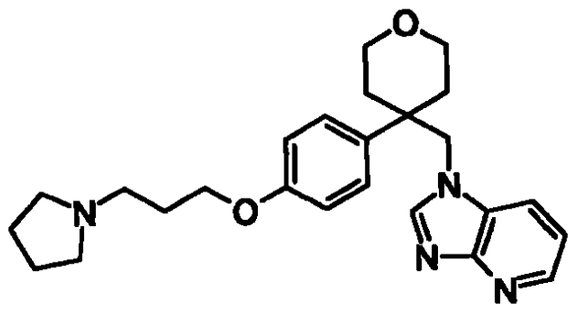
Se agitó *N**2*-[4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-ilmetil]-piridina-2,3-diamina (350 mg, 0,85 mmol), trimetilortoformiato (5 ml) y ácido fórmico (0,5 ml) a 40°C durante 3 horas. La mezcla de reacción se concentró *al vacío* y el residuo se dividió entre una solución saturada de $NaHCO_3$ (40 ml) y DCM (2 x 40 ml). Los extractos orgánicos se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío* dando un aceite pardo. El producto en bruto se purificó por cromatografía ultrarrápida

sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (97:3:0,3 a 93:7:0,7 en volumen) proporcionando el compuesto del título en forma de un aceite pardo (255 mg, 71%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,78-1,82 (m, 4H), 1,99-2,10 (m, 6H), 2,57 (m, 4H), 2,64 (t, 2H), 3,56 (m, 2H), 3,92 (m, 2H), 4,03 (t, 2H), 4,40 (s, 2H), 6,82 (s, 1H), 6,90 (d, 2H), 7,02 (d, 2H), 7,20 (m, 1H), 7,99 (d, 1H), 8,38 (d, 1H).

EMAR IEN$^+$ m/z 421,2586 $[MH]^+$.

Ejemplo 249: 1-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)-1*H*-imidazol[4,5-b]piridina



Etapa 1:

Se agitó éster 2-nitro-piridin-3-ilo del ácido trifluoro-metanosulfónico (1,1 g, 4,1 mmol), {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il}metilamina (1,3 g, 4,1 mmol) y Base de Hunig (1,7 ml, 9,8 mmol) a 60ºC durante 72 horas. La mezcla se diluyó con DCM (30 ml) y se lavó con agua (10 ml). La fase de DCM se secó sobre sulfato sódico, se filtró y se concentró *al vacío* dando un aceite pardo oscuro. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (98:2:0,2 a 90:10:1, en volumen) dando un residuo oleoso verde después de concentración *al vacío*.

Etapa 2:

A una solución de este residuo en metanol (10 ml) se le añadió dicloruro de metil viológeno hidrato (5 mg, 0,02 mmol) y una solución de ditionito sódico (1,07 g, 6,13 mmol) y $NaHCO_3$ (940 mg, 11,2 mmol) en agua (10 ml). La mezcla se agitó a temperatura ambiente durante 10 minutos y después se extrajo con DCM (2 x 30 ml). Los extractos orgánicos se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío* dando un aceite verte oscuro. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (94:6:0,6 a 90:10:1, en volumen) dando un sólido verde oscuro después de concentración *al vacío*.

Etapa 3:

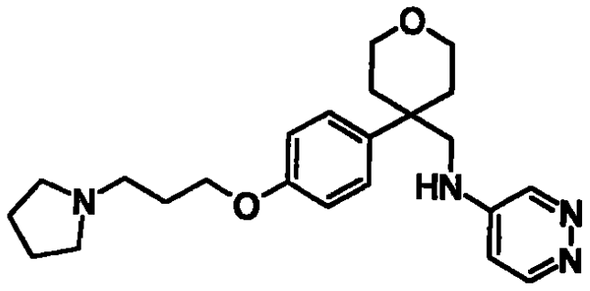
Este sólido verde, trimetilortoformiato (5 ml) y ácido fórmico (0,5 ml) se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se concentró *al vacío* y el residuo se dividió entre una solución saturada de NaOH 2 M (20 ml) y DCM (2 x 20 ml). Los extractos orgánicos se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío* dando un aceite naranja. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (96:4:0,4 a 90:10:1 en volumen) proporcionando el compuesto del título en forma de un aceite amarillo pálido (95 mg, 6%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,80 (m, 4H), 1,90-2,02 (m, 4H), 2,17 (m, 2H), 2,52 (m, 4H), 2,61 (t, 2H), 3,41 (t, 2H), 3,80 (m, 2H), 3,98 (t, 2H), 4,16 (s, 2H), 6,78 (d, 2H), 6,90 (d, 2H), 7,02 (m, 1H), 7,17 (d, 1H), 7,31 (s, 1H), 8,43 (m, 1H)
EMAR APCI$^+$ m/z 421 $[MH]^+$.

Ejemplo 250: *N*-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-

541

il)metil)piridazin-4-amina



Etapa 1:

Una mezcla de {4-[4-(3-Pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il} metilamina (500 mg, 1,57 mmol), 3,4,5-tricloro-piridazina (403 mg, 2,20 mmol) y carbonato potásico (240 mg, 1,73 mmol) en acetonitrilo (5 ml) se agitó a temperatura ambiente durante 72 horas. La mezcla se concentró *al vacío* y se dividió entre agua (30 ml) y DCM (2 x 30 ml). Los extractos orgánicos combinados se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío* dando un aceite rojo oscuro. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (96:4:0,4 a 93:70:7, en volumen) dando un aceite roja oscuro después de concentración *al vacío*.

Etapa 2:

Una solución de este aceite e hidróxido sódico (110 mg, 2,7 mmol) en etanol (~5 ml) se hidrogenó durante 18 horas a temperatura ambiente a 50 psi en presencia de Pd al 10%/C (60 mg, 10% p/p). La mezcla de reacción se filtró sobre Arbocel® y se aclaró con etanol. El filtrado se concentró *al vacío* dando un residuo oleoso. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (94:6:0,6 a 90:10:1, en volumen) proporcionando el compuesto del título (230

mg, 37%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,80 (m, 4H), 1,88 (m, 2H), 2,01 (m, 2H), 2,20 (m, 2H), 2,55 (m, 4H), 2,63(t, 2H), 3,25 (d, 2H), 3,55 (m, 2H), 3,80 (m, 2H), 3,90 (t, 1H), 4,02 (t, 2H), 6,33 (m, 1H), 6,96 (d, 2H), 7,20 (d, 2H), 8,40 (d, 1H), 8,57 (d, 1H)

EMAR IEN$^+$ m/z 397,2591 $[MH]^+$.

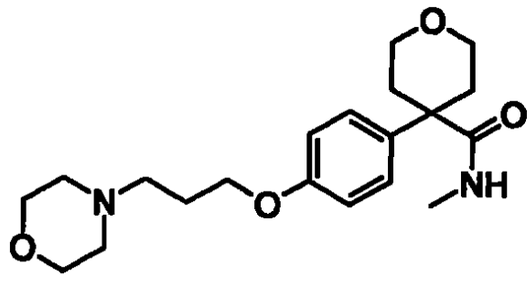
Intermedio 99: Clorhidrato del ácido 4-[4(3-morfolin-4-il-propoxi)-fenil]-tetrahidro-piran-4-carboxílico

Una solución de 4-[4-(3-morfolin-4-ilpropoxi)fenil]tetrahidropiran-4-carbonitrilo (2,0 g, 6,05 mmol) en ácido clorhídrico concentrado (30 ml, 10 vol) se calentó a reflujo durante 16 horas. La solución se enfrió a temperatura ambiente produciendo un precipitado. Esto se filtró, se lavó con agua (~5 ml) y éter dietílico (~ 10 ml) y después se secó dando el compuesto del título (1,34 g, 57%) en forma de un sólido naranja pálido.

EMBR (APCI$^-$) 348 $(M-H^+)^-$.

Microanálisis: Encontrado: C, 58,16; H, 7,30; N, 3,45%. $C_{19}H_{28}NO_5Cl.0,3H_2O$ requiere C, 58,32; H, 7,37; N, 3,58%.

Ejemplo 251: *N*-metil-4-[4(3-morfolin-4-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxamida



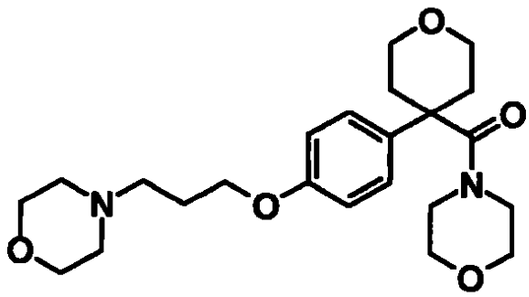
Se añadió hexafluorofosfato de O-(1*H*-benzotriazol-1-il)-*N*,*N*,*N*,*N*'-

tetrametiluronio (640 mg, 1,7 mmol) a una solución de clorhidrato de ácido 4-[4-(3-morfolin-4-il-propoxi)-fenil]-tetrahidro-piran-4-carboxílico (500 mg, 1,3 mmol), hidrógeno cloruro de metilamina (130 mg, 1,9 mmol) y Base de Hunig (790 µl, 4,5 mmol) en *N,N*-dimetilformamida (5 ml). La mezcla se agitó a temperatura ambiente durante 2 horas y después se concentró *al vacío*. El residuo se dividió entre una solución de NaOH 2 M (20 ml) y DCM (2x20 ml). Los extractos orgánicos se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron a presión reducida. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:5:0,5 a 90:10:1, en volumen) proporcionando el compuesto del título (355 mg, 76%) en forma de un sólido blanquecino.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,93-2,00 (m, 2H), 2,01-2,08 (m, 2H), 2,37-2,40 (m, 2H), 2,48 (m, 4H), 2,50 (t, 2H), 2,70 (d, 3H), 3,67-3,80 (m, 8H), 4,02 (t, 2H), 6,88 (d, 2H), 7,22 (d, 2H).

EMBR APCI$^+$ m/z 363 $[MH]^+$.

Ejemplo 252: 4-(3-{4-[4-(morfolin-4-ilcarbonil)tetrahidro-2*H*-piran-4-il]fenoxil}propil)morfolina



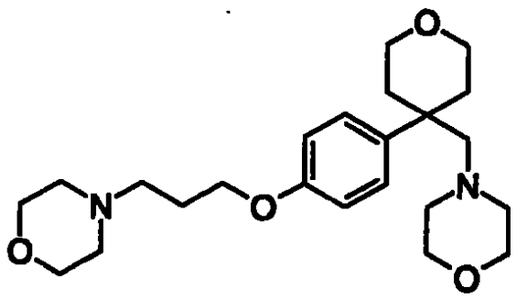
Se añadió hexafluorofosfato de O-(1*H*-benzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (200 mg, 0,5 mmol) a una solución de clorhidrato de ácido 4-[4-

(3-Morfolin-4-il-propoxi)-fenil]-tetrahidro-piran-4-carboxílico (160 mg, 0,4 mmol), morfolina (54 µl, 0,6 mmol) y base de Hunig (180 µl, 1 mmol) en *N,N*-dimetilformamida (2 ml). La mezcla se agitó a temperatura ambiente durante 3 horas y después se concentró *al vacío*. El residuo se dividió entre una solución de NaOH 2 M (20 ml) y DCM (2x20 ml). Los extractos orgánicos se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron a presión reducida. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:5:0,5 a 90:10:1, en volumen) proporcionando el compuesto del título (182 mg, 100%) en forma de un sólido pardo pálido.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,93-2,04 (m, 4H), 2,20 (m, 2H), 2,42-2,55 (m, 6H), 3,22-3,43 (m a, 8H), 3,72 (t, 4H), 3,79 (m, 2H), 3,90 (m, 2H), 4,00 (t, 2H), 6,88 (d, 2H), 7,17 (d, 2H).

EMBR APCI$^+$ m/z 419 $[MH]^+$.

Ejemplo 253: 4-(3-{4-[4-(morfolin-4-ilmetil)tetrahidro-2*H*-piran-4-il]fenoxi}propil)morfolina



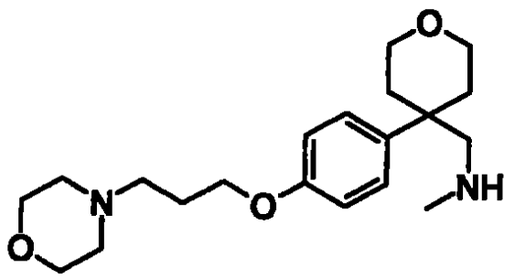
A una solución agitada de 4-(3-{4-[4-(morfolin-4-ilcarbonil)tetrahidro-2*H*-piran-4-il]fenoxi}propil)morfolina (160 mg, 0,38 mmol) en THF (4 ml) a 0ºC se le añadió gota a gota una solución de $LiAlH_4$ (solución 1,0 M en Et_2O, 1,15 ml, 1,15 mmol). La mezcla de reacción se agitó a 0ºC durante 20 minutos después

se calentó a reflujo durante 1,5 horas. La reacción se enfrió posteriormente a 0ºC, se le añadió gota a gota agua (0,10 ml) seguido de hidróxido sódico (2,0 M, 0,10 ml) y agua (0,30 ml). La mezcla se filtró a través de una capa corta de celite, eluyendo con metanol al 1% en diclorometano (15 ml) y los lavados orgánicos se concentraron *al vacío*. El producto en bruto se purificó por cromatografía en columna sobre gel de sílice, eluyendo con diclorometano:metanol:amoniaco, 97:3:0,3 a 92:8:0,8, dando el compuesto del título en forma de un aceite transparente (125 mg, 81%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,83 (m, 2H), 1,95 (m, 2H), 2,07-2,16 (m, 6H), 2,40 (s, 2H), 2,43-2,50 (m, 4H), 2,52 (t, 2H), 3,51 (m, 6H), 3,76 (m, 6H), 4,01(t, 2H), 6,82 (d, 2H), 7,21 (d, 2H).

EMAR IEN$^+$ m/z 405,2742 $[MH]^+$.

Ejemplo 254: *N*-metil-1-[4-[4-(3-morfolin-4-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il]metanamina



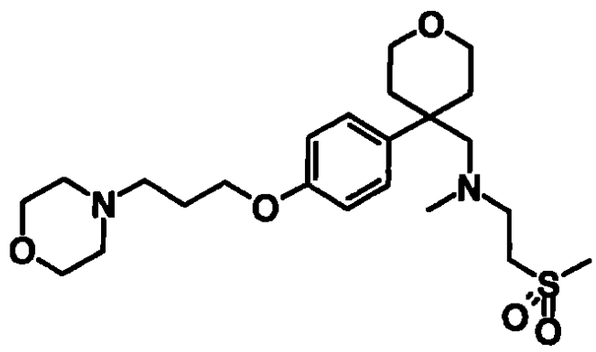
El compuesto del título (252 mg, 77%) se preparó a partir de *N*-metil-4-[4-(3-morfolin-4-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxamida y una solución de $LiAlH_4$ (solución 1,0 M en Et_2O) de forma similar al procedimiento usado para 4-(3-[4-[4-(morfolin-4-ilmetil)tetrahidro-2*H*-piran-4-il]fenoxi}propil)morfolina.

^{1}H RMN (400 MHz, CD_3OD) δ 1,85-2,00 (m, 6H), 2,12 (m, 2H), 2,24 (s, 3H), 2,45 (m, 4H), 2,53 (t, 2H), 2,63 (s, 2H), 3,57 (m, 2H), 3,70-3,80 (m, 6H), 4,01 (t,

1H), 6,88 (d, 2H), 7,20 (d, 2H).

EMAR IEN$^+$ m/z 349,2477 $[MH]^+$.

Ejemplo 255: *N*-metil-2-(metilsulfonil)-*N*-({4-[4-(3-morfolin-4-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)etanamina



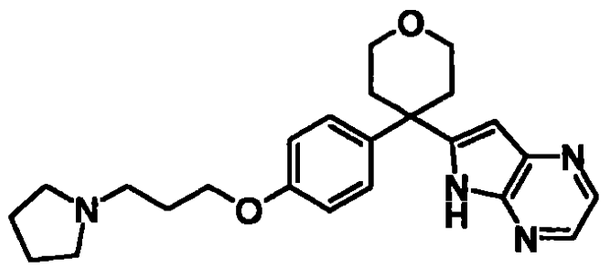
A una solución agitada de *N*-metil-1-{4-[4-(3-morfolin-4-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metanamina (230 mg, 0,66 mmol) en metanol (2 ml) se le añadió metanosulfonil-eteno (64 µl, 0,72 mmol) y la mezcla se agitó a temperatura ambiente durante 18 horas. La mezcla se concentró *al vacío* y se trituró con éter dietílico dando el compuesto del título en forma de un sólido blanco (274 mg, 91%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,81 (m, 2H), 1,97 (m, 2H), 2,04 (s, 3H), 2,13 (m, 2H), 2,42-2,58 (m, 8H), 2,62 (t, 2H), 2,74 (s, 3H), 2,81 (t, 2H), 3,50 (m, 2H), 3,70-3,80 (m, 6H), 4,00 (t, 2H), 6,86 (d, 2H), 7,20 (d, 2H).

EMAR IEN$^+$ m/z 455,2570 $[MH]^+$.

Microanálisis: Encontrado: C, 60,61; H, 8,47; N, 6,09%. $C_{23}H_{38}N_2O_5S$ requiere C, 60,76; H, 8,42; N, 6,16%.

Ejemplo 256: 6-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}-5*H*-pirrolo[2:3-b]pirazina

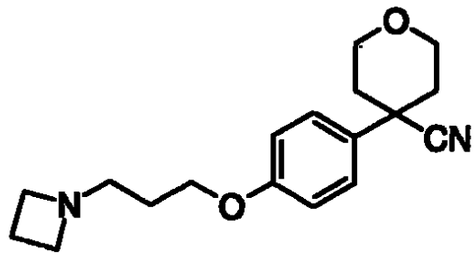


Una solución de 2-metil-pirazina (580 µl, 6,4 mmol) en THF (4 ml) se añadió a 4,7 ml de complejo diisopropilamida de litio:THF 1,5 M en hexanos a -40°C y la solución roja oscuro resultante se agitó a -40°C durante 0,5 horas. Se añadió una solución de 4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-carbonitrilo (1,00 g, 3,2 mmol) en THF (5 ml) a -40°C y la mezcla de reacción se agitó a esta temperatura durante 0,5 horas, después a temperatura ambiente durante 18 horas. Se añadió 1 equivalente más de complejo de diisopropilamida de litio y la mezcla de reacción se agitó a reflujo durante 24 horas. La mezcla se enfrió a temperatura ambiente, se añadió agua (10 ml) y la mezcla se concentró *al vacío*. El residuo se dividió entre agua (60 ml) y DCM (2 x 60 ml). Los extractos orgánicos se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron a presión reducida. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:5:0,5 a 90:10:1, en volumen) proporcionando el compuesto del título (65 mg, 6%) en forma de un aceite pardo.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,74-1,80 (m, 6H), 2,00 (m, 2H), 2,42-2,55 (m, 6H), 2,60 (t, 2H), 3,80 (m, 4H), 4,00 (t, 2H), 6,60 (s, 1H), 6,86 (d, 2H), 7,21 (d, 2H), 8,05 (d, 1H), 8,39 (d, 1H).

EMAR IEN$^+$ m/z 407,2437 $[MH]^+$.

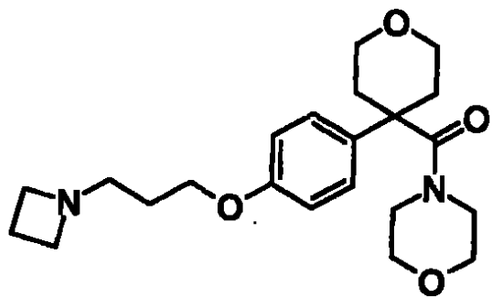
Ejemplo 257: 4-[4-(3-azetidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbonitrilo



Una mezcla de 4-[4-(3-cloro-propoxi)-fenil]-tetrahidropiran-4-carbonitrilo y 4-[4-(3-bromo-propoxi)-fenil]-tetrahidropiran-4-carbonitrilo (7,5 g, 27 mmol), K_2CO_3 (9,6 g, 70 mmol) y clorhidrato de azetidina (4,0 g, 43 mmol) en acetonitrilo (80 ml) se calentó a 40°C durante 18 horas. La mezcla se concentró *al vacío* y se dividió posteriormente entre agua (150 ml) y acetato de etilo (150 ml). La fase orgánica se extrajo con una solución de HCl 2 M (2 x 104 ml) y las fases orgánicas combinadas se basificaron con una solución de hidróxido potásico al 40%, después se extrajeron con DCM (2 x 150 ml). Las fases de DCM se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron a presión reducida dando el compuesto del título (1,1 g, 57%) en forma de un aceite viscoso transparente.

^{1}H RMN (400 MHz, DMSO) δ 1,80 (quintuplete, 2H), 2,00-2,14 (m, 6H), 2,58 (t, 2H), 3,20 (t, 4H), 3,88 (m, 2H), 4,00-4,11 (m, 4H), 6,90 (d, 2H), 7,38 (d, 2H); EMBR (APCI$^+$) m/z 301 $(MH)^+$.

Ejemplo 258: 4-({4-[4-(3-azetidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}carbonil)morfolina



Etapa 1:

Una solución de 4-[4-(3-azetidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbonitrilo (1,1 g, 3,7 mmol) en ácido clorhídrico concentrado (15 ml, 10 vol) se calentó y se agitó a reflujo durante 24 horas. La solución se enfrió a temperatura ambiente y después se concentró *al vacío* produciendo un sólido oleoso pardo. Se añadió base de Hunig (6 ml) y la mezcla se concentró *al vacío* dando un residuo oleoso pardo.

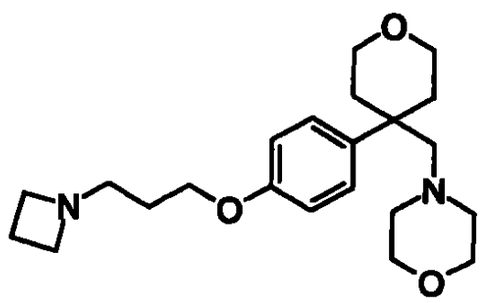
Etapa 2:

Se añadió hexafluorofosfato de O-(1*H*-benzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (1,7 g, 4,5 mmol) a una solución de este residuo, se añadieron morfolina (600 µl, 6,9 mmol) y base de Hunig (780 µl, 4,5 mmol) en *N,N*-dimetilformamida (5 ml). La mezcla se agitó a temperatura ambiente durante 72 horas y después se concentró *al vacío.* El residuo se dividió entre agua (50 ml) y DCM (2 x 50 ml). Los extractos orgánicos se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron a presión reducida. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:5:0,5 a 90:10:1, en volumen) proporcionando el compuesto del título (128 mg, 9%) en forma de una espuma rosa pálido después de triturar con éter dietílico.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,93-2,04 (m, 4H), 2,20 (m, 2H), 2,51-2,60 (m, 2H), 3,22-3,45 (m a, 10H), 3,78 (m, 2H), 3,86 (m, 2H), 4,02 (t, 2H), 4,13 (t, 4H), 6,88 (d, 2H), 7,18 (d, 2H).

EMAR IEN$^+$ m/z 389,2426 $[MH]^+$.

Ejemplo 259: 4-({4-[4-(3-azetidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)morfolina



A una solución agitada de 4-({4-[4-(3-azetidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il)carbonil]morfolina (120 mg, 0,31 mmol) en THF (1 ml) a 0°C se le añadió gota a gota una solución de $LiAlH_4$ (solución 1,0 M en Et_2O, 1,00 ml, 1,00 mmol). La mezcla de reacción se agitó a 0°C durante 20 minutos y después se calentó a reflujo durante 3 horas. La reacción se enfrió posteriormente a 0°C, se añadió gota a gota agua (0,10 ml) seguid de hidróxido sódico (2,0 M, 0,10 ml) y agua (0,30 ml). La mezcla se filtró a través de una capa corta de celite, eluyendo con metanol al 1% en diclorometano (15 ml) y los lavados orgánicos se concentraron *al vacío*. El producto en bruto se purificó por cromatografía en columna sobre gel de sílice, eluyendo con diclorometano:metanol:amoniaco, 97:3:0,3 a 94:6:0,6, dando el compuesto del título en forma de un aceite transparente (25 mg, 22%).

^{1}H RMN (400 MHz, $CDCl_3$) 1,78-1,90 (m, 8H), 2,08 (m, 2H), 2,13 (m, 4H), 2,38 (s, 2H), 2,59 (t, 2H), 3,20 (t, 2H), 3,51 (m, 6H), 3,76 (m, 2H), 4,00 (t, 2H), 6,82

(d, 2H), 7,21 (d, 2H).

EMBR APCI$^+$ m/z 375 $[MH]^+$.

Intermedio 100: 4-(4-{[1-(difenilmetil)azetidin-3-il]metoxi}fenil)tetrahidro-2*H*-piran-4-carbonitrilo

Se hizo reaccionar de forma conjunta 4-(4-hidroxi-fenil)-tetrahidro-piran-4-carbonitrilo (6,18 g, 30,4 mmol), (1-benzhidril-azetidin-3-il)-metanol (7 g, 28 mmol), PPh_3 (8 g, 30,4 mmol), y DIAD (69 ml, 30,4 mmol) de forma similar al procedimiento general C. El material en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con pentano:acetato de etilo:dietilamina (50:45:5 a 0:95:5) proporcionando el compuesto del título (5,03 g, 41%) en forma de un sólido amarillo.

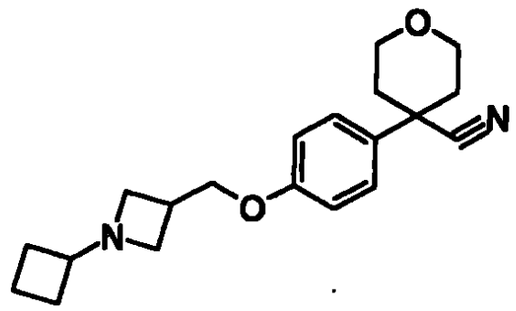
EMBR APCI$^+$ m/z 439 $[MH]^+$.

Intermedio 101: 4-[4-(azetidin-3-ilmetoxi)fenil]tetrahidro-2*H*-piran-4-carbonitrilo

Se combinó 4-(4-{[1-(difenilmetil)azetidin-3-il]metoxi}fenil)tetrahidro-2*H*-piran-4-carbonitrilo (0,605 g, 1,38 mmol), hidróxido de paladio (0,089), ácido clorhídrico concentrado (0,115 ml, 1,38 mmol) y etanol (8 ml) y se hidrogenó durante 18 horas a 40ºC a 40 psi (0,28 MPa). La mezcla se filtró a través de Arbocel® y se aclaró con etanol. El filtrado se concentró *al vacío*. El residuo se disolvió en DCM (50 ml) y se lavó con carbonato sódico acuoso al 10% (20 ml). Los extractos orgánicos se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío* proporcionando un aceite verde. Este aceite se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:5:0,5 a 90:10:1) proporcionando el compuesto del título (0,145 g, 39%) en forma de un aceite amarillo.

EMBR APCI$^+$ m/z 273 $[MH]^+$.

Ejemplo 260: 4-[4-[(1-ciclobutilazetidin-3-il)metoxi]fenil]tetrahidro-2*H*-piran-4-carbonitrilo



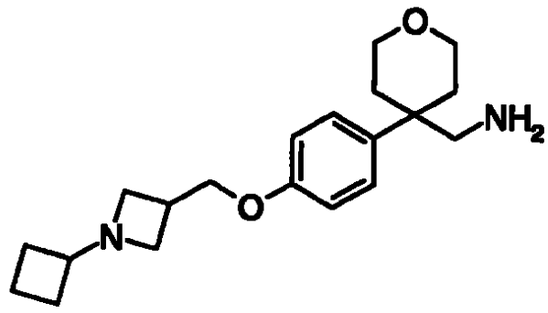
Se disolvió 4-[4-(azetidin-3-ilmetoxi)fenil]tetrahidro-2*H*-piran-4-carbonitrilo (0,2 g, 0,73 mmol) en THF (2 ml).Se añadió ciclobutanona (0,06 ml, 0,80 mmol) y ácido acético (0,042 ml, 0,73 mmol). La mezcla se agitó a temperatura ambiente durante 30 minutos. Se añadió triacetoxiborohidruro sódico (0,311 g, 1,47 mmol). La mezcla se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se diluyó con carbonato sódico acuoso al 10% (5 ml) después se extrajo con DCM (2 x 50 ml). Los extractos orgánicos se combinaron, se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío* proporcionando un aceite transparente. Este aceite se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (96:4:0,4 a 95:5:0,5) proporcionando el compuesto del título (0,194 g, 81%) en forma de un aceite transparente.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,60-1,70 (m, 2H), 1,70-1,80 (m, 2H), 1,80-1,90 (m, 2H), 1,95-2,00 (m, 2H), 2,0-2,15 (m, 2H), 2,9 (m, 1H), 3,1 (t, 2H), 3,16 (m, 1H), 3,4 (t, 2H), 3,9 (m, 2H), 4,10 (m, 4H), 6,90 (d, 2H), 7,40 (d, 2H)

EMAR IEN$^+$ m/z 327,2059 $[MH]^+$.

Ejemplo 261: 1-(4-[4-[(1-ciclobutilazetidin-3-il)metoxi]fenil]tetrahidro-2*H*-

piran-4-il)metanamina

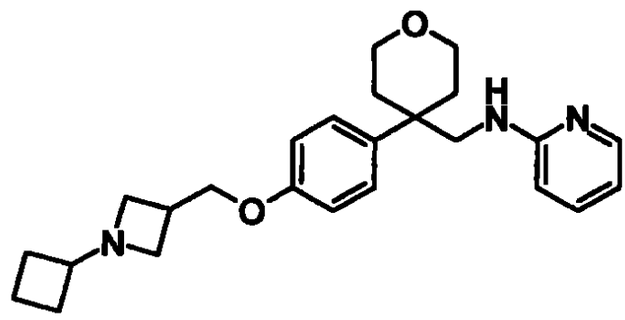


Se disolvió 4-[4-[(1-ciclobutilazetidin-3-il)metoxi]fenil)tetrahidro-2*H*-piran-4-carbonitrilo (0,29 g, 0,89 mmol) en THF (5 ml). La solución se enfrió a 0°C en una atmósfera de nitrógeno. Se añadió gota a gota hidruro de aluminio litio (2,7 ml, solución 1,0 M en éter dietílico). La reacción se agitó a 0°C durante 30 minutos, después se calentó a temperatura ambiente durante 4 horas en una atmósfera de nitrógeno hasta que se completa. La reacción se enfrió a 0°C, se añadió gota a gota agua (0,1 ml)seguido de hidróxido sódico (2,0 M, 0,1 ml) y agua (0,3 ml). La mezcla se filtró (usando diclorometano:metanol (90:10)) a través de celite. Los extractos orgánicos se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío* proporcionando un aceite transparente. Este aceite se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (96:4:0,4 a 90:10:1) proporcionando el compuesto del título (0,175 g, 59%) en forma de un aceite incoloro transparente.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,60-1,70 (m, 2H), 1,70-1,85 (m, 2H), 1,85-1,95 (m, 2H), 1,95-2,06 (m, 2H), 2,1-2,18 (m, 2H), 2,79 (s, 2H), 2,9 (m, 1H), 3,1 (t, 2H), 3,2 (m, 1H), 3,48 (m, 2H), 3,54 (m, 2H), 3,8 (m, 2H), 4,10 (d, 2H), 6,9 (d, 2H), 7,2 (d, 2H)

EMAR IEN$^+$ m/z 331,2374 $[MH]^+$.

Ejemplo 262: *N*-[(4-{4-[(1-ciclobutilazetidin-3-il)metoxi]fenil}tetrahidro-2*H*-piran-4-il)metil]piridin-2-amina



Se disolvió 1-(4-{4-[(1-ciclobutilazetidin-3-il)metoxi]fenil}tetrahidro-2*H*-piran-4-il)metanamina (0,175 g, 0,53 mmol) en tolueno (5 ml) y se añadieron 2-bromopiridina (0,051 ml, 0,53 mmol), 2,2'-bis(difenilfosfino)-1,1'binaftilo (0,013 g, 0,02 mmol) y *terc*-butóxido sódico (0,076 g, 0,79 mmol). La mezcla de reacción se purgó con nitrógeno y se añadió tris(dibencilidenacetona)dipaladio (0) (0,011 g, 0,01 mmol). La mezcla se calentó en una atmósfera de nitrógeno a 70ºC durante 18 horas. La mezcla de reacción se diluyó con agua (20 ml) y se extrajo con DCM (2 x 30 ml). Los extractos orgánicos combinados se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío* proporcionando un aceite amarillo. Esto se purificó por HPLC eluyendo con metanol: formiato amónico 10 nM (ac) (1:1), las fracciones se combinaron y se concentraron *al vacío* dejando un aceite transparente. Esto se disolvió en DCM (50 ml) y se lavó con una solución de hidrogenocarbonato sódico acuoso en agua (10 ml). La fase orgánica se secó sobre sulfato sódico, se filtró y se concentró *al vacío* proporcionando el compuesto del título (0,016 g, 7%) en forma de un aceite incoloro transparente.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,60-1,70 (m, 2H), 1,70-1,80 (m, 2H), 1,80-1,92

(m, 2H), 1,92-2,0 (m, 2H), 2,18 (m, 2H), 2,90 (m, 1H), 3,10 (t, 2H), 3,15 (m, 1H), 3,40 (t, 2H), 3,50 (d, 2H), 3,60 (m, 2H), 3,80 (m, 2H), 4,0 (m, 1H), 4,10 (d, 2H), 6,22 (d, 1H), 6,50 (d, 1H), 6,90 (d, 2H), 7,28 (d, 2H), 7,32 (t, 1H), 8,0 (d, 1H)

EMAR IEN$^+$ m/z 408,2641 $[MH]^+$.

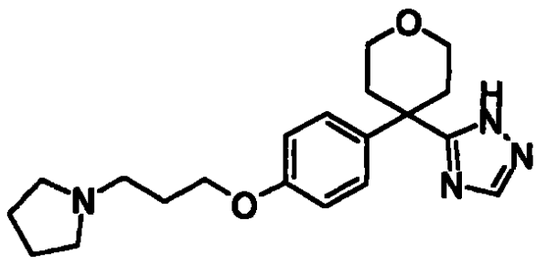
Intermedio 102: *N*-[(dimetilamino)metilen]-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxamida

Se combinó amida del ácido 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxílico (0,561 g, 1,69 mmol) y *N*,*N*-dimetilformamida dimetil acetal (5 ml) y se calentó a reflujo durante 4 horas. La mezcla de reacción se concentró *al vacío* y formó un azeótropo con tolueno (2 x 10 ml) proporcionando el compuesto del título (0,655 g, 100%) en forma de un sólido pardo.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,80-1,85 (m, 4H), 1,85-1,95 (m, 2H), 2,0-2,10 (m, 2H), 2,6-2,78 (m, 8H), 3,0 (s, 3H), 3,05 (s, 3H), 3,60 (m, 2H), 3,90 (m, 2H), 4,0 (t, 2H), 6,80 (d, 2H), 7,35 (d, 2H), 8,30 (s, 1H)

EMBR APCI$^+$ m/z 388 $[MH]^+$.

Ejemplo 263: 3-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il]-1*H*-1,2,4-triazol



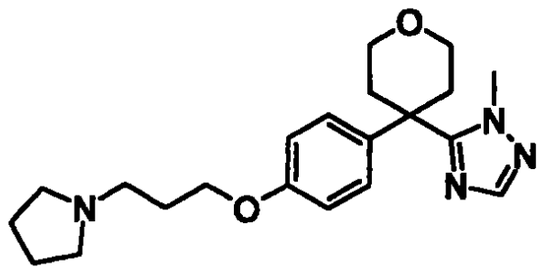
Se combinó *N*-[(dimetilamino)metilen]-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxamida (0,15 g, 0,39 mmol), hidrato

de hidrazina (0,048 ml, 0,98 mmol) y ácido acético (1 ml) y se calentó a 100°C durante 1,5 horas. La mezcla de reacción se concentró *al vacío*. El residuo se disolvió en diclorometano (100 ml) y se lavó con carbonato sódico acuoso al 10% (20 ml). La fase orgánica se secó sobre sulfato sódico y se evaporó proporcionando un aceite transparente. Esto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (92:8:0,8 a 90:10:1) produciendo un aceite transparente que se trituró con éter dietílico (3 ml), se aisló un sólido blanco como el compuesto del título (0,034 g, 24%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,82-1,95 (m, 4H), 2,0-2,10 (m, 2H), 2,30 (m, 2H), 2,60-2,70 (m, 2H), 2,70-2,80 (m, 6H), 3,62 (t, 2H), 3,89 (m, 2H), 3,95 (t, 2H), 6,80 (d, 2H), 7,20 (d, 2H), 7,95 (d, 1H)

EMAR IEN$^+$ m/z 357,2279 $[MH]^+$.

Ejemplo 264: 1-metil-5-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}-1*H*-1,2,4-triazol



Se combinó *N*-[(dimetilamino)metilen]-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxamida (0,34 g, 0,88 mmol), metil hidrazina (0,116 ml, 2,19 mmol) y ácido acético (1 ml) y se calentó a 100°C durante 2 horas. La mezcla de reacción se diluyó con agua (10 ml), se añadió carbonato sódico sólido hasta que la mezcla alcanzó pH 9. Se usó

Diclorometano (2 x 50 ml) para la extracción. Los extractos orgánicos combinados se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío* proporcionando un aceite amarillo. Esto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (96:4:0,4 a 90:10:1) produciendo el compuesto del título (0,065 g, 20%) en forma de un sólido blanco.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,83-1,93 (m, 4H), 2,05-2,16 (m, 2H), 2,30 (m, 2H), 2,48 (m, 2H), 2,60-2,85 (m, 6H), 3,37 (s, 3H), 3,80 (m, 2H), 3,90 (m, 2H), 4,0 (t, 2H), 6,85 (d, 2H), 7,07 (d, 2H), 7,88 (s, 1H)

EMAR IEN$^+$ m/z 371,2434 $[MH]^+$.

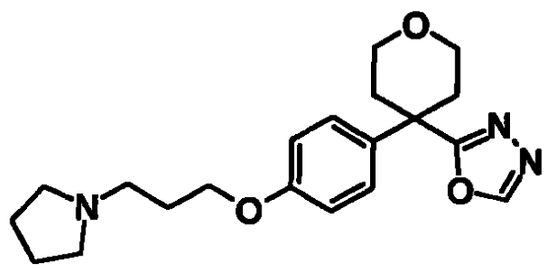
Intermedio 103: *N'*-formil-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbohidrazida

Se agitó ácido 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carboxílico (0,75 g, 0,225 mmol), hidrazida fórmica (0,162 g, 0,27 mmol), 1-hidroxibenzotriazol (0,304 g, 0,225 mmol), diisopropiletilamina (1,18 ml, 0,68 mmol), clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (0,431 g, 0,225 mmol) en diclorometano (10 ml) a temperatura ambiente durante 18 horas. La mezcla de reacción se diluyó con diclorometano (100 ml) y se lavó con agua (2 x 20 ml) Los extractos orgánicos se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío* proporcionando un sólido de color crema. Esto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:5:0,5 a 90:10:1) proporcionando el compuesto del título (0,145 g, 17%) en forma de un aceite transparente.

EMBR IEN$^+$ m/z 376 $[MH]^+$, IEN$^+$ m/z 374 $[M-H^+]^+$

Ejemplo 265: 2-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il]-

1,3,4-oxadiazol



Se disolvió trifenilfosfina (0,203 g, 0,78 mmol), yodo (0,198 g, 0,78 mmol) y trietilamina (0,217 ml, 1,56 mmol) en diclorometano (5 ml). La mezcla se agitó a temperatura ambiente durante 10 minutos. Se añadió *N'*-formil-4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbohidrazida (0,145 g, 0,39 mmol) en diclorometano (5 ml). La mezcla se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se diluyó con diclorometano (100 ml) y se lavó con agua (25 ml). La fase orgánica se secó sobre sulfato sódico, se filtró y se concentró *al vacío* proporcionando un aceite amarillo. Esto se purificó usando HPLC preparativa en Fraction-Lynx® eluyendo con agua:acetonitrilo: ácido trifluoroacético (95:5:0,1) proporcionando el compuesto del título (0,0289, 20%) en forma de un aceite transparente.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,78-1,85 (m, 4H), 2,05 (m, 2H), 2,30 (m, 2H), 2,56-2,60 (m, 4H), 2,60-2,70 (m, 4H), 3,59 (m, 2H), 3,90-4,05 (m, 4H), 6,90 (d, 2H), 7,20 (d, 2H), 8,30 (s, 1 H).

EMAR IEN$^+$ m/z 358,2117 $[MH]^+$.

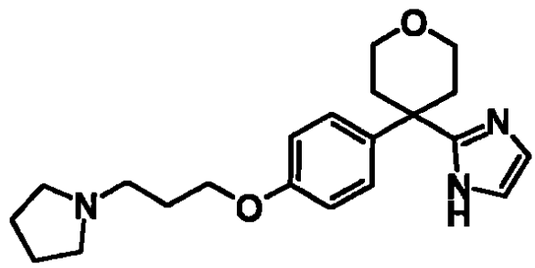
Intermedio 104: 2-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il]-4,5-dihidro-1*H*-imidazol

Se combinó 4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-carbonitrilo (0,5 g, 3,1 mmol), etilendiamina (1,5 ml, 22 mmol), acetato de cobre

(II) (0,07 g, 0,3 mmol) y *N*-metilpirrolidinona (1,5 ml) y se sometió a irradiación en microondas (Smith Personal Synthesiser) a 220ºC durante 1 hora. La mezcla de reacción se concentró *al vacío* proporcionando un aceite pardo. esto se purificó por cromatografía ultrarrápida en columna sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (94:6:0,6 a 85:15:1,5) proporcionando el compuesto del título (0,157 g, 31%) en forma de un aceite amarillo.

EMBR IEN$^+$ m/z 358 $[MH]^+$.

Ejemplo 266: 2-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}-1*H*-imidazol



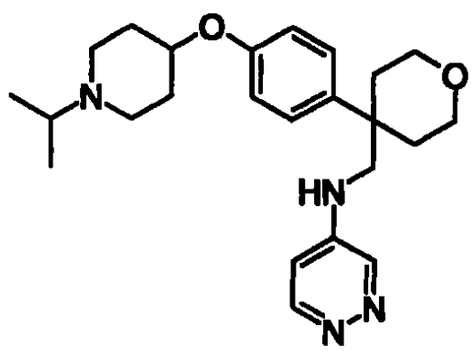
Se combinó dimetilsulfóxido (0,156 ml, 2,19 mmol) y diclorometano (15 ml) y se enfrió a -78ºC en una atmósfera de nitrógeno, se añadió cloruro de oxalilo (0,191 ml, 2,19 mmol) y la mezcla de reacción se agitó a -78ºC en una atmósfera de nitrógeno durante 1 hora. Se añadió lentamente una solución de 2-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il)-4,5-dihidro-1*H*-imidazol (0,314 g, 0,88 mol) en diclorometano (15 ml). La reacción se agitó a -78ºC durante 1 hora. Después se añadió trietilamina (0,611 ml, 4,4 mmol) y la reacción se agitó durante una hora más. La mezcla de reacción se dejó calentar a temperatura ambiente durante 1 hora. La mezcla de reacción se diluyó con diclorometano (100 ml) y se lavó con una solución acuosa de

amoniaco (20 ml). La fase orgánica se secó sobre sulfato sódico, se filtró y se concentró *al vacío* proporcionando un aceite amarillo. Esto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (96:4:0,4 a 90:10:1) proporcionando un aceite amarillo, que se trituró con éter dietílico. Se filtró un sólido de color crema proporcionando el compuesto del título (0,07 g, 22%)

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,80 (m, 4H), 2,05 (m, 2H), 2,30 (m, 2H), 2,50 (m, 2H), 2,60-2,78 (m, 6H), 3,73 (m, 2H), 3,83 (m, 2H) (4,0 (t, 2H), 6,85 (d, 2H), 6,95 (s, 2H), 7,15 (d, 2H)

EMAR IEN$^+$ m/z 356,2327 $[MH]^+$.

Ejemplo 267: *N*-[(4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metil]piridazin-4-amina



Etapa 1:

Se combinó (4-{4-[(1-isopropilpiperidin-4-il)oxi]fenil}tetrahidro-2*H*-piran-4-il)metilamina (0,5 g, 1,5 mmol), 3,4,5-tricloropiridazina (0,2759, 1,5 mmol), carbonato potásico (0,690 g, 5 mmol) y acetonitrilo (5 ml) y se agitó a temperatura ambiente durante 20 horas. La mezcla de reacción se dividió entre agua (20 ml) y diclorometano (2 x 50 ml). Los extractos orgánicos combinados

se secaron sobre sulfato sódico, se filtraron y se concentraron *al vacío* proporcionando un aceite naranja. Esto se purificó por cromatografía ultrarrápida eluyendo con diclorometano:metanol:amoniaco (100:0:0 a 90:10:1) proporcionando un aceite pardo.

Etapa 2:

El producto de la etapa 1 (0,162 g, 0,34 mmol) e hidróxido sódico (0,033 g, 0,82 mmol) se disolvieron en etanol (3 ml). Se añadió paladio al 10% sobre carbón (0,02 g). La mezcla se hidrogenó durante 18 horas a temperatura ambiente a 50 psi. La mezcla de reacción se filtró a través de Arbocel®, el filtrado se concentró *al vacío* proporcionando un aceite amarillo. Esto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (94:6:0,6 a 90:10:1) proporcionand el compuesto del título (0,08 g, 60%) en forma de un aceite amarillo.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,08 (d, 6H), 1,78-1,90 (m, 4H), 2,05 (m, 2H), 2,20 (m, 2H), 2,43 (m, 2H), 2,72-2,82 (m, 3H), 3,28 (d, 2H), 3,55 (m, 2H), 3,78 (m, 2H), 4,30 (m, 1H), 4,35 (m, 1H), 6,25 (d, 1H), 6,90 (d, 2H), 7,20 (d, 2H), 8,40 (s, 1H), 8,48 (d, 1H)

EMAR IEN$^+$ m/z 411,2749 $[MH]^+$.

Intermedio 105: 4-[4-(3-[1,4]Oxazepan-4-il-propoxi)-fenil]-tetrahidro-piran-4-carbonitrilo

Se recogió 4-[4-(3-cloro-propoxi)-fenil]-tetrahidro-piran-4-carbonitrilo (5,3 g, 19 mmol) en acetonitrilo (30 ml), a lo que se le añadió base de Hunig (6 g, 47 mmol) e hidrogeno cloruro de homo-morfolina (2,8 g, 20 mmol). Esta solución se calentó a reflujo durante 18 horas. El disolvente se retiró *al vacío* y el residuo se purificó por cromatografía en columna sobre gel de sílice eluyendo

con un gradiente de DCM:MeOH:NH_3 (de 98:2:0,2 a 94:6:0,6) produciendo el compuesto del título en forma de un aceite amarillo (3,35 g, 51%).

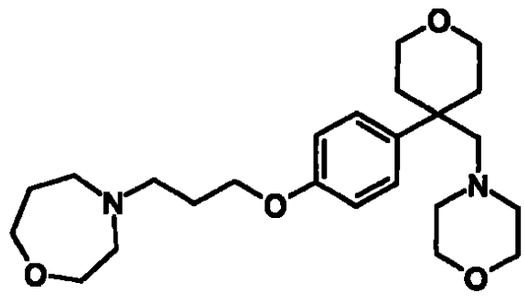
EMAR IEN$^+$ m/z 345,2166 $[MH]^+$

Intermedio 106: C-[4-[4-(3-[1,4]Oxazepan-4-il-propoxi)-fenil]-tetrahidro-piran-4-il]-metilamina

Se disolvió 4-[4-(3-[1,4]Oxazepan-4-il-propoxi)-fenil]-tetrahidro-piran-4-carbonitrilo (900 mg, 26 mmol) en THF (5 ml) y se enfrió a 0ºC en una atmósfera de nitrógeno. Se añadió gota a gota hidruro de aluminio litio (1 M en Et_2O, 7,8 ml, 78 mmol) y se dejó agitar durante 10 minutos antes de calentar a reflujo durante 18 horas. La solución se enfrió a 0ºC antes de inactivar con agua (0,78 ml), seguido de hidróxido sódico (2 M, 0,78 ml) y finalmente agua (2,4 ml). La suspensión resultante se filtró a través de Arbocel®, lavando con DCM (2 x 10 ml). El filtrado se concentró al vacío produciendo el compuesto del título en forma de un aceite incoloro (650 mg, 72%).

EMAR IEN$^+$ m/z 349,2480 $[MH]^+$

Ejemplo 268: 4-(3-{4-[4-(morfolin-4-ilmetil)tetrahidro-2*H*-piran-4-il]fenoxi}propil)-1,4-oxazepan



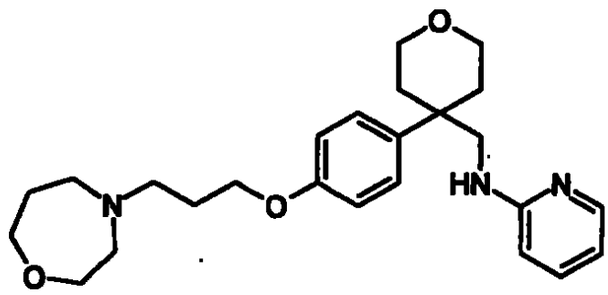
Se disolvió C-[4-[4-(3-[1,4]oxazepan-4-il-propoxi)-fenil]-tetrahidro-piran-4-il]-metilamina (150 mg, 0,43 mmol) y 1-bromo-2-(2-bromo-etoxi)-etano (110 mg, 0,47 mmol) en acetonitrilo (10 ml) y se añadió K_2CO_3 (130 mg, 0,95 mmol). La

solución se calentó a 60°C durante 18 horas antes de filtrar la solución retirando el K_2CO_3 sólido. El filtrado se concentró al vacío antes de purificar usando cromatografía en columna, eluyendo con un gradiente de DCM:MeOH:NH_3 (de 99:1:0,1 a 90:10:1) produciendo el compuesto del título en forma de un aceite incoloro (75 mg, 42%).

^{1}H RMN (400 MHz, CD_3OD) δ 1,80-2,00 (m, 6H), 2,11-2,20 (m, 6H), 2,41 (s, 2H), 2,69-2,79 (m, 6H), 3,48 (m, 6H), 3,72-3,80 (m, 6H), 4,02 (t, 2H)6,87 (d, 2H), 7,15 (d, 2H)

EMAR IEN$^+$ m/z 419,2896 $[MH]^+$

Ejemplo 269: *N*-[(4-{4-[3-(1,4-oxazepan-4-il)propoxi]fenil}tetrahidro-2*H*-piran-4-il)metil]piridin-2-amina



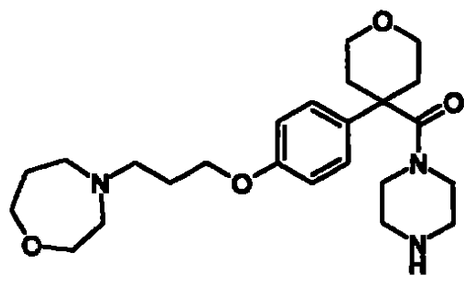
Se añadió *C*-(4-[4-(3-[1,4]oxazepan-4-il-propoxi)-fenil]-tetrahidro-piran-4-il)-metilamina (210 mg, 0,48 mmol) a una solución de 2-bromopiridina (70 mg, 0,42 mmol), $Pd_2(dba)_3$ (91 mg, 0,1 mmol), BINAP (126 mg, 2 mmol) y *terc*-butóxido sódico (56 mg, 5,7 mmol) en tolueno (3 ml). Esta solución se calentó en el microondas (Smith Personal Synthesiser) a 110°C durante 15 minutos. La solución se filtró a través de Celite y el filtrado se concentró *al vacío*. El residuo se purificó por cromatografía en columna, eluyendo con un gradiente de DCM:MeOH:NH_3 (de 99:1:0,1 a 95:5:0,5) produciendo el compuesto del título

en forma de un aceite amarillo (120 mg, 59%).

^{1}H RMN (400 MHz, CD_3OD) δ 1,88-2,00 (m, 6H), 2,17 (m, 2H), 2,68-2,79 (m, 6H), 3,43 (s, 2H), 3,50 (m, 2H), 3,76 (m, 2H), 3,80 (m, 4H), 4,03 (t, 2H), 6,39 (d, 1H), 6,44 (t, 1H), 6,91 (d, 2H), 7,33 (m, 3H), 7,81 (d, 1H)

EMAR IEN$^+$ m/z 426,2741 $[MH]^+$

Ejemplo 270: 4-(3-{4-[4-piperazin-1-ilcarbonil)tetrahidro-2*H*-piran-4-il]fenoxi}propil)-1,4-oxazepan



Etapa 1:

Se disolvió 4-[4-(3-[1,4]oxazepan-4-il-propoxi)-fenil]-tetrahidro-piran-4-carbonitrilo (1 g, 29 mmol) en ácido clorhídrico concentrado (15 ml) y se calentó a 90ºC durante 24 horas, y el disolvente se retiró posteriormente al *vacío*. Después se añadió 2-*terc*-butil 1,1,2,2 tetrametil guanidina (2 ml) y agua (1 ml) al residuo y se concentró *al vacío* y formó un azeótropo con tolueno (2 x 4 ml) produciendo sal guanidina del ácido 4-[4-(3-[1,4]Oxazepan-4-il-propoxi)-fenil]-tetrahidro-piran-4-carboxílico en bruto (3 g) en forma de un aceite naranja.

Etapa 2:

La sal guanidina del ácido 4-[4-(3-[1,4]oxazepan-4-il-propoxi)-fenil]-tetrahidro-piran-4-carboxílico (1,2 g, 0,88 mmol de ácido libre) se disolvió en DMF (5 ml) a lo que se le añadió *N*-BOC piperidina (200 mg, 1,06 mmol), HBTU (400 mg, 1,06 mmol) y base de Hunig (129 mg, 1,06 mmol). La reacción se

agitó a temperatura ambiente durante 3 horas antes de añadir una solución de bicarbonato sódico saturado (15 ml) y extraer el producto en EtOAc (15 ml). La fase orgánica se lavó con salmuera (15 ml), se secó sobre Na_2SO_4 y se concentró *al vacío* antes de purificar el residuo por cromatografía en columna, eluyendo con un gradiente de DCM:MeOH:NH_3 (de 99:1:0,1 a 92:8:0,8). Esto produjo éster *terc*-butilo del ácido 4-[4-[4-(3-[1,4]Oxazepan-4-il-propoxi)-fenil]-tetrahidro-piran-4-carbonil)-piperazin-1-carboxílico en forma de un aceite incoloro que se convirtió en un sólido blanco (260 mg, 55%) al reposar durante una noche.

Etapa 3:

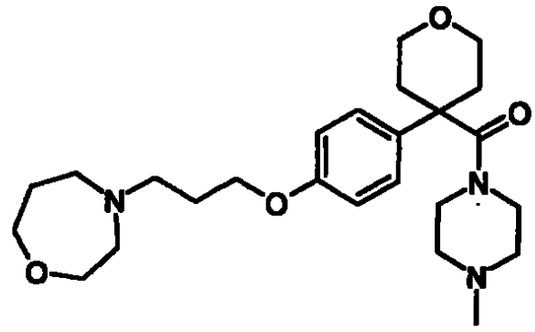
Se disolvió éster *terc*-butilo de ácido 4-[4-[4-(3-[1,4]oxazepan-4-il-propoxi)-fenil]-tetrahidro-piran-4-carbonil)-piperazin-1-carboxílico (260 mg, 0,48 mmol) en una solución de cloruro de hidrógeno en dioxano (4 M, 5 ml) y se agitó a temperatura ambiente durante 2 horas. El disolvente se retiró *al vacío* y el residuo se disolvió en DCM (10 ml) y se lavó con una solución de bicarbonato sódico saturado (15 ml). La fase orgánica se secó sobre Na_2SO_4 y se concentró *al vacío* antes de purificar el residuo usando cromatografía en columna, eluyendo con un gradiente de DCM:MeOH:NH_3 (de 99:1:0,1 a 92:8:0,8) produciendo el compuesto del título en forma de un sólido blanco (80 mg, 37%).

^{1}H RMN (400 MHz, d_6-DMSO) δ 1,70-1,88 (m, 6H), 2,08 (m, 2H), 2,52-2,63 (m, 6H), 3,04-3,35 (m, 8H), 3,58 (m, 4H), 3,64 (m, 2H), 3,72 (m, 2H), 3,98 (t, 2H), 6,92 (d, 2H), 7,12 (d, 2H)

EMBR IEN$^+$ m/z 432 $[MH]^+$

Ejemplo 271: 4-[3-(4-[4-[(4-metilpiperazin-1-il)carbonil]tetrahidro-2*H*-

piran-4-il}fenoxi)propil]-1,4-oxazepan

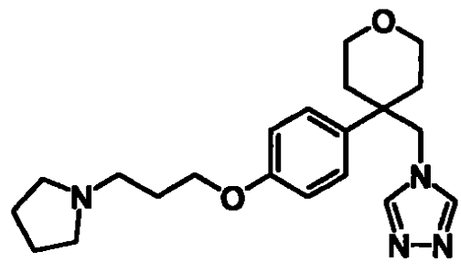


Se disolvió 4-(3-{4-[4-(piperazin-1-ilcarbonil)tetrahidro-2*H*-piran-4-il]fenoxi}propil)-1,4-oxazepan (45 mg, 0,1 mmol) en DCM (3 ml) a lo que se le añadió formaldehído (37% p/p en H_2O, 12 mg, 0,12 mmol) y ácido acético (8 mg, 0,12 mmol) y se agitó a temperatura ambiente durante 30 minutos antes de añadir STAB (25 mg, 0,12 mmol). La solución se dejó agitar durante 45 minutos más antes de lavar la solución con bicarbonato sódico saturado (10 ml), seguido de salmuera (10 ml). La fase orgánica se secó sobre Na_2SO_4 y se concentró *al vacío* produciendo el compuesto del título en forma de un sólido blanco (25 mg, 56%).

^{1}H RMN (400 MHz, d_6-DMSO) δ 1,76-2,13 (m, 11H), 2,55-2,78 (m, 6H), 3,16-3,39 (m, 8H), 3,50-3,62 (m, 4H), 3,63 (m, 2H), 3,72 (M, 2H), 3,99 (t, 2H), 6,92 (d, 2H), 7,12 (d, 2H).

EMBR IEN$^+$ m/z 446 $[MH]^+$

Ejemplo 272: 4-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)-4*H*-1,2,4-triazol



Una mezcla de {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il} metilamina (200 mg, 0,63 mmol), *N'*-[(1*E*)-(dimetilamino)metilen]-*N*,*N*-dimetilhidrazonoformamida (300 mg, 2,11 mmol) y monohidrato de ácido *p*-toluenosulfónico (10 mg, 0,05 mmol) se calentó a reflujo en tolueno (2 ml) durante 24 horas. La mezcla de reacción se concentró *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (95:5:0,5 a 80:20:2 en volumen) proporcionando 160 mg de una goma beige. Esta goma se trituró con éter dietílico (3 ml) dando el compuesto del título en forma de un polvo blanco (120 mg, 51%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,46 (s, 2H), 6,97 (d, 2H), 6,89 (d, 2H), 4,02 (m, 4H), 3,82 (m, 2H), 3,43-3,52 (m, 2H), 2,62 (t, 2H), 2,51 (m, 4H), 2,12 (m, 2H), 2,02 (m, 2H), 1,84 (m, 2H), 1,80 (m, 4H).

EMBR IEN$^+$ m/z 371 $[M+H]^+$

EMAR IEN$^+$ m/z 371,2433 $[M+H]^+$

Intermedio 107: Clorhidrato de (1-isopropilazetidin-3-il)metanol

Una mezcla de (1-benzhidrilazetidin-3-il)metanol (4,0 g, 15,8 mmol), acetona (20 ml), 2-propanol (80 ml), HCl (1,5 ml) y $Pd(OH)_2$ se hidrogenó a 50 psi (0,34 MPa)/50ºC durante 18 horas. La mezcla de reacción se filtró a través de Arbocel® y se concentró *al vacío*, el residuo se trituró con éter de

diisopropilo (50 ml) dando el compuesto del título en forma de un polvo higroscópico verde pálido (2,6 g, 99%)

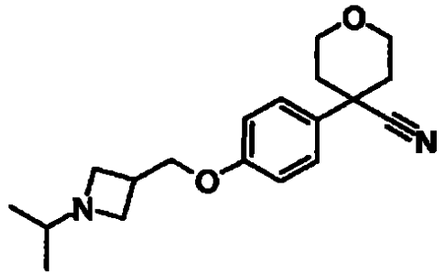
EMBR IEN$^+$ m/z 130 $[M+H]^+$

Intermedio 108: Clorhidrato de 3-(clorometil)-1-isopropilazetidina

Se disolvió clorhidrato de (1-isopropilazetidin-3-il)metanol (2,6 g, 15,7 mmol) en diclorometano (50 ml) y se enfrió a 0ºC. Se añadió gota a gota cloruro de tionilo (1,4 ml, 19,2 mmol) durante 5 minutos. La mezcla de reacción se agitó mientras se calentaba a temperatura ambiente. Se agitó a temperatura ambiente durante 48 horas. La mezcla de reacción se concentró *al vacío* y formó un azeótropo con tolueno (40 ml) dando el compuesto del título en forma de un polvo higroscópico beige (2,8 g, 99%).

EMBR IEN$^+$ m/z 148/150 $[M+H]^+$ (isótopos Cl)

Ejemplo 273: 4-[4-[4(1-isopropilazetidin-3-il)metoxi]fenil]tetrahidro-2*H*-piran-4-carbonitrilo

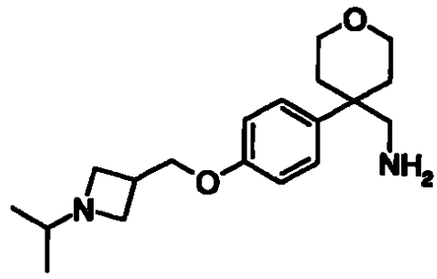


Se combinó clorhidrato de 3-(clorometil)-1-isopropilazetidina (2,8 g, 15,2 mmol), 4-(4-hidroxifenil)tetrahidropiran-4-carbonitrilo (3,1 g, 15,2 mmol) y carbonato potásico (8,5 g, 61,6 mmol) en DMF (40 ml) y se agitó a 50° durante 2 horas. Se añadió yoduro potásico (0,5 g 3,0 mmol)y la mezcla se agitó a 50° durante 18 horas después a 90-95° durante 5 horas más. La mezcla de reacción se concentró *al vacío* se dividió posteriormente entre acetato de etilo

(80 ml) y agua (50 ml). La fase de acetato de etilo se lavó con NaCl saturado (50 ml) y después se secó sobre Na_2SO_4 y se concentró *al vacío* dando un material semi-cristalino pardo que se trituró con éter de diisopropilo (25 ml) dando el compuesto del título en forma de un polvo beige (2,9 g, 60%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,38 (d, 2H), 6,91 (d, 2H), 4,08 (m, 4H), 3,89 (m, 2H), 3,41 (t, 2H), 3,02 (t, 2H), 2,87 (m, 1H), 2,31 (m, 1H), 2,15-2,00 (m, 4H), 0,94 (d, 6H).

Ejemplo 274: 1-{4-{4-[(1-isopropilazetidin-3-il)metoxi]fenil}tetrahidro-2*H*-piran-4-il)metanamina



Una solución de 4-{4-[(1-isopropilazetidin-3-il)metoxi]fenil}tetrahidro-2*H*-piran-4-carbonitrilo (1,8 g, 5,73 mmol) en THF (80 ml) se enfrió a 0ºC en una atmósfera de nitrógeno. Se añadió gota a gota una solución de hidruro de aluminio litio (solución 1,0 M en Et_2O, 17 ml, 17 mmol) durante 5 minutos. La mezcla se agitó mientras se calentaba a temperatura ambiente durante 18 horas. La reacción se enfrió a 0ºC y se inactivó con agua (0,5 ml) después NaOH 2 M (0,5 ml) y después agua (1,5 ml). Se añadió Celite® (3 g) y la mezcla se agitó a temperatura ambiente durante 0,5 hora. Se diluyó con acetato de etilo (50 ml), se filtró y se concentró *al vacío* dando un aceite incoloro (1,8 g). El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (97:3:0,3 a

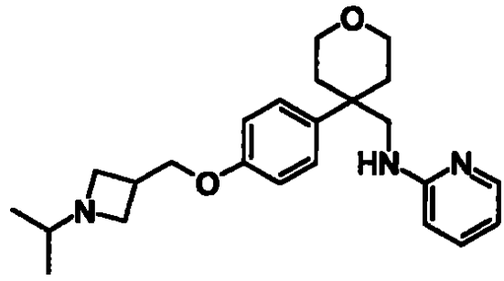
88:12:1,2 en volumen) dando el compuesto del título en forma de un sólido cristalino blanco (1,55 g, 85%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 7,18 (d, 2H), 6,89 (d, 2H), 4,18 (d, 2H), 3,77 (m, 2H), 3,54 (m, 2H), 3,41 (t, 2H), 3,02 (t, 2H), 2,88 (m, 1H), 2,75 (s, 2H), 2,31 (quintuplete, 1H), 2,11 (m, 2H), 1,80 (m, 2H), 0,95 (d, 6H).

EMBR IEN$^+$ m/z 319 $[M+H]^+$

EMAR IEN$^+$ m/z 319,2375 $[MH]^+$

Ejemplo 275: *N*-[(4-{4[(1-isopropilazetidin-3-il)metoxi]fenil}tetrahidro-2*H*-piran-4-ilmetil]piridin-2-amina



Se agitó 1-(4-{4-[(1-isopropilazetidin-3-il)metoxi]fenil)tetrahidro-2*H*-piran-4-il)metanamina con 2-bromopiridina (600, 0,63 mmol), tris(dibencilidenacetona)dipaladio (0) (15 mg, 0,018 mmol), 2,2'-bis(difenilfosfino)-1,1'-binaftilo (19 mg, 0,036 mmol) y *terc*-butóxido sódico (90 mg, 0,94 mmol) y se calentó a 80°C en tolueno (5 ml) durante 3 horas en una atmósfera de nitrógeno. La mezcla de reacción se dividió entre hidróxido sódico acuoso (50 ml) y acetato de etilo (80 ml). Los extractos orgánicos se secaron sobre Na_2SO_4, se filtraron y se concentraron *al vacío*. El producto en bruto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (97:3:0,3 a 90:10:1 en volumen) dando el producto que requirió purificación adicional por cromatografía ultrarrápida sobre

gel de sílice eluyendo con diclorometano:metanol:amoniaco (96:4:0,4 a 94:6:0,6 en volumen) dando un aceite amarillo pálido que cristalizó en reposo, Esto se trituró con éter dietílico (2 ml) dando el compuesto del título en forma de un polvo amarillo pálido (65 mg, 26%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 8,02 (d, 1H), 7,31 (t, 1H), 7,25 (d, 2H), 6,91 (d, 2H), 6,50 (t, 1H), 6,20 (d, 1H), 4,09 (d, 2H), 3,99 (t, 1H), 3,82 (m, 2H), 3,59 (m, 2H), 3,48 (d, 2H), 3,45 (m, 2H), 3,03 (m, 2H), 2,88 (m, 1H),2,33 (m, 1H), 2,13 (m, 2H), 1,92 (m, 2H), 0,93 (d, 6H).

EMBR IEN$^+$ m/z 396 $[M+H]^+$

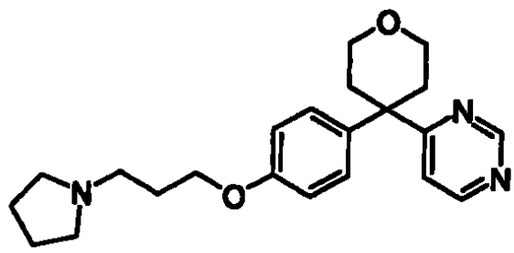
EMAR IEN$^+$ m/z 396,2639 $[M+H]^+$

Intermedio 109: 1-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il]etanona

A una solución de 4-[4-(3-Pirrolidin-1-ilpropoxi)-fenil]tetrahidropiran-4-carbonitrilo (2,0 g, 6,37 mmol) en éter dietílico (30 ml) y THF (5 ml) se le añadió complejo de metil litio/bromuro de litio (solución 1,5 M en éter dietílico, 4,5 ml, 6,75 mmol), la mezcla de reacción se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se inactivó añadiendo agua (5 ml) y se concentró *al vacío*. El residuo se dividió entre DCM (100 ml) y agua (30 ml), Las fases orgánicas se secaron sobre Na_2SO_4, se filtraron y se concentraron *al vacío* dando un producto en bruto que se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (98:2:0,2 a 92:8:0,8 en volumen) proporcionando una goma incolora (500 mg, 24%).

EMBR IEN$^+$ m/z 332 $[M+H]^+$

Ejemplo 276: 4-[4[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il]pirimidina



Etapa 1.

Se disolvió 1-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il)etanona (500 mg, 1,51 mmol) en dimetilformamida dimetilacetal (3 ml) y se calentó en un tubo cerrado herméticamente en un reactor de microondas (Smiths Personal Synthesizer) a 150ºC durante 1800 segundos después a 170ºC durante 2400 segundos. La mezcla de reacción se concentró al *vacío* dando un producto en bruto (3-Dimetilamino-1-[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il]propenona, 500 mg) que se usó sin purificación en la siguiente etapa.

Etapa 2.

El producto en bruto Intermedio se disolvió en etanol (10 ml), se añadió acetato de formamidina (320 mg, 3,07 mmol) y etóxido sódico (solución al 21% p/v en etanol, 1,0 ml, 3,09 mmol) y la mezcla se agitó a temperatura ambiente durante 1,5 horas después se calentó a 70ºC durante 2 horas. Se añadió acetato de formamidina (500 mg, 4,80 mmol) y se agitó a 70ºC durante 18 horas. Se añadió acetato de formamidina (500 mg, 4,80 mmol) y carbonato potásico (2,0 g, 14,5 mmol) y se agitó a reflujo durante 5 horas. Se añadió acetato de formamidina (500 mg, 4,80 mmol) y se agitó a reflujo durante 18 horas. La mezcla de reacción se dividió entre DCM (80 ml) y Na_2CO_3 al 10% (50 ml), las fases orgánicas se secaron sobre Na_2SO_4, se filtraron y se concentraron *al vacío* dando un sólido negro. El producto en bruto se purificó

por cromatografía ultrarrápida sobre gel de sílice eluyendo con diclorometano:metanol:amoniaco (100:0:0 a 94:6:0,6 en volumen) dando el compuesto del título en forma de un aceite pardo (45 mg, 8%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 9,16 (s, 1H), 8,53 (d, 1H), 7,20 (d, 2H), 7,08 (d, 1H), 6,83 (d, 2H), 3,96 (t, 2H), 3,78 (m, 2H), 3,66 (m, 2H), 2,68-2,55 (m, 2H), 2,50 (m, 4H), 2,33 (m, 2H), 1,96 (m, 4H), 1,76 (m, 4H).

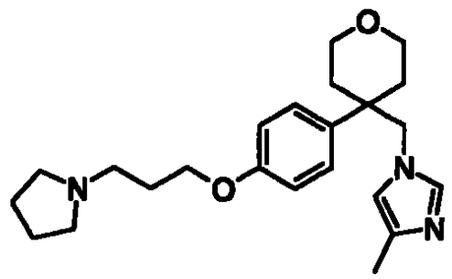
EMBR IEN$^+$ m/z 368 $[M+H]^+$

Intermedio 110: 4-metil-1-{[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)-1*H*-imidazol-2-tiol

Se agitó 2-aminopropionaldehído dimetil acetal (0,2 g, 1,7 mmol), tiocarbonildiimidazol (0,36 g, 2,0 mmol) y trietilamina (0,23 ml, 1,7 mmol) en DMF (2,0 ml) a temperatura ambiente durante 30 minutos antes de calentar a 50ºC durante 18 horas. Se añadió {4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidropiran-4-il}metilamina (540 mg, 1,7 mmol) y se agitó a temperatura ambiente durante 4 horas. Se añadió HCl 2 M (6 ml) se agitó a 70ºC durante 18 horas, después se añadió HCl (1,0 ml) y la mezcla se agitó a 110ºC durante 18 horas. La mezcla de reacción se enfrió y se dividió entre acetato de etilo (100 ml) y carbonato sódico acuoso diluido (50 ml). Los extractos orgánicos se secaron sobre Na_2SO_4 y se concentraron *al vacío* dando el compuesto del título en forma de un sólido gris (600 mg, 84%).

EMBR IEN$^+$ m/z 416 $[M+H]^+$ 200

Ejemplo 277: 4-metil-1-{[4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)-1*H*-imidazol

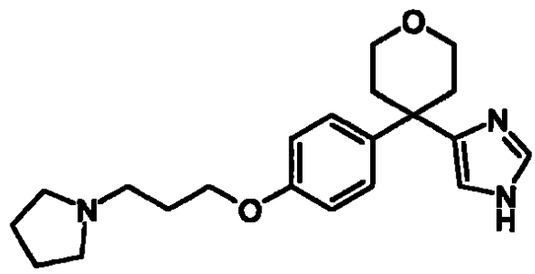


Se disolvió 4-metil-1-({4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}metil)-1*H*-imidazol-2-tiol (0,6 g, 1,44 mmol) en etanol (20 ml), se añadió agua (5 ml) y la mezcla se enfrió en hielo. Se añadió níquel Raney (4 g), la mezcla de reacción se calentó a temperatura ambiente y se agitó durante 2 horas. La mezcla de reacción se filtró a través de Arbocel® y se concentró *al vacío* proporcionando un aceite pardo. Esto se purificó por cromatografía ultrarrápida sobre gel de sílice eluyendo con acetato de etilo:dietilamina (95:5) proporcionando el compuesto del título (0,086, 16%) en forma de un aceite transparente.

^{1}H RMN (400 MHz $CDCl_3$) δ 1,80-1,90 (m, 6H), 2,08-2,18 (m, 7H), 2,65-2,80 (m, 6H), 3,50 (t, 2H), 3,80 (m, 2H), 3,90 (s, 2H), 4,05 (t, 2H), 6,10 (s, 1H), 6,70 (s, 1H), 6,89 (d, 2H), 7,0 (d, 2H).

EMBR IEN$^+$ m/z 384 $[MH]^+$

Ejemplo 278: 4-{4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-il}-1*H*-imidazol



Etapa 1:

Se disolvió 4-[4-(3-pirrolidin-1-ilpropoxi)fenil]tetrahidro-2*H*-piran-4-carbaldehído (500 mg, 1,6 mmol) y TosMIC (340 mg, 1,7 mmol) en EtOH (20 ml), a lo que se le añadió NaCN (12 mg, 0,25 mmol). La solución se volvió amarillo pálido inmediatamente y se dejó agitar durante 2 horas a temperatura ambiente. El disolvente se retiró *al vacío* y el residuo se recogió en DCM (10 ml) y se lavó con una solución de bicarbonato sódico saturado (15 ml), seguido de salmuera (15 ml). La fase orgánica se secó sobre Na_2SO_4 y se concentró *al vacío* produciendo 5-{4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-il}-4-(tolueno-4-sulfonil)-4,5-dihidro-oxazol en forma de una espuma parda pálida (500 mg).

EMBR IEN$^+$ m/z 513 $[MH]^+$

Etapa 2:

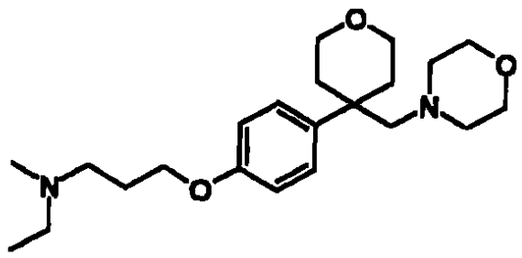
El 5-{4-[4-(3-pirrolidin-1-il-propoxi)-fenil]-tetrahidro-piran-4-il}-4-(tolueno-4-sulfonil)-4,5-dihidrooxazol (500 mg) se disolvió en EtOH saturado con amoniaco (7 ml) antes de calentar en una bomba a 110ºC durante 18 horas. El disolvente se retiró al vacío y el residuo se recogió en DCM (10 ml) y se lavó con solución de bicarbonato sódico saturado (15 ml), seguido de salmuera (15 ml). La fase orgánica se secó sobre Na_2SO_4 y se concentró al vacío, antes de purificar por cromatografía en columna, eluyendo con un gradiente de

DCM:MeOH:NH_3 (de 99:1:0,1 a 90:10:1), pero esto no separó el producto de una impureza cercana. Por lo tanto, el residuo se purificó usando cromatografía en columna por segunda vez eluyendo con una solución isocrática de ciclohexano:DCM:Et_2O:MeOH:NH_3 (10:5:3:2:0,2) produciendo el compuesto del título en forma de un sólido incoloro (70 mg, 12%).

^{1}H RMN (400 MHz, $CDCl_3$) δ 1,8 (m, 4H), 1,93-2,05 (m, 2H), 2,24-2,39 (m, 4H), 2,57 (m, 4H), 2,63 (t, 2H), 3,67 (m, 2H), 3,79 (m, 2H), 4,00 (t, 2H), 6,77 (s, 1 H), 6,81 (d, 2H), 7,18 (d, 2H), 7,38 (s, 1H)

EMBR IEN$^+$ m/z 356 $[MH]^+$, 354 $(M-H)^+$

Ejemplo 279: 4-[4-(4-[3-[etil(metil)amino]propoxi]fenil)tetrahidro-2*H*-piran-4-ilmetil]-morfolina



Etapa 1:

Una mezcla de 4-[4-(3-cloro-propoxi)-fenil]-tetrahidropiran-4-carbonitrilo (3,0 g, 10,7 mmol), yoduro potásico (100 mg, 0,60 mmol) y etilmetilamina (5,0 ml, 58,3 mmol) en acetonitrilo (30 ml) se calentó 0 a 60°C durante una noche La mezcla se enfrió, se concentró al vacío y se dividió entre una solución de Na_2CO_3 diluida (40 ml) y acetato de etilo (80 ml). La fase orgánica se secó (Na_2SO_4), se filtró y se concentró al vacío. La purificación del material en bruto se realizó por cromatografía ultrarrápida (gel de sílice, acetato de etilo/metanol/amoniaco acuoso 98:2:0,2 a 85:15:1,5) produciendo 4-(4-[3-

[etil(metil)amino]propoxi}fenil)tetrahidro-2*H*-piran-4-carbonitrilo en forma de un aceite amarillo pálido (2,0 g, 6,65 mmol, 62%).

^{1}H RMN (400 MHz $CDCl_3$) δ 1,06 (t, 3H), 1,91-2,00 (m, 2H), 2,00-2,14 (m, 4H), 2,25 (s, 3H), 2,40-2,50 (m, 2H), 2,53 (t, 2H), 3,89 (m, 2H), 4,00-4,11 (m, 4H), 6,91 (d, 2H), 7,38 (d, 2H).

EMBR IEN$^+$ m/z 303 $[MH]^+$

Etapa 2:

Se añadió hidruro de aluminio litio (9,93 ml de una solución 1 M en tetrahidrofurano, . 9,93 mmol) a una solución de 4-(4-{3-[etil(metil)amino]propoxi}fenil)tetrahidro-2*H*-piran-4-carbonitrilo (2,0 g, 6,6 mmol) en tetrahidrofurano (10 ml) a 0ºC en una atmósfera de N_2. La mezcla de reacción se calentó a temperatura ambiente durante 18 horas y después se inactivó por adición secuencial de agua (0,4 ml), una solución de NaOH 2 M (0,4 ml) y agua (0,4 ml). La mezcla se filtró a través de arbocel y se concentró al vacío produciendo 3-{4-[4-(aminometil)tetrahidro-2*H*-piran-4-il]fenoxi}-*N*-etil-*N*-metilpropan-1-amina en forma de un aceite amarillo pálido (1,93 g, 6,3 mmol, 95%).

^{1}H RMN (400 MHz $CDCl_3$) δ 1,02-1,08 (t, 3H), 1,73-1,83 (m, 2H), 1,90-2,00 (m, 2H), 2,06-2,16 (m, 2H), 2,23 (s, 3H), 2,40-2,48 (q, 2H), 2,50-2,58 (t, 2H), 2,75 (s, 2H), 3,48-3,58 (m, 2H), 3,70-3,80 (m, 2H), 3,93-4,04 (t, 2H), 6,89 (d, 2H), 7,19 (d, 2H).

EMBR APCI$^+$ m/z 307 $[MH]^+$

Etapa 3:

A una solución agitada de 3-{4-[4-(aminometil)tetrahidro-2*H*-piran-4-il]fenoxi}-*N*-etil-*N*-metilpropan-1-amina (500 mg, 1,6 mmol) y bis(2-

bromoetil)éter (345 mg, 1,5 mmol) en acetonitrilo anhidro (50 ml) se le añadió carbonato potásico (450 mg, 3,3 mmol). La mezcla se calentó a 60ºC durante una noche y después se concentró al vacío. El producto en bruto se dividió entre diclorometano (50 ml) y agua (50 ml), la fase acuosa se extrajo con diclorometano (25 ml) y los extractos orgánicos combinados se secaron (Na_2SO_4), se filtraron y se concentraron al vacío. La purificación del material en bruto se realizó por cromatografía ultrarrápida (gel de sílice, diclorometano/metanol/amoniaco acuoso 100:0:0 a 96:4:0,4) produciendo el compuesto del título en forma de un aceite incoloro transparente (315 mg, 0,84 mmol, 52%).

^{1}H RMN (400 MHz $CDCl_3$) δ 1,05 (t, 3H), 1,82-1,93 (m, 2H), 1,92,2.00 (m, 2H), 2,08-2,20 (m, 6H), 2,25 (s, 3H), 2,39 (s, 2H), 2,40-2,50 (q, 2H), 2,50-2,59 (m, 2H), 3,48-3,60 (m, 6H), 3,70-3,80 (m, 2H), 4,00 (t, 2H), 6,86 (d, 2H), 7,20 (d, 2H).

EMBR APCI$^+$ m/z 377 $[MH]^+$

EMAR IEN$^+$ m/z 377,2792 $[MH]^+$

Ensayo Funcional Basado en Células H_3

Los compuestos se evaluaron usando un ensayo funciona basado en células que mide AMPc mediante la actividad del gen informador de β-lactamasa. Se generó una línea celular estable partiendo de células HEK-293 que expresan un gen indicador de CRE β-lactamasa y se transfectan con ADNc de receptor humano de histamina H_3. Las células se sembraron con una densidad de 500.000 células/ml y se cultivaron durante una noche en MEM (Invitrogen) suplementado con FBS dializado al 1% (Sigma), glutamina 2 mM (Sigma), piruvato sódico 1 mM (Sigma), aminoácidos no esenciales 0,1 mM

(Invitrogen) y HEPES 25 mM (Sigma) en placas de 384 pocillos recubiertas con poli D lisina (BO Biosciences). El agonista del receptor H_3 imetit (Tocris) inhibió de forma dependiente de la dosis la síntesis estimulada con forskolina 10 μM (Calbiochem) de AMPc medida después de 4,5 horas mediante la escisión de β-lactamasa del pigmento CCF4-AM (Invitrogen). Para la determinación de CI_{50}, los compuesto de ensayo se prepararon en PBS (Sigma) y DMSO (Sigma) con una respuesta a dosis de $5x10^{-10}$ a $5x10^{-5}$ M con una concentración final de DMSO en el ensayo de 0,5%. Las células se incubaron durante 15 minutos más/menos compuesto y se midió su capacidad para permitir la síntesis de AMPc estimulada con forskolina 10 μM en presencia de imetit 1 nM como se ha descrito anteriormente. Los valores K_i funcionales se calcularon a partir de la CI_{50} de los compuestos ensayados como antagonistas en base a una CE_{50} de imetit determinada experimentalmente (representada en la ecuación como K_d) de 350 pM y una concentración de imetit [L] de 1 nM, de acuerdo con la ecuación de Cheng-Prussoff en la que $K = (CI_{50})/(1+([L]/K_d))$.

Se descubrió que todos los ejemplos ensayados en este ensayo descrito anteriormente tenían un valor K_i inferior a 5 μM. La mayoría de los ejemplos tienen un valor K_i menor de 100 nM.

A continuación se dan los datos de algunos de dichos compuestos preferidos como ejemplo:

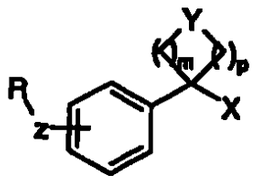
Número de Ejemplo	K_i (ensayo basado en células H3 - nM)	Número de Ejemplo	K_i (ensayo basado en células H3 - nM)	Número de ejemplo	K_i (ensayo basado en células H3 - nM)

29	0,4	190	2,4	249	9,7
133	12,4	191	10,3	250	4,6
136	3,9	196	0,6	254	1,3
155	1,0	205	5,8	266	9,7
156	2,0	206	12,9	267	5,8
160	1,5	213	2,6	268	6,5
187	7,3	220	2,2	276	6,2
188	6,8	247	3,9	272	10,8
189	14,3	248	0,3		

Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes

REIVINDICACIONES

1. Un compuesto de fórmula (1):



(1)

o una sal farmacéuticamente aceptable y/o un solvato (incluyendo hidrato) del mismo donde:

el sustituyente de fórmula -Z-R está en la posición meta o para del grupo fenilo;

X se selecciona entre -CN, $-CH_2OH$, $-CH_2$-O-alquilo (C_1-C_4), -C(O)OH, -C(O)Oalquilo (C_1-C_4), $-CH_2-NR^1R^2$, $-C(O)NR^3R^4$, $-CH_2$-O-het^2, $-CH_2-het^1$ y het^1, estando el grupo het^1 tanto en $-CH_2-het^1$ como en het^1 opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, ciano, alquilo (C_1-C_4), -S-alquilo (C_1-C_4) y alcoxi(C_1-C_4);

R^1 es hidrógeno o alquilo (C_1-C_4) opcionalmente sustituido con cicloalquilo (C_3-C_8);

R^2 se selecciona entre el grupo compuesto por:

hidrógeno,

alquilo (C_1-C_8) opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre cicloalquilo (C_3-C_8), hidroxi, -S-alquilo (C_1-C_4), -O-alquilo (C_1-C_4), $-SO_2$-alquilo (C_1-C_4), -SO-alquilo (C_1-C_4), halo, het^1, amino, alquil (C_1-C_4)amino, [alquil

$(C_1-C_4)]_2$amino y fenilo, estando dicho fenilo opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, hidroxi, ciano, alquilo (C_1-C_4) y alcoxi(C_1-C_4),

cicloalquilo (C_3-C_6),

het^2, opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, ciano, alquilo (C_1-C_4), NH_2 y alcoxi(C_1-C_4),

$-SO_2-R^5$ donde R^5 se selecciona entre el grupo compuesto por alquilo (C_1-C_4), amino, alquil (C_1-C_4)amino, [alquil $(C_1-C_4)]_2$amino, fenilo y -alquil (C_1-C_4)-fenilo, estando dicho fenilo opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, ciano, alquilo (C_1-C_4) y alcoxi(C_1-C_4), y

$-C(O)-R^6$ donde R^6 se selecciona entre el grupo compuesto por alquilo (C_1-C_4), amino, alquil (C_1-C_4)amino, [alquil $(C_1-C_4)]_2$amino, fenilo y -alquil (C_1-C_4)-fenilo, estando dicho fenilo opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, ciano, alquilo (C_1-C_4) y alcoxi(C_1-C_4);

o R^1 y R^2 forman conjuntamente con el átomo de N al que están unidos un heterociclo saturado de 3, 4, 5, 6 ó 7 miembros donde un átomo de C puede reemplazarse por N, O, S, SO o SO_2 y donde dicho heterociclo saturado está opcionalmente sustituido con uno o dos grupos seleccionados independientemente entre hidroxi, halo, =O, alquilo (C_1-C_4), -alquil (C_1-C_4)cicloalquilo (C_3-C_6), alcoxi(C_1-C_4), hidroxialquilo (C_1-C_4), alcoxi(C_1-C_4)alquilo (C_1-C_4), $-SO_2$alquilo (C_1-C_4), -C(O)alquilo (C_1-C_4), [alquil $(C_1-C_4)]_2$amino, amino,

alquil (C_1-C_4)amino, -C(O)NH_2, C(O)Oalquilo (C_1-C_4) y pirrolidinona;

Cada uno de R^3 y R^4 se selecciona independientemente entre hidrógeno, cicloalquilo (C_3-C_8), y alquilo (C_1-C_4), estando dicho cicloalquilo (C_3-C_8) y alquilo (C_1-C_4) opcionalmente sustituidos con amino, alquil (C_1-C_4)amino, [alquil (C_1-C_4)]$_2$amino o cicloalquilo (C_3-C_8), o R^3 y R^4 forman junto con el átomo de N al que están unidos un heterocicio saturado de 4, 5, 6 ó 7 miembros donde un átomo de C puede reemplazarse por N u O y donde dicho heterocicio saturado está opcionalmente sustituido con alquilo (C_1-C_4), [alquil (C_1-C_4)]$_2$amino, amino, alquil (C_1-C_4)amino, o -C(O)alquilo (C_1-C_4), estando dicho -C(O)alquilo (C_1-C_4) opcionalmente sustituido con metoxi o etoxi,

Y se selecciona entre CH_2, CH(OH), O, C=O y N, estando dicho N sustituido con H, alquilo (C_1-C_4), C(O)alquilo (C_1-C_4) o alcoxi (C_1-C_4)alquilo (C_1-C_4);

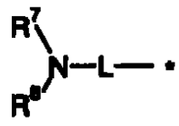
Z se selecciona entre O, S, SO y SO_2;

m y p son ambos números enteros que son independientemente 1, 2 ó 3, con la condición de que m+p sea igual a o menor que 4 de forma que el anillo formado por:



sea un anillo de 4, 5 ó 6 miembros;

y R es un grupo de fórmula:



en la que * representa el punto de unión a Z, L es un alquileno (C_2-C_6) de

cadena lineal o ramificada y cada uno de R^7 y R^8 se selecciona independientemente entre hidrógeno, alquilo (C_1-C_8), cicloalquilo (C_3-C_8), hidroxialquilo (C_1-C_8) o R^7 y R^8 forman junto con el átomo de N al que están unidos un heterociclo saturado de 4, 5, 6 ó 7 miembros donde un átomo de C está opcionalmente reemplazado por N, O, S, SO o SO_2 y donde dicho heterociclo saturado está opcionalmente sustituido con uno o dos grupos seleccionados independientemente entre alquilo (C_1-C_4), alcoxi (C_1-C_4), alcoxi (C_1-C_4)-alquilo (C_1-C_4), hidroxialquilo (C_1-C_4), hidroxi, C(O)Oalquilo (C_1-C_4), -C(O)-alquil (C_1-C_4)-NH_2, -$C(O)NH_2$, halo, amino, alquil (C_1-C_4)amino y [alquil (C_1-C_4)]$_2$amino,

o R es un grupo de fórmula:



en la que * representa el punto de unión a Z, el anillo que contiene N es un heterociclo saturado de 4 a 7 miembros, n es un número entero igual a 0, 1 ó 2, y R^9 representa un sustituyente seleccionado entre hidrógeno, alquilo (C_1-C_4), hidroxi(alquilo C_1-C_8) y cicloalquilo (C_3-C_8);

het^1 se selecciona entre grupos heteroaromáticos monocíclicos o bicíclicos que tienen de 5 a 10 miembros en el anillo, que contienen 1, 2, 3 ó 4 heteroátomo(s) seleccionado(s) entre nitrógeno, oxígeno y azufre y het^2 se selecciona entre grupos heteroaromáticos monocíclicos o bicíclicos que tienen de 5 a 10 miembros en el anillo, que contienen 1, 2, 3 ó 4 heteroátomo(s) seleccionado(s) entre nitrógeno, oxígeno y azufre.

2. Un compuesto de fórmula (1) como se define en la reivindicación 1, en la que X se selecciona entre -CH_2-NR^1R^2, -C(O)NR^3R^4, -CH_2-het^1 y het^1, estando el grupo het^1 opcionalmente sustituido una o dos veces con alquilo (C_1-C_4), donde R^1, R^2, R^3, R^4 y het^1 son como se han definido anteriormente en la reivindicación 1.

3. Un compuesto de fórmula (1) como se define en la reivindicación 2, en la que X es -CH_2-het^1 o het^1, y het^1 se selecciona entre un grupo heteroaromático monocíclico de 5 ó 6 miembros, o un grupo heteroaromático bicíclico de 9 miembros, conteniendo cada grupo heteroaromático de 1 a 3 átomos de nitrógeno, o de 1 a 2 átomos de nitrógeno y 1 átomo de oxígeno, o 1 átomo de nitrógeno y 1 átomo de azufre, y estando cada grupo heteroaromático opcionalmente sustituido una o dos veces con alquilo (C_1-C_4).

4. Un compuesto de fórmula (1) como se define en la reivindicación 3, en la que X es tiazolilo, bencimidazolilmetil-, piridinilo, oxazolilo, imidazopiridinilmetil-, pirimidinilo, imidazolilo, imidazolilmetil- o triazolilmetil-, estando cada uno de dichos tiazolilo, bencimidazolilmetil-, piridinilo, oxazolilo, imidazopiridinilmetil-, pirimidinilo, imidazolilo, imidazolilmetil- y triazolilmetil- opcionalmente sustituido con un grupo metilo.

5. Un compuesto de fórmula (1) como se define en la reivindicación 1 o en la reivindicación 2, en la que R^1 es hidrógeno, metilo o etilo.

6. Un compuesto de fórmula (1) como se define en la reivindicación 1, en la

reivindicación 2 o en la reivindicación 5, en la que R^2 se selecciona entre el grupo compuesto por

hidrógeno,

alquilo (C_1-C_8) opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre -S-alquilo (C_1-C_4), -O-alquilo (C_1-C_4), -SO_2-alquilo (C_1-C_4), y fenilo, estando dicho fenilo opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, hidroxi, ciano, alquilo (C_1-C_4) y alcoxi(C_1-C_4),

cicloalquilo (C_3-C_6),

het^2, opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, ciano, alquilo (C_1-C_4) y alcoxi(C_1-C_4), donde het^2 se define como en la reivindicación 1,

-SO_2-R^5 donde R^5 se selecciona entre el grupo compuesto por alquilo (C_1-C_4), [alquil (C_1-C_4)]$_2$amino, fenilo y -alquil (C_1-C_4)-fenilo, estando dicho fenilo opcionalmente sustituido con un sustituyente seleccionado independientemente entre halo y ciano y

-C(O)-R^6 donde R^6 se selecciona entre el grupo compuesto por alquilo (C_1-C_4), [alquil (C_1-C_4)]$_2$amino, amino, y -alquil (C_1-C_4)-fenilo, estando dicho fenilo opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, ciano, alquilo (C_1-C_4) y alcoxi(C_1-C_4).

7. Un compuesto de fórmula (1) como se define en la reivindicación 6, en la que R^2 se selecciona entre el grupo compuesto por

alquilo (C_1-C_3) opcionalmente sustituido con -O-alquilo (C_1-C_3),

cicloalquilo (C_3-C_6),

het^2, donde het^2 se selecciona entre el grupo compuesto por grupos heteroaromáticos monocíclicos que tienen 5 ó 6 miembros, que contienen de 1 a 2 átomos de nitrógeno o 1 átomo de nitrógeno y 1 átomo de oxígeno o 1 átomo de nitrógeno y 1 átomo de azufre, estando dicho het^2 opcionalmente sustituido con alquilo (C_1-C_4),

-SO_2-R^5 donde R^5 es alquilo (C_1-C_4) y

-C(O)-R^6 donde R^6 es alquilo (C_1-C_4).

8. Un compuesto de fórmula (1) como se define en la reivindicación 7, en la que R^2 es alquilo (C_1-C_3) opcionalmente sustituido con metoxi.

9. Un compuesto de fórmula (1) como se define en la reivindicación 7, en la que R^2 es het^2, y het^2 se selecciona entre el grupo compuesto por grupos heteroaromáticos monocíclicos que tienen 5 ó 6 miembros, que contienen 1 ó 2 átomos de nitrógeno .

10. Un compuesto de fórmula (1) como se define en la reivindicación 9, en la que R^2 es un grupo piridazinilo.

11. Un compuesto de fórmula (1) como se define en la reivindicación 1 o la reivindicación 2, en la que R^1 y R^2 forman conjuntamente con el átomo de N al que están unidos un heterociclo saturado de 4, 5, 6 ó 7 miembros donde un átomo de C puede reemplazarse por N, O, S, SO o SO_2 y donde dicho heterociclo saturado está opcionalmente sustituido con uno o dos grupos seleccionados independientemente entre hidroxi, halo, =O, alquilo (C_1-C_4), -

alquil (C_1-C_4)cicloalquilo (C_3-C_8), alcoxi(C_1-C_4), hidroxialquilo (C_1-C_4), alcoxi(C_1-C_4)alquilo (C_1-C_4), -SO_2alquilo (C_1-C_4), -C(O)alquilo (C_1-C_4), [alquil (C_1-C_4)]$_2$amino, -C(O)NH_2, C(O)Oalquilo (C_1-C_4) y pirrolidinona.

12. Un compuesto de fórmula (1) como se define en la reivindicación 11, en la que R^1 y R^2 forman conjuntamente con el átomo de N al que están unidos un grupo morfolinilo.

13. Un compuesto de fórmula (1) como se define en la reivindicación 1 o la reivindicación 2, en la que cada uno de R^3 y R^4 se selecciona independientemente entre hidrógeno y alquilo (C_1-C_4) o R^3 y R^4 forman junto con el átomo de N al que están unidos un heterociclo saturado de 4, 5 ó 6 miembros donde un átomo de C puede reemplazarse por N u O y donde dicho heterociclo saturado está opcionalmente sustituido con alquilo (C_1-C_4).

14. Un compuesto de fórmula (1) como se define en la reivindicación 13, en la que R^3 y R^4 se seleccionan independientemente entre hidrógeno, metilo y etilo, o R^3 y R^4 forman junto con el átomo de N al que están unidos un anillo de pirrolidinilo, piperidinilo, piperazinilo o azetidinilo, estando cada anillo pirrolidinilo, piperidinilo, piperazinilo y azetidinilo opcionalmente sustituido con metilo.

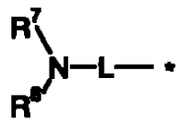
15. Un compuesto de fórmula (1) como se define en una cualquiera de las reivindicaciones anteriores, en la que Y se selecciona entre CH_2, CH(OH), O y C=O.

16. Un compuesto de fórmula (1) como se define en la reivindicación 15, en la que Y es O.

17. Un compuesto de fórmula (1) como se define en una cualquiera de las reivindicaciones anteriores, en la que Z es O.

18. Un compuesto de fórmula (1) como se define en una cualquiera de las reivindicaciones anteriores, en la que m y p son ambos 2.

19. Un compuesto de fórmula (1) como se define en una cualquiera de las reivindicaciones anteriores, en la que R es un grupo de fórmula:



en la que * representa el punto de unión a Z, L es un alquileno (C_2-C_5) y cada uno de R^7 y R^8 se selecciona independientemente entre hidrógeno, alquilo (C_1-C_8), cicloalquilo (C_3-C_8), hidroxialquilo (C_1-C_8) o R^7 y R^8 forman junto con el átomo de N al que están unidos un heterociclo saturado de 4, 5, 6 ó 7 miembros donde un átomo de C está opcionalmente reemplazado por N, O, S, SO o SO_2 y donde dicho heterociclo saturado está opcionalmente sustituido con uno o dos grupos seleccionados independientemente entre alquilo (C_1-C_4), alcoxi (C_1-C_4), alcoxi (C_1-C_4)alquilo (C_1-C_4), hidroxialquilo (C_1-C_4), hidroxi, C(O)Oalquilo (C_1-C_4), -C(O)-alquil (C_1-C_4)-NH_2, -C(O)NH_2 y halo.

20. Un compuesto de fórmula (1) como se define en la reivindicación 19, en

la que R^7 y R^8 forman junto con el átomo de N al que están unidos un grupo morfolinilo u oxazepanilo.

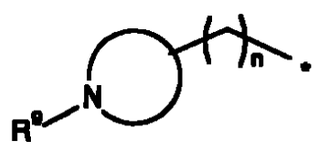
21. Un compuesto de fórmula (1) como se define en la reivindicación 19, en la que R^7 y R^8 forman junto con el átomo de N al que están unidos un heterociclo saturado de 4, 5 ó 6 miembros, opcionalmente sustituido con uno o dos grupos alquilo (C_1-C_4).

22. Un compuesto de fórmula (1) como se define en la reivindicación 21, en la que el heterociclo saturado es un grupo pirrolidinilo, opcionalmente sustituido con uno o dos grupos metilo.

23. Un compuesto de fórmula (1) como se define en la reivindicación 19, en la que R^7 y R^8 son alquilo (C_1-C_3).

24. Un compuesto de fórmula (1) como se define en una cualquiera de las reivindicaciones 19 a 23, en la que L es propileno.

25. Un compuesto de fórmula (1) como se define en una cualquiera de las reivindicaciones 1 a 18, en la que R es un grupo de fórmula:



en la que * representa el punto de unión a Z, el anillo que contiene N es un heterociclo saturado de 4 ó 6 miembros, n es un número entero igual a 0 ó 1 y

R^9 representa un sustituyente seleccionado entre hidrógeno, alquilo (C_1-C_4) y cicloalquilo (C_3-C_6).

26. Un compuesto de fórmula (1) como se define en la reivindicación 25, en la que R^9 es isopropilo o ciclobutilo.

27. Un compuesto de fórmula (1) como se define en uno cualquiera de los Ejemplos de este documento.

28. Una composición farmacéutica que incluye un compuesto de fórmula (1) o una sal y/o solvato farmacéuticamente aceptable del mismo, como se define en una cualquiera de las reivindicaciones anteriores, junto con un excipiente farmacéuticamente aceptable.

29. Un compuesto de la fórmula (1) como se define en una cualquiera de las reivindicaciones 1 a 27 o una sal y/o solvato farmacéuticamente aceptable del mismo, para usar como medicamento.

30. El uso de un compuesto de la fórmula (1) como se define en una cualquiera de las reivindicaciones 1 a 27 o de una sal y/o solvato farmacéuticamente aceptable del mismo, para la fabricación de un medicamento para tratar una enfermedad para la que está indicada un ligando H_3.

31. El uso de un compuesto de la fórmula (1) de acuerdo con la

reivindicación 30, para la fabricación de un medicamento para el tratamiento de trastornos del sueño, migraña, disquinesia, ansiedad inducida por estrés, trastornos psicóticos, epilepsia, enfermedades por deficiencia cognitiva tales como la enfermedad de Alzheimer o deterioro cognitivo leve, depresión, trastornos del estado emocional, esquizofrenia, trastornos de ansiedad, trastorno por déficit de atención con hiperactividad (ADHD), trastornos psicóticos, obesidad, mareos, vértigo, epilepsia, enfermedad del movimiento, enfermedades inflamatorias, síndrome de insuficiencia respiratoria en adultos, síndrome de insuficiencia respiratoria aguda, bronquitis, bronquitis crónica, enfermedad pulmonar obstructiva crónica, fibrosis quística, asma, enfisema, rinitis, sinusitis crónica, alergia, respuestas de las vías respiratorias inducidas por alergia, rinitis alérgica, rinitis vírica, rinitis no alérgica, rinitis perenne y estacional, congestión nasal, congestión alérgica, disfunción sexual masculina o disfunción sexual femenina.

32. Un procedimiento de tratamiento de un mamífero, incluyendo un ser humano, que padece una enfermedad para la que está indicado un ligando H_3, que comprende administrar a dicho mamífero una cantidad eficaz de un compuesto de la fórmula (1) como se define en una cualquiera de las reivindicaciones 1 a 27 o una sal y/o solvato farmacéuticamente aceptable del mismo, o una composición del mismo.

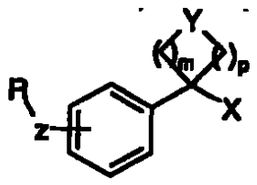
33. Una combinación de un compuesto de fórmula (1) como se define en una cualquiera de las reivindicaciones 1 a 27, y otro agente farmacológicamente activo.

34. Una combinación como se reivindica en la reivindicación 33, en la que el otro agente farmacológicamente activo es un antagonista del receptor H_1 de histamina.

35. Un compuesto de la fórmula (1) como se define en una cualquiera de las reivindicaciones 1 a 27 o una sal y/o solvato farmacéuticamente aceptable del mismo, para usar como se describe en el reivindicación 30 ó 31.

Esp
594

RESUMEN



(1)

La invención se refiere a derivados de fenol y tiofenol 3- ó 4-monosustituidos de fórmula (1) y a procedimientos para la preparación de, a intermedios usados en la preparación de, a composiciones que contienen y a los usos de, tales derivados. Tales derivados de fenol y tiofenol 3- ó 4-monosustituidos son ligandos H_3 y son útiles en numerosas enfermedades, trastornos y afecciones, en particular enfermedades, trastornos y afecciones inflamatorias, alérgicas y respiratorias.

TRATADO DE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES

Remitente: EL ORGANISMO DE EXAMEN PRELIMINAR INTERNACIONAL

A

FULLER, Grover, F., Jr.
c/o WOOD, David, J.
Pfizer Research & Development
Ramsgate Road
Sandwich, Kent CT13 9NJ
Gran Bretaña

PCT

NOTIFICACIÓN DE ENVÍO DEL INFORME DEL EXAMEN PRELIMINAR INTERNACIONAL

(regla PCT Nº 71.1)

		Fecha de envío (*día/mes/año*) 29.03.2006
Referencia del Solicitante o Agente PC32016A		NOTIFICACIÓN IMPORTANTE
Referencia Internacional PCT/IB2005/001114	Fecha de Presentación Internacional (*día/mes/año*) 19.04.2005	Fecha de Prioridad (*día/mes/año*) 07.05.2004
Solicitante WARNER-LAMBERT COMPANY LLC et al.		

1. Se notifica al solicitante que el organismo encargado del Examen Preliminar Internacional envía mediante la presente el Informe de Examen Preliminar Internacional elaborado para esta Solicitud Internacional, en casos dados, con los anexos correspondientes.

2. Una copia del Informe – en casos dados, con los anexos correspondientes – es enviada a la Oficina Internacional para su derivación a todos los organismos seleccionados.

3. A petición de un organismo seleccionado, la Oficina Internacional traducirá el Informe (pero no sus anexos) al inglés y lo enviará a tal organismo.

4. **RECORDATORIO**

Para el ingreso en la fase nacional, el solicitante debe proceder, dentro de los 30 meses de la fecha de prioridad (o más tarde en otros organismos), a llevar a cabo ciertos trámites (presentación de traducciones y pago de tasas nacionales) (artículo 39 (1)) (ver también la información brindada por la Oficina Internacional por medio del formulario PCT/IB/301).

Cuando se debe enviar a un organismo seleccionado una traducción de la solicitación internacional, esta traducción debe contener también las traducciones de todos los anexos del Informe del Examen Preliminar Internacional. Es responsabilidad del solicitante elaborar tales traducciones y enviarlas directamente al organismo correspondiente seleccionado.

Otros detalles de los plazos y requisitos normativos de los organismos seleccionados se pueden tomar del Manual PCT para solicitantes.

El solicitante es advertido acerca del artículo 33 (5) en el cual se aclara que los criterios de novedad, actividad inventiva y aplicabilidad industrial descriptos en el artículo 33 (2) a (4) solo tiene significado para el Examen Preliminar Internacional, y que "cada estado adherido puede disponer atributos adicionales o modificatorios en tal estado para la determinación de la patentabilidad de la invención reivindicada" (ver también artículo 27 (5)). Tales atributos adicionales se pueden referir, por ejemplo, a excepciones de patentabilidad, a requisitos para la revelación de la invención, así como a claridad y apoyo de las reivindicaciones.

Nombre y Dirección Postal del Organismo encargado del Examen Preliminar Internacional Oficina de Patentes Europea D-80298 Munich Tel. +49 89 2399-0, Tx: 523656 epmu d Fax: +49 89 2399-4465	Funcionario Apoderado Hebert, W Tel: +49.89.2399-2152

Formulario PCT/IPEA/409 (enero 2004)

TRATADO DE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES

PCT

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL SOBRE PATENTABILIDAD

(Capítulo II del Tratado de Cooperación Internacional en Materia de Patentes)
(PCT Artículo 36 y Regla 70)

Referencia del Solicitante o Agente PC32018A	PROCEDER Ver formulario PCT/IPEA/416)	
Referencia Internacional PCT/IB2005/001114	Fecha de Presentación Internacional (*día/mes/año*) 19.04.2005	Fecha de Prioridad (*día/mes/año*) 07.05.2004
Clasificación Internacional de Patente (CIP) o Clasificación Nacional y CIP INV. C07D309/06 C07D405/12 C07D309/08 C07D295/12 C07D405/06 C07D405/14 C07D295/14 C07D417/04 C07D417/06 A61K31/55 A61P25/06 C07D405/04 C07D413/04 C07D413/12 C07D295/22 C07D471/04		
Solicitante WARNER-LAMBERT COMPANY LLC et al.		

1. *Este informe se trata del reporte de Examen Preliminar Internacional, confeccionado por el organismo encargado del* Examen Preliminar Internacional según el Artículo 35 y enviado al solicitante según el Artículo 36.

2. Este INFORME comprende, en total, 9 hojas, incluida esta carátula.

3. Además, este informe posee ANEXOS; los mismos comprenden:

   a. ☐ (*remitidos al solicitante y a la Oficina Internacional*) en total hojas; aquí se trata de:
      - ☐ hojas con las descripciones, reivindicaciones, y/o ilustraciones que fueron modificadas y en las cuales se basa este informe y/u hojas con correcciones que aprobó el organismo (ver regla 70.16 y sector 607 de los reglamentos administrativos).
      - ☐ hojas que reemplazan hojas anteriores pero que, según opinión del organismo, contienen una modificación por los motivos indicados en el punto 4, campo Nº 1,superando el contenido revelado en la Solicitud Internacional en la versión presentada originalmente.

   b. ☐ (*remitidos solo a la Oficina Internacional*) un total de (indicar tipo y cantidad del (los) soporte(s) electrónico(s) que contiene(n), una lista de secuencias y/o las tablas correspondientes, solo en formato electrónico, tal como está indicado en el campo suplementario relativo a listas de secuencias (ver Instrucción Administrativa 802).

4. Este informe contiene indicaciones acerca de los siguientes puntos:

   - ☒ Campo Nº I — Fundamento del informe
   - ☐ Campo Nº II — Prioridad
   - ☒ Campo Nº III — No formulación de opinión sobre la novedad, la actividad inventiva y la aplicabilidad industrial
   - ☐ Campo Nº IV — Falta de unidad de la invención
   - ☒ Campo Nº V — Declaración fundada según el Artículo 35(2) con respecto a la novedad, la actividad inventiva y la aplicabilidad industrial; documentos y aclaraciones destinadas a apoyar esta declaración.
   - ☐ Campo Nº VI — Documentos específicos citados
   - ☐ Campo Nº VII — Defectos específicos de la solicitud internacional
   - ☒ Campo Nº VIII — Observaciones específicas a la solicitud internacional

Fecha de presentación de la solicitud 24.09.2005	Fecha de confección de este informe 29.03.2006
Nombre y Dirección Postal del organismo encargado del Examen Internacional Oficina de Patentes Europea D-80298 Munich Tel. ++49 89 2399-0; Tlx 523656 epmu d Fax: +49 89 2399-4465	Funcionario Apoderado Walabrod, T Tel: +49 89 2399-

599
597

Campo Nº I Fundamento del Informe

1. Con respecto al idioma, el informe está basado sobre la solicitud internacional en el idioma en que fue presentada, en tanto en este punto no se indique otra cosa.

   ☐ El informe está basado sobre una traducción del idioma original al siguiente idioma, el que se trata del idioma de la traducción suministrada a los siguientes efectos:
   - ☐ búsqueda internacional (según Reglas 12.3 y 23.1 (b))
   - ☐ publicación de la solicitud internacional (según Regla 12.4)
   - ☐ examen preliminar internacional (según Regla 55.2 y/o 55.3)

2. Con respecto a los elementos* de la Solicitud Internacional, el informe se basa en (*las hojas de reemplazo que fueron presentadas al organismo como requisito según el Artículo 14 son válidas como "presentadas originalmente" en el marco de este informe y no se adjuntan):*

   Descripción, páginas

   1 – 203 presentadas originalmente.

   Reivindicaciones, Nº

   1 – 35 presentadas originalmente.

   ☐ un listado de secuencias y/o eventual(es) tabla(s) relacionada(s) – con respecto al listado de secuencias, ver campo adicional.

3. ☐ Como consecuencia de las modificaciones caducaron los siguientes documentos:

   - ☐ Descripción: páginas
   - ☐ Reivindicaciones Nº:
   - ☐ Ilustraciones: hoja/figura
   - ☐ Listado de secuencias *(especificar)*:
   - ☐ Eventual(s) tabla(s) perteneciente(s) al listado de secuencias *(especificar)*:

4. ☐ Este informe fue elaborado sin tomar en consideración (algunas de) las modificaciones, dado que las mismas, según opinión del organismo y por los motivos expresados, exceden el contenido revelado en el texto presentado originalmente (Regla 70.2(c)), tal como se indica en el campo suplementario.

   - ☐ Descripción: páginas
   - ☐ Reivindicaciones Nº:
   - ☐ Ilustraciones: hojas/figuras
   - ☐ Listado de secuencias *(especificar)*:
   - ☐ Eventual(s) tabla(s) perteneciente(s) al listado de secuencias *(especificar)*:

* *Cuando corresponde el punto 4, algunas o todas estas hojas pueden estar provistas de la observación "reemplazada".*

600
493

Campo Nº III **No establecimiento de un informe con respecto a la novedad, la actividad inventiva y la aplicabilidad industrial**

La cuestión acerca de si la invención reivindicada parece ser novedosa, involucra actividad inventiva (no obvia) o es aplicable industrialmente no fue examinada con respecto a:

☐ toda la solicitud internacional

☒ reivindicaciones Nº 32

Porque

☒ las mencionadas solicitud internacional o reivindicaciones Nº 32 se refieren al siguiente objeto, el que no requiere un examen preliminar internacional (*especificar*):

ver hoja adjunta

☐ la descripción, reivindicaciones o ilustraciones (*indicar elementos particulares abajo*) o las mencionadas reivindicaciones Nº son tan poco claras que no se puede establecer un informe coherente (*especificar*):

☐ las reivindicaciones o las mencionadas reivindicaciones Nº está apoyadas tan inadecuadamente por la descripción que no se puede establecer un informe coherente.

☐ no se estableció ningún informe de búsqueda para toda la solicitud o para las mencionadas reivindicaciones Nº .

☐ el listado de secuencias de nucleótidos y/o aminoácidos no cumple con el estándar provisto para ello en el Anexo C de las Instrucciones Administrativas, porque:

la forma escrita	☐	no fue suministrada
	☐	no cumple con el estándar
la forma legible por computadora	☐	no fue suministrada
	☐	no cumple con el estándar

☐ las tablas relacionadas con el listado de secuencias de nucleótidos y/o aminoácidos, si está forma legible por computadora, no cumple con los requerimientos técnicos provistos por el Anexo C-*bis* de las Instrucciones Administrativas.

☒ para otros detalles, ver hoja adjunta

60
599

Campo Nº V **Declaración fundada según el Artículo 35(2) con respecto a la novedad, la actividad inventiva y la aplicabilidad industrial; documentos y declaraciones destinadas a apoyar esta Declaración**

1. Resolución

Novedad (N)	SI	Reivindicaciones:	1-35
	No	Reivindicaciones:	
Actividad inventiva (IS)	SI	Reivindicaciones:	1-35
	No	Reivindicaciones:	
Aplicabilidad industrial (IA)	SI	Reivindicaciones:	1-31, 33-35
	No	Reivindicaciones:	

2. Documentos y aclaraciones (regla 70.7):

ver hoja adjunta

Campo Nº VII. **Observaciones definidas acerca de la Solicitud Internacional**

Para aclarar las reivindicaciones, la descripción y las ilustraciones de la invención o la cuestión de su las reivindicaciones son apoyadas en todo su contenido por la descripción, se observa lo siguiente:

Ver hoja adjunta

602
600

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL – HOJA ANEXA
Solicitud Internacional No. PCT/IB2005/001114

Ítem I
Fundamento del concepto

La solicitud está relacionada con
(i) derivados de fenol y tiofenol de la fórmula (1) (reivindicaciones 1- 27),
(ii) una composición farmacéutica que comprende compuestos (1) (reivindicación 28),
(iii) el uso médico de compuestos (1) (reivindicaciones 29- 31 y 35),
(iv) el correspondiente método de tratamiento (reivindicación 32), y
(v) una combinación de un compuesto (1) con otro agente farmacológicamente activo (reivindicaciones 33- 34).

Ítem II
Prioridad

La fecha de prioridad reivindicada es por lo menos no válida para los compuestos (1) en donde Z es S, SO, y SO_2, y para compuestos (1) en donde Y es N, puesto que tales realizaciones no están divulgadas en el documento de prioridad.

Ítem III
No formulación de concepto con respecto a la novedad, nivel inventivo y aplicación industrial

1 La reivindicación 32 se relaciona con materia considerada cubierta por esta Autoridad por las provisiones establecidas en la Regla 67.1(iv) del PCT. De manera que ningún concepto se formulará con respecto a la aplicación industrial de la materia de estas reivindicaciones (Artículo 34(4)(a)(I) del PCT).

2 La ISA (Autoridad Internacional de Búsqueda) no ha entregado un reporte de búsqueda en cuanto a la solicitud se relaciona con metabolitos e isómeros de los compuestos (1) (compare con la solicitud, página 16, línea 21, y página 17, líneas 15-16). Por lo tanto, no se llevará a cabo ninguna Evaluación Preliminar Internacional completa con respecto a la novedad y nivel inventivo para materia no cubierta por el reporte de búsqueda (Regla 66.1(e) del PCT).

Ítem V
Declaración razonada con respecto a la novedad, nivel inventivo y aplicación industrial; citas y explicaciones sustentando dicha declaración

1 Se hace referencia a los siguientes documentos:

D1: WO 02/06223 A, 24 de enero de 2002; citado en la solicitud
D2: WO 02/12190 A, 14 de febrero de 2002; citado en la solicitud
D3: WO 02/076925, 3 de octubre de 2002; citado en la solicitud
D4: EP- A- 0 269 363, 1 de junio de 1988
D5: Beilstein Crossfire, citación No. 5690069
D6: DE- A- 30 24 836, 28 de enero de 1982.

2 La solicitud no cumple con los requisitos de los Artículos 5 y 6 del PCT por las siguientes razones.

2.1 La declaración en la descripción que reza que profármacos, isómeros y metabolitos están incluidos en el invento (la solicitud, páginas 16- 17) implica que la materia para la cual se busca la protección podría ser diferente de lo que se define en las reivindicaciones. Esta inconsistencia entre la descripción y las reivindicaciones no otorga claridad a las reivindicaciones.

Independiente de este razonamiento, la diferencia relevante entre profármacos de los compuestos (1) y compuestos (1) en donde X es por ejemplo $-C(O)O(C_{1-4})$alquilo o $-CH_2-NR^1R^2$ siendo R^2 igual a $-C(O)R^6$, o en donde Y es $N-C(O)(C_{1-4})$alquilo es por ahora no evidente y suma a la poca claridad de las reivindicaciones y de la solicitud.

Adicionalmente, los isómeros de los compuestos (1) representan todos los compuestos que tengan las mismas fórmulas moleculares como los compuestos (1). Sin embargo, la solicitud ni divulga la preparación ni ejemplifica isómeros que tengan diferentes fórmulas estructurales a las de los compuestos (1). Por lo tanto, los isómeros per se de los compuestos (1) ni están los suficientemente divulgados (Artículo 5 del PCT) ni tampoco están soportados por la solicitud (Artículo 6 del PCT).

2.2 La reivindicación 27 será objetada bajo el Artículo 6 junto con la Regla 6.2(a) del PCT por referirse a la descripción.

2.3 Las reivindicaciones 30, 32, y 35 serán objetadas bajo el Artículo 6 del PCT porque la aplicación terapéutica es funcionalmente definida mediante un mecanismo de acción ("una enfermedad para la cual está indicado un ligando H_3) lo cual no permite ninguna aplicación práctica en forma de un tratamiento real y definido de una condición patológica. La objeción podría superarse al introducirse en las reivindicaciones un listado de condiciones patológicas citadas en la solicitud, o demostrando que están disponibles medios que permitirían a la persona capacitada reconocer cuáles condiciones adicionales estarían por dentro de la definición funcional.

2.4 La expresión "tal como" usada en la reivindicación 31 no tiene ningún efecto limitante sobre el alcance de la reivindicación. Las características que siguen luego de la expresión son por consiguiente superfluas, y por lo tanto resultando en una falta de concisión en la reivindicación.

3 Novedad

D1 se relaciona con ligandos del receptor de histamina- 3 (H_3). Los compuestos de D1 generalmente ya comprenden ciertos compuestos (1) del presente en donde Y es oxígeno o nitrógeno (compare con D1, reivindicación 1, R^8 = heterociclo sustituido con aminoalquilo, carboxilo, carboxi- alquilo, ciano correspondiente con el sustituto X del presente), pero el documento no divulga de manera específica los compuestos (1) con los heterociclos sustituidos con X y que comprenden Y. De manera que la materia reivindicada si se considera novedosa comparado con D1.

604
602

D2 divulga ligandos H_3, a partir de los cuales difieren los compuestos de la presente por el sustituto X (compare con D2, reivindicación 1, en donde R^2 o R^3 = W = cicloalquilo opcionalmente sustituido con halo, amino, nitro, hidroxilo, alquilo; o en donde R^2 o R^3 = G(iii) en donde R^7 es hidrógeno, hidroxilo, halo, C_{2-6}alcoxilo; y por ejemplo, página 131, ejemplo 80). Por lo tanto, la materia reivindicada es novedosa a la luz de D2.

D3 divulga ligandos H_3 adicionales, a partir de los cuales difieren los compuestos de la presente por el tamaño de anillo de la fracción cíclica que comprende Y, y por la naturaleza de X (compare con D3, reivindicación 1, R^4 y R^5 juntos forman un anillo de ciclopropano, X=O, NR^7, S; y por ejemplo página 111, ejemplos 240, 241).

D4 ilustra fungicidas los cuales generalmente comprenden los presentes compuestos (I) (compare con D4, reivindicación 1, R^1 = alquilo sustituido, y páginas 26- 27, ejemplos 168- 170). Sin embargo, el documento no divulga de manera específica compuestos con el valor X presente. Por lo tanto, la materia reivindicada si se considera novedosa comparado con D4.

D5 se relaciona con la amisina (*ilegible*) alcaloide, a partir de la cual difieren los compuestos (I) solo por el sustituto X (D5: - $(CH_2)_2$- NMe_2; por ejemplo –CH_2-NR^1R^2). La materia reivindicada si se considera novedosa comparado con D5.

D6 se relaciona con 4'- (3- alquilamino- 2- hidroxi- propoxi)- benzonitrilos beta-adrenolíticos a partir de los cuales los compuestos (I) de la presente difieren solo por el grupo 2- hidroxilo faltante. La materia de las presentes reivindicaciones es por lo tanto considerada novedosa frente al antecedente D6. Sin embargo, los metabolitos de los compuestos (I) no se considerarían novedosos con respecto a los compuestos de D6, a menos que el solicitante pudiera proporcionar evidencia soportada que los compuestos de D6 no fueran metabolitos de los presentes compuestos (I).

En vista de los antecedentes citados, el presente capítulo reivindicatorio parece cumplir con el criterio de la novedad.

4 Nivel Inventivo

4.1 La solicitud describe la síntesis de ciertos compuestos (I) y demuestra que tales compuestos se fijan al receptor H_3 con $K_i < 5$ μM (la solicitud, páginas 202- 203).

4.2 D1 a D3 divulgan de antemano ligandos H_3. Los presentes compuestos (I) difieren de aquellos encontrados en D1 por la fracción cíclica sustituida por X y que comprende Y. Difieren de los compuestos encontrados en D2 por el sustituto X; y difieren de los compuestos encontrados en D3 debido al tamaño del anillo del anillo que comprende Y, y la naturaleza de X. D2 puede considerarse como el antecedente más relevante puesto que divulga ligandos H_3 estructuralmente relacionados con anterioridad (por ejemplo el ejemplo 80) a partir de los cuales los presentes compuestos (I) difieren solo por el sustituto X adicional. Con base en D2, el problema planteado en la solicitud puede considerarse como intentar proporcionar ligandos H_3 adicionales. En general, D2 y los documentos D1 y D3 permiten ya ciertos sustitutos en un anillo que corresponden con la fracción cíclica que comprende Y de la presente. Sin embargo, no indican inequívocamente que los presente compuestos (I), que tienen sustitutos X específicos sobre una posición muy específica del anillo que comprende Y, retendrían la actividad

deseada. De manera que la materia de las reivindicaciones 1- 35 parece poseer nivel inventivo.

4.3 Sin embargo, no se reconocería ningún nivel inventivo para isómeros o metabolitos de los compuestos (I), puesto que es inverosímil que sustancialmente todos los isómeros y metabolitos de los presentes compuestos (I) exhiban la actividad deseada sobre el receptor H_3 y proporcionen una solución al problema planteado por la solicitud.

5 Aplicación Industrial

Para la evaluación de la presente reivindicación 32 sobre si es industrialmente aplicable, no existen criterios unificados entre los Estados pertenecientes al PCT. La patentabilidad también puede depender de la formulación de las reivindicaciones. La Oficina de Patentes Europea, EPO, por ejemplo, no reconoce como cumplimiento del requisito de la aplicación industrial, un contenido de reivindicaciones con respecto al uso de un compuesto en un tratamiento médico, pero si permite sin embrago, reivindicaciones con respecto a un compuesto para primer uso en un tratamiento médico y el uso de tal compuesto para la producción de un medicamento para un tratamiento médico nuevo.

Ítem VIII
Ciertas observaciones sobre la solicitud internacional

Ver el ítem V.2 anterior.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

FULLER, Grover, F., Jr.
c/o WOOD, David, J.
Pfizer Research and Development
Ramsgate Road
Sandwich, Kent CT13 9NJ
GRANDE BRETAGNE

EUROPEAN PHARMA
PATENT DEPARTMENT
03 APR 2006

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing (day/month/year)	29.03.2006
Applicant's or agent's file reference: PC32016A	IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/IB2005/001114	19.04.2005	07.05.2004

Applicant
WARNER-LAMBERT COMPANY LLC et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed invention is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hebert, W Tel. +49 89 2399-2152

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REP RT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
PC32016A		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/IB2005/001114	19.04.2005	07.05.2004

International Patent Classification (IPC) or national classification and IPC

INV. C07D309/06 C07D405/12 C07D309/08 C07D295/12 C07D405/06 C07D405/14 C07D295/14 C07D417/04 C07D417/06 A61K31/55 A61P25/06 C07D405/04 C07D413/04 C07D413/12 C07D295/22 C07D471/04

Applicant

WARNER-LAMBERT COMPANY LLC et al.

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 8 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 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the International application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the International application
   - ☒ Box No. VIII Certain observations on the International application

Date of submission of the demand	Date of completion of this report
24.06.2005	29.03.2006
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Weisbrod, T Telephone No. +49 89 2399-

Form PCT/IPEA/409 (Cover Sheet) (April 2005)

INTERNATIONAL PRELIMINARY REPORT N PATENTABILITY

International application No.
PCT/IB2005/001114

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, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

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

   1-203 as originally filed

   Claims, Numbers

   1-35 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

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. 32

because:

☒ the said international application, or the said claims Nos. 32 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See separate sheet for further details

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	1-35
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-35
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-31,33-35
	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

Re Item I
Basis of the opinion

The application is directed to
(i) phenol and thiophenol derivatives of formula (1) (claims 1-27),
(ii) a pharmaceutical composition comprising compounds (1) (claim 28),
(iii) the medical use of compounds (1) (claims 29-31 and 35),
(iv) the corresponding method of treatment (claim 32), and
(v) a combination of a compound (1) with another pharmacologically active agent (claims 33-34).

Re Item II
Priority

The claimed date of priority is at least not valid for compounds (1) wherein Z is S, SO, and SO_2, and for compounds (1) wherein Y is N, because such embodiments are not disclosed in the priority document.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1 Claim 32 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

2 The ISA has not issued a search report insofar as the application relates to metabolites and isomers of compounds (1) (cf. the application, page 16, line 21, and page 17, lines 15-16). No full International Preliminary Examination will thus be carried out with regard to novelty and inventive step for subject-matter which is not covered by the search report (cf. Rule 66.1(e) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents.

D1: WO 02/06223 A, 24 January 2002; cited in the application.
D2: WO 02/12190 A, 14 February 2002; cited in the application.
D3: WO 02/076925, 3 October 2002; cited in the application.
D4: EP-A-0 269 363, 1 June 1988.
D5: Bellstein Crossfire, Citation No. 5690069.
D6: DE-A-30 24 836, 28 January 1982.

2 The application does not comply with the requirements of the Articles 5 and 6 PCT for the following reasons.

2.1 The statement in the description that prodrugs, isomers and metabolites are included in the invention (the application, pages 16-17) implies that the subject-matter for which protection is sought might be different from what is defined in the claims. This inconsistency between the description and the claims renders the claims unclear.

Independent from this reasoning the relevant difference between prodrugs of compounds (1) and compounds (1) wherein X is for instance -C(O)O(C_{1-4})alkyl or -CH_2-NR^1R^2 with R^2 equal to -C(O)R^4, or wherein Y is N-C(O)(C_{1-4})alkyl is at present not evident and adds to the unclarity of the claims and the application.

Furthermore, isomers of compounds (1) represent all compounds having the same molecular formulae as the compounds (1). The application, however, neither discloses the preparation nor does it exemplify isomers having different structural formulae than the compounds (1). Hence, isomers per se of compounds (1) are neither sufficiently disclosed (Article 5 PCT) nor supported by the application (Article 6 PCT).

2.2 Claim 27 is to be objected under Article 6 in combination with Rule 6.2(a) PCT for referring to the description.

2.3 Claims 30, 32, and 35 are to be objected under Article 6 PCT, because the therapeutic application is functionally defined by a mechanism of action ("a disease for

which a H_3 ligand is indicated") which does not allow any practical application in the form of a defined, real treatment of a pathological condition. The objection could be overcome by either introducing in the claims a list of pathological conditions cited in the application, or by showing that means are available which would allow the skilled person to recognise which additional conditions would fall within the functional definition.

2.4 The expression "such as" used in claim 31 has no limiting effect on the scope of the claim. The features following this expression are therefore superfluous, thereby resulting in a lack of conciseness of the claim.

3 Novelty

D1 relates to ligands of the histamine-3 (H_3) receptor. The compounds of D1 generally comprise already certain present compounds (1) wherein Y is oxygen or nitrogen (cf. D1, claim 1, R^5 = heterocycle substituted with aminoalkyl, carboxy, carboxy-alkyl, cyano corresponding with the present substituent X), but the document does not specifically disclose compounds (1) with the present X-substituted Y-comprising heterocycles. Consequently, the present claimed matter is considered novel vis-à-vis D1.

D2 discloses H_3 ligands, from which the present compounds differ through the substituent X (cf. D2, claim 1, wherein R^2 or R^3 = W = cycloalkyl optionally substituted with halo, amino, nitro, hydroxyl, alkyl; or wherein R^2 or R^3 = G(II) wherein R^7 is hydrogen, hydroxyl, halo, C_{1-6}alkoxy; and e.g. page 131, example 80). The claimed matter is thus novel in view of D2.

D3 discloses further H_3 ligands, from which the present compounds differ through the ring size of the Y-comprising ring moiety and through the nature of X (cf. D3, claim 1, R^4 and R^5 together form a cyclopropane ring, X = O, NR^7, S; and e.g. page 111, examples 240, 241).

D4 shows fungicides which generally comprise the present compounds (1) (cf. D4, claim 1, R^1 = substituted alkyl, and pages 26-27, examples 168-170). However, the document does not specifically disclose compounds with the present value X. The claimed matter is thus considered novel vis-à-vis D4.

D5 relates to the alkaloid arnisin, from which the present compounds (1) differ only through the substituent X (D5: $-(CH_2)_2-NMe_2$; present e.g. $-CH_2-NR^1R^2$). The claimed matter is novel vis-à-vis D5.

D6 relates to beta-adrenolytic 4'-(3-alkylamino-2-hydroxy-propoxy)-benzonitriles from which the present compounds (1) differ only through the missing 2-hydroxy group. The subject-matter of the present claims is thus considered novel vis-à-vis D6. However, metabolites of compounds (1) would not be considered novel over the compounds of D6, unless the applicant was able to provide substantiated evidence that the compounds of D6 were not metabolites of the present compounds (1).

In view of the cited prior art, the present set of claims appears to comply with the criterion of novelty.

4 Inventive Step

4.1 The application describes the synthesis of certain compounds (1) and shows that such compounds bind to the H_3 receptor with $K_i < 5$ µM (the application, pages 202-203).

4.2 D1 to D3 disclose already H_3 ligands. The present compounds (1) differ from those of D1 through the X-substituted and Y-comprising ring moiety. They differ from the compounds of D2 through the substituent X; and they differ from the compounds of D3 through the ring size of the Y-comprising ring and the nature of X. D2 may be considered as most relevant state of the art, because it discloses already structurally related H_3 ligands (e.g. example 80) from which the present compounds (1) differ only through the additional X substituent. Starting from D2 the problem underlying the application may be seen in the provision of further H_3 ligands. D2 and the documents D1 and D3 in general allow already certain substituents at a ring corresponding with the present Y-comprising ring moiety. However, they not unequivocally indicate that the present compounds (1), having specific X-substituents at a very specific position at the Y-comprising ring, would retain the desired activity. Consequently, the subject-matter of the claims 1-35 appears to involve an inventive step.

4.3 However, no inventive step would be acknowledged for isomers and metabolites of compounds (1), because it is not plausible that substantially all isomers and

metabolites of the present compounds (1) exhibit the desired activity at the H_3 receptor and provide a solution of the problem underlying the application.

5 Industrial Applicability

For the assessment of the present claim 32 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

See item V.2 above.

OLARTERAISBECK 06/21/2006

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-108741- -00000-0000
Fec: 2006-10-26 17:22:36 Dep: 2000 NUECREACIONES
Tra: 11 PATENTEIYII
Eve: 979 FASENACIONALII

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL 07-Dic-06

SOLICITUD DE:

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

[ ] Capítulo I. [X] Capítulo II.

(3) **SOLICITANTE (71)**	**Nombre:** WARNER LAMBERT COMPANY LLC **Dirección:** 201 Tabor Road, Morris Plains, New Jersey 07950, E.U.A. **Nacionalidad o Domicilio:** ESTADOUNIDENSE **Lugar de Constitución:** Estados Unidos de América. **Teléfono:** _____ **Fax:** _____ **E-mail:** _____	**IDENTIFICACIÓN** **C.C.** [ ] **NIT** [ ] **C.E.** [ ] **tro** [ ] **Cual** _____ **Número** _____
REPRESENTANTE APODERADO	**Nombre:** CARLOS R. OLARTE **Dirección:** World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10 **Teléfono:** 601-7700 **Fax:** 601-7799 **E-mail:** office@olarteraisbeck.com	**IDENTIFICACIÓN** **C.C.** [X] **NIT** [ ] **C.E.** [ ] **tro** [ ] **Cual** _____ **Número** 79782747Bta **TP** 74.295
INVENTOR (ES) (72)	**Nombre:** VER PAGINA ADJUNTA **Dirección:** VER PAGINA ADJUNTA **Nacionalidad o Domicilio:** VER PAGINA ADJUNTA	

(5) **PCT (86)**

Solicitud Internacional No. PCT/IB2005/001114 Fecha Abril 19, 2005

Publicación Internacional No. WO 2005/108384 A1 Fecha Noviembre 17, 2005

(6) **Título (54)** **DERIVADOS DE FENOL Y TIOFENOL 3- O 4-MONOSUSTITUIDOS UTILES COMO LIGANDOS DE H3.**

Clasificación Internacional (51) **C07D 309/06, 405/12, 309/08, 295/12, 405/06, 405/14, 295/14, 417/04, 417/06, A61K 31/55, A61P 25/06, C07D 405/14, 405/06, 405/12, 405/04.**

Prioridad SI [X] N [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
EP	Mayo 7, 2004	04291187.5
GB	Marzo 4, 2005	0504564.6

(9) **Comprobante de pago No.** 06-81.843 **Fecha** ctubre 24, 2006

615
3

LISTA DE INVENTORES PCT/IB2005/001114

Patrick BERNARDELLI
Ramsgate Road, Sandwich,
Kent CTI3 9NJ,
Reino Unido,
Nacionalidad: Francesa

ANDREW MICHAEL CRONIN
Ramsgate Road, Sandwich,
Kent CTI3 9NJ,
Reino Unido
Nacionalidad: Británica

ALEXIS DENIS
Ramsgate Road, Sandwich,
Kent CTI3 9NJ,
Reino Unido
Nacionalidad: Francesa

STEPHEN MARTIN DENTON
Ramsgate Road, Sandwich,
Kent CTI3 9NJ,
Reino Unido
Nacionalidad: Británica

HENRY JACOBELLI
Ramsgate Road, Sandwich,
Kent CTI3 9NJ,
Reino Unido
Nacionalidad: Francesa

MARK IAN KEMP
Ramsgate Road, Sandwich,
Kent CTI3 9NJ,
Reino Unido
Nacionalidad: Británica

EDWIGE LORTHIOIS
Ramsgate Road, Sandwich,
Kent CTI3 9NJ,
Reino Unido
Nacionalidad: Francesa

FIONA ROUSSEAU
Ramsgate Road, Sandwich,
Kent CTI3 9NJ,
Reino Unido
Nacionalidad: Británica

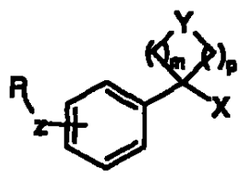
DELPHINE SERRADEIL-CIVIT
Ramsgate Road, Sandwich,
Kent CTI3 9NJ,
Reino Unido
Nacionalidad: Francesa

FABRICE VERGNE,
Ramsgate Road, Sandwich,
Kent CTI3 9NJ,
Reino Unido
Nacionalidad: Francesa

Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes

REIVINDICACIONES

1. Un compuesto de fórmula (1):



(1)

o una sal farmacéuticamente aceptable y/o un solvato (incluyendo hidrato) del mismo donde:

el sustituyente de fórmula -Z-R está en la posición meta o para del grupo fenilo;

X se selecciona entre -CN, $-CH_2OH$, $-CH_2$-O-alquilo (C_1-C_4), -C(O)OH, -C(O)Oalquilo (C_1-C_4), $-CH_2-NR^1R^2$, $-C(O)NR^3R^4$, $-CH_2$-O-het^2, $-CH_2$-het^1 y het^1, estando el grupo het^1 tanto en $-CH_2$-het^1 como en het^1 opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, ciano, alquilo (C_1-C_4), -S-alquilo (C_1-C_4) y alcoxi(C_1-C_4);

R^1 es hidrógeno o alquilo (C_1-C_4) opcionalmente sustituido con cicloalquilo (C_3-C_6);

R^2 se selecciona entre el grupo compuesto por:

hidrógeno,

alquilo (C_1-C_6) opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre cicloalquilo (C_3-C_6), hidroxi, -S-alquilo (C_1-C_4), -O-alquilo (C_1-C_4), $-SO_2$-alquilo (C_1-C_4), -SO-alquilo (C_1-C_4), halo, het^1, amino, alquil (C_1-C_4)amino, [alquil

$(C_1-C_4)]_2$amino y fenilo, estando dicho fenilo opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, hidroxi, ciano, alquilo (C_1-C_4) y alcoxi(C_1-C_4),

cicloalquilo (C_3-C_8),

het^2, opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, ciano, alquilo (C_1-C_4), NH_2 y alcoxi(C_1-C_4),

$-SO_2-R^5$ donde R^5 se selecciona entre el grupo compuesto por alquilo (C_1-C_4), amino, alquil (C_1-C_4)amino, [alquil $(C_1-C_4)]_2$amino, fenilo y -alquil (C_1-C_4)-fenilo, estando dicho fenilo opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, ciano, alquilo (C_1-C_4) y alcoxi(C_1-C_4), y

$-C(O)-R^6$ donde R^6 se selecciona entre el grupo compuesto por alquilo (C_1-C_4), amino, alquil (C_1-C_4)amino, [alquil $(C_1-C_4)]_2$amino, fenilo y -alquil (C_1-C_4)-fenilo, estando dicho fenilo opcionalmente sustituido con uno o dos sustituyentes seleccionados independientemente entre halo, ciano, alquilo (C_1-C_4) y alcoxi(C_1-C_4);

o R^1 y R^2 forman conjuntamente con el átomo de N al que están unidos un heterociclo saturado de 3, 4, 5, 6 ó 7 miembros donde un átomo de C puede reemplazarse por N, O, S, SO o SO_2 y donde dicho heterociclo saturado está opcionalmente sustituido con uno o dos grupos seleccionados independientemente entre hidroxi, halo, =O, alquilo (C_1-C_4), -alquil (C_1-C_4)cicloalquilo (C_3-C_8), alcoxi(C_1-C_4), hidroxialquilo (C_1-C_4), alcoxi(C_1-C_4)alquilo (C_1-C_4), $-SO_2$alquilo (C_1-C_4), -C(O)alquilo (C_1-C_4), [alquil $(C_1-C_4)]_2$amino, amino,

alquil (C_1-C_4)amino, -C(O)NH_2, C(O)Oalquilo (C_1-C_4) y pirrolidinona;

Cada uno de R^3 y R^4 se selecciona independientemente entre hidrógeno, cicloalquilo (C_3-C_8), y alquilo (C_1-C_4), estando dicho cicloalquilo (C_3-C_8) y alquilo (C_1-C_4) opcionalmente sustituidos con amino, alquil (C_1-C_4)amino, [alquil (C_1-C_4)]$_2$amino o cicloalquilo (C_3-C_8), o R^3 y R^4 forman junto con el átomo de N al que están unidos un heterociclo saturado de 4, 5, 6 ó 7 miembros donde un átomo de C puede reemplazarse por N u O y donde dicho heterociclo saturado está opcionalmente sustituido con alquilo (C_1-C_4), [alquil (C_1-C_4)]$_2$amino, amino, alquil (C_1-C_4)amino, o -C(O)alquilo (C_1-C_4), estando dicho -C(O)alquilo (C_1-C_4) opcionalmente sustituido con metoxi o etoxi,

Y se selecciona entre CH_2, CH(OH), O, C=O y N, estando dicho N sustituido con H, alquilo (C_1-C_4), C(O)alquilo (C_1-C_4) o alcoxi (C_1-C_4)alquilo (C_1-C_4);

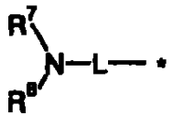
Z se selecciona entre O, S, SO y SO_2;

m y p son ambos números enteros que son independientemente 1, 2 ó 3, con la condición de que m+p sea igual a o menor que 4 de forma que el anillo formado por:



sea un anillo de 4, 5 ó 6 miembros;

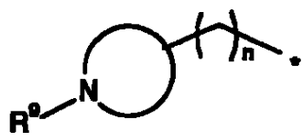
y R es un grupo de fórmula:



en la que * representa el punto de unión a Z, L es un alquileno (C_2-C_6) de

cadena lineal o ramificada y cada uno de R^7 y R^8 se selecciona independientemente entre hidrógeno, alquilo (C_1-C_8), cicloalquilo (C_3-C_8), hidroxialquilo (C_1-C_8) o R^7 y R^8 forman junto con el átomo de N al que están unidos un heterociclo saturado de 4, 5, 6 ó 7 miembros donde un átomo de C está opcionalmente reemplazado por N, O, S, SO o SO_2 y donde dicho heterociclo saturado está opcionalmente sustituido con uno o dos grupos seleccionados independientemente entre alquilo (C_1-C_4), alcoxi (C_1-C_4), alcoxi (C_1-C_4)-alquilo (C_1-C_4), hidroxialquilo (C_1-C_4), hidroxi, C(O)Oalquilo (C_1-C_4), -C(O)-alquil (C_1-C_4)-NH_2, -$C(O)NH_2$, halo, amino, alquil (C_1-C_4)amino y [alquil (C_1-C_4)]$_2$amino,

o R es un grupo de fórmula:



en la que * representa el punto de unión a Z, el anillo que contiene N es un heterociclo saturado de 4 a 7 miembros, n es un número entero igual a 0, 1 ó 2, y R^9 representa un sustituyente seleccionado entre hidrógeno, alquilo (C_1-C_4), hidroxi(alquilo C_1-C_8) y cicloalquilo (C_3-C_8);

het^1 se selecciona entre grupos heteroaromáticos monocíclicos o bicíclicos que tienen de 5 a 10 miembros en el anillo, que contienen 1, 2, 3 ó 4 heteroátomo(s) seleccionado(s) entre nitrógeno, oxígeno y azufre y het^2 se selecciona entre grupos heteroaromáticos monocíclicos o bicíclicos que tienen de 5 a 10 miembros en el anillo, que contienen 1, 2, 3 ó 4 heteroátomo(s) seleccionado(s) entre nitrógeno, oxígeno y azufre.

620

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-108741- -00000-0000
Fec: 2006-10-25 17:22:36 Dep: 2000 NUECREACIONES
Tra: 11 PATENTES II
Ens: 379 PAGENACIONALES
Anex: 13 PRESENTACION ... Folios: 615

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [X]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [X] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Fdo B

Firma Responsable

Fecha 25-oct-6

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

621

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCI

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
WARNER LAMBERT COMPANY LLC.

REFERENCIA	Radicación No.	6 108741
	Solicitud internacional	PCT/IB2005/001114
	Fecha inicio fase nacional	07/12/2006
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	879

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 26 ENE 2007
lerazo