PCT

Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INVEN

10-35482

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: COMPUESTOS Y COMPOSICIONES COMO MODULARES DE LA ACTIVIDAD DE GPR119

SOLICITANTE: IRM LLC

DIRECCIÓN: 131 Front Street, P.O. Box HM 2899, Hamilton HM LX, Bermuda

APODERADO: CARLOS R. OLARTE

BOGOTÁ 25 de Marzo de 2010

P2010/000020

20-04-2010
No Excluir

OLARTERAISBECK

OLARTE RAISBECK MOURE &

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-035482- -00000-0000
Fecha: 2010-03-25 17:18:39 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 511

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2010/000020**

SOLICITUD DE:

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

[X] Capítulo I. [ ] Capítulo II.

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Lugar de Constitución: Bermuda
Teléfono: **Fax:**
E-mail:

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C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual
Número

REPRESENTANTE O APODERADO

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TP 74.295

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(5) **PCT (86)**

Solicitud Internacional No. PCT/US2008/075145 Fecha Septiembre 3, 2007

Publicación Internacional No. WO 2009/038974 Fecha Marzo 26, 2009

(6) **Título (54)** **COMPUESTOS Y COMPOSICIONES COMO MODULADORES DE LA ACTIVIDAD DE GPR119**

Clasificación Internacional (51) C07D 401/10, C07D 401/14, C07D 413/06, C07D 413/14, C07D 417/14, C07D 487/04, C07D 491/048, A61K 31/44, A61K 31/496, A61K 31/4965, A61P 3/10.

Prioridad **SI** [X] **NO** [ ]

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US	Septiembre 20, 2007	60/974.064
US	Abril 15, 2008	61/045.263

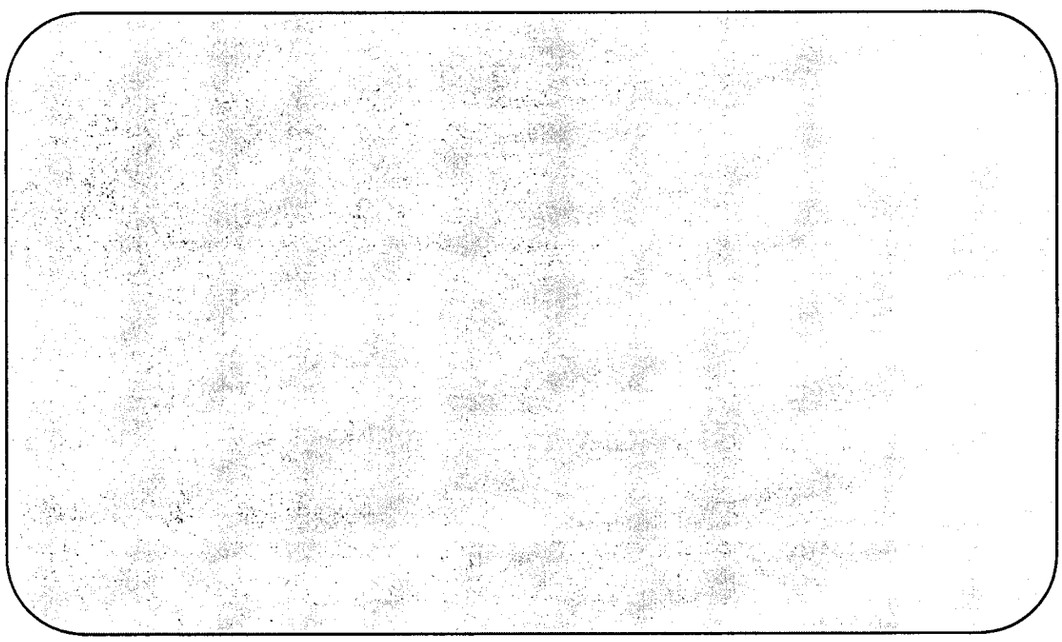
(9) **Comprobante de pago No.** **Fecha** Marzo 23, 2010

2

(10) **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple. Ver Exp. Nº 10-033.947.
- [ ] 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).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**



(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 23,449
FECHA : MARZO 25 DE 2010

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Tra. 11 PATENTEIYII Eve. 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 511

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	325578492	25/03/2010	3,794,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN		554,000.00
		TOTAL :	$	554,000.00

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Traducción oficial de un documento que está originalmente en inglés

CERTIFICACIÓN

Yo, el suscrito Notario de Derecho Común de Basilea, Suiza, Dr. Matthias Staehelin, certifico por medio del presente que las firmas adjuntas previamente son las firmas genuinas de la señora Biljana Colovic, ciudadana de Serbia, residente en Basilea, Suiza; y del Doctor Georg von Sprecher, ciudadano de Luzein, Suiza, y Parpan, Suizak, residente en Oberwill/BL, Suiza, ambos actuando en nombre de IRM LLC, en Hamilton, Bermuda, ambos como titulares comisionados, ambos con firma conjunta.

La autenticidad de las firmas se estableció por comparación.

Basilea, Suiza, este día 14 (catorce) de diciembre de 2009 (dos mil nueve).

(Firmado) M. Staehelin, Notario

Sello: Dr. M. Staehelin, Notario

Protocolo de Legalización No. 3253/2009

Apostilla:

Notaría Cuarenta y Seis del Círculo de Bogotá, como Notaría Cuarenta y Seis hago constar que esta copia coincide con documento original presentado para su autenticación. Bogotá D. C. - República de Colombia

03 FEB 2010

Eugenia Rojas de Arnedo
NOTARÍA CUARENTA Y SEIS

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

APOSTILLA:
(Convention de La Haye du 5 octobre 1961)

1. País:	Suiza
	El presente documento público
2. Ha sido firmado por:	Doctor en Jurisprudencia. M. Staehelin
3. Actuando en calidad de:	Notario Público
4. Lleva el sello/estampilla de:	El anteriormente mencionado
	Certificado
5. En:	Basilea.
6. El:	14 de diciembre de 2009
7. Por:	Cancillería municipal del Cantón de la ciudad de Basilea.
8. Bajo el No.:	8576/16899
9. Sello / estampilla:	Cancillería municipal · Ciudad de Basilea.
10. Firma:	Helena Schaffner

FIN DE LA TRADUCCIÓN

Certificación:
Certifico que la presente es una traducción auténtica y completa del inglés al español del documento adjunto, la cual he elaborado según mi leal saber y entender.
Documento: "IRM LLC – Certificación"
Fecha: 16 de enero de 2010.
Traductor: Jorge Enrique Sierra Reyes (Sello y firma digital debidamente registrados ante el Ministerio de Relaciones Exteriores de Colombia)
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NOTARIA CUARENTA Y SEIS

Traductor Oficial
JORGE E. SIERRA REYES
-encia 376 - 1993 Minjusticia

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OLARTE RAISBECK MOURE & CASTRO LTDA.

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Power of Attorney

The undersigned,
IRM LLC
a Delaware Limited Liability Company

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by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right** 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, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications, collect refunds, desist, settle, conciliate or negotiate. 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,

domiciliado en

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Juan Guillermo Moure y/o Natalia Castro** poder amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las **Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual** 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, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir, transigir, 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.

IRM LLC

Signature/Firma:

Biljana Colovic Dr. Georg von Sprecher
Authorized Signatories

Date/Fecha: December 9, 2009
City,Country/Ciudad,País: Basel, Switzerland

Notaría Cuarenta y Seis del Círculo de Bogotá, como Notaría Cuarenta y Seis hago constar que esta copia concuerda con documento original presentado para su autenticación. Bogotá, D.C. - República de Colombia
03 FEB 2010
Nohora Eugenia Rojas de Urquiza
NOTARIA CUARENTA Y SEIS

8

Attestation

I, the undersigned Civil Law Notary in Basel, Switzerland, Dr. Matthias Staehelin, certify herewith that the signatures attached heretofore are the genuine signatures of **Ms. Biljana Colovic**, citizen of Serbia, residing in Basel, Switzerland, and **Dr. Georg von Sprecher**, citizen of Luzein, Switzerland, and Parpan, Switzerland, residing in Oberwil/BL, Switzerland, both acting for **IRM LLC**, in Hamilton, Bermuda, both as proxy holders, both with joint signature.

The authenticity of the signatures was established by means of comparison.

BASEL, Switzerland, this 14th (fourteenth) day of December 2009 (two thousand and nine)

M. Staehelin, Notar

Dr. M. Staehelin
Notar

Leg.Prot.Nr. 3753 /2009

APOSTILLE
(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz/Suisse)
This official document
2. is signed by M. Staehelin
3. in his/her function as Notary public
and certified by the seal of the State Chancery
Certified 14. Dez. 2009
5. in Basel (Bâle) 6. on
7. by the State Chancery of the Canton of Basel-Stadt
8. no. 21726/6899
9. Seal/stamp: 10. Signature:

STATE CHANCERY * BASLE-CITY *

Notaría Quince y Seis del Círculo de Montevideo / Sexta Sede de Montevideo
Se deja constancia como Notaría Colaboradora que esta copia coincide con documento original presentado para su autenticación.
Montevideo - República de Colombia
05 FEB 2010
María Eugenia Rojas de Urgeia
NOTARIA

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

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61/045,263 15 April 2008 (15.04.2008) US

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

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Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report*

(54) Title: COMPOUNDS AND COMPOSITIONS AS MODULATORS OF GPR119 ACTIVITY

(57) Abstract: The invention provides compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with the activity of GPR119.

WO 2009/038974 A1

COMPOUNDS AND COMPOSITIONS AS MODULATORS OF GPR119 ACTIVITY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Patent Application Number 60/974,064, filed 20 September 2007 and U.S. Provisional Patent Application Number 61/045,263, filed 15 April 2008. The full disclosures of these applications are incorporated herein by reference in their entirety and for all purposes.

BACKGROUND OF THE INVENTION

Field of the Invention

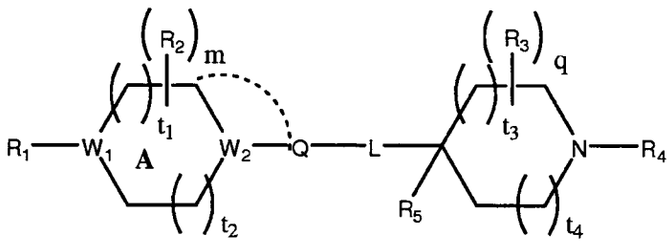
[0002] The invention provides compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with the activity of GPR119.

Background

[0003] GPR119 is a G-protein coupled receptor (GPCR) that is mainly expressed in the pancreas, small intestine, colon and adipose tissue. The expression profile of the human GPR119 receptor indicates its potential utility as a target for the treatment of obesity and diabetes. The novel compounds of this invention modulate the activity of GPR119 and are, therefore, expected to be useful in the treatment of GPR119-associated diseases or disorders such as, but not limited to, diabetes, obesity and associated metabolic disorders.

SUMMARY OF THE INVENTION

[0004] In one aspect, the present invention provides a compound of Formula I:



[0005] in which:

[0006] Q is a divalent or trivalent radical selected from C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}cycloalkyl and C_{3-8}heterocycloalkyl; wherein said aryl, heteroaryl, cycloalkyl or heterocycloalkyl of Q is optionally substituted with up to 3 radicals independently selected from halo, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, $-C(O)R_{20}$ and $-C(O)OR_{20}$; wherein R_{20} is selected from hydrogen and C_{1-6}alkyl; and optionally connecting a carbon adjacent to W_2 through a CR_{31}, O, S or NR_{31} with a carbon of Q (indicated by the dotted line) to form a 5-membered ring fused to rings A and Q (such as the fused rings in examples V1-V5, *infra*); wherein R_{31} is selected from hydrogen and C_{1-6}alkyl;

[0007] W_1 and W_2 are independently selected from CR_{21} and N; wherein R_{21} is selected from hydrogen, cyano, C_{1-6}alkyl and $-C(O)OR_{25}$; wherein R_{25} is selected from hydrogen and C_{1-6}alkyl; ring A can have up to 2 ring carbons substituted with a group selected from –C(O)–, –C(S)– and $-C(=NOR_{30})-$ and can be partially unsaturated with up to 2 double bonds; wherein R_{30} is selected from hydrogen and C_{1-6}alkyl;

[0008] L is selected from C_{1-6}alkylene, C_{2-6}alkenylene, $-(CH_2)_nO-$, $-OC(O)(CH_2)_n-$, $-C(O)O(CH_2)_n-$, $-NR_{26}(CH_2)_n-$ and $-O(CH_2)_n-$; wherein R_{26} is selected from hydrogen and C_{1-6}alkyl; and n is selected from 0, 1, 2, 3, 4 and 5; wherein any alkyl of L can be optionally substituted with 1 to 3 radicals independently selected from halo, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, $-C(O)R_{22}$ and $-C(O)OR_{22}$; wherein R_{22} is selected from hydrogen and C_{1-6}alkyl;

[0009] m is selected from 0, 1, 2, 3 and 4;

[0010] q is selected from 0, 1, 2, 3 and 4;

[0011] t_1, t_2, t_3 and t_4 are each independently selected from 0, 1 and 2;

[0012] R_1 is selected from $-X_1S(O)_{0-2}X_2R_{6a}$, $-X_1S(O)_{0-2}X_2OR_{6a}$, $-X_1S(O)_{0-2}X_2C(O)R_{6a}$, $-X_1S(O)_{0-2}X_2C(O)OR_{6a}$, $-X_1S(O)_{0-2}X_2OC(O)R_{6a}$ and $-X_1S(O)_{0-2}NR_{6a}R_{6b}$; wherein X_1 is selected from a bond, O, $NR_{7a}R_{7b}$ and C_{1-4}alkylene; X_2 is selected from a bond and C_{1-4}alkylene; R_{6a} is selected from hydrogen, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}heterocycloalkyl and C_{3-8}cycloalkyl; wherein said aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R_{6a} is optionally substituted with 1 to 3 radicals independently selected from hydroxy, halo, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, cyano-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy and C_{6-10}aryl-C_{1-4}alkoxy; R_{6b} is selected from hydrogen and C_{1-6}alkyl; and R_{7a} and R_{7b} are independently selected from hydrogen and C_{1-6}alkyl;

[0013] R_2 and R_3 are independently selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, $-C(O)R_{23}$, and $-C(O)OR_{23}$; wherein R_{23} is selected from hydrogen and C_{1-6}alkyl;

[0014] R_4 is selected from R_8 and $-C(O)OR_8$; wherein R_8 is selected from C_{1-6}alkyl, C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}cycloalkyl and C_{3-8}heterocycloalkyl; wherein said aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_8 is optionally substituted with 1 to 3 radicals independently selected from halo, C_{1-6}alkyl, C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy and halo-substituted-C_{1-6}alkoxy;

[0015] R_5 is selected from hydrogen, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy and halo-substituted-C_{1-6}alkoxy.

[0016] In a second aspect, the present invention provides a pharmaceutical composition which contains a compound of Formula I or a N-oxide derivative, individual isomers and mixture of isomers thereof; or a pharmaceutically acceptable salt thereof, in admixture with one or more suitable excipients.

[0017] In a third aspect, the present invention provides a method of treating a disease in an animal in which modulation of GPR119 activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the diseases, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula

I or a N-oxide derivative, individual isomers and mixture of isomers thereof, or a pharmaceutically acceptable salt thereof.

[0018] In a fourth aspect, the present invention provides the use of a compound of Formula I in the manufacture of a medicament for treating a disease in an animal in which GPR119 activity contributes to the pathology and/or symptomology of the disease.

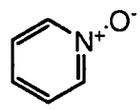
[0019] In a fifth aspect, the present invention provides a process for preparing compounds of Formula I and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixture of isomers thereof, and the pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0020] "Alkyl" as a group and as a structural element of other groups, for example halo-substituted-alkyl and alkoxy, can be straight-chained, branched, cyclic or spiro. C_{1-6}alkoxy includes methoxy, ethoxy, and the like. Halo-substituted alkyl includes trifluoromethyl, pentafluoroethyl, and the like.

[0021] "Aryl" means a monocyclic or fused bicyclic aromatic ring assembly containing six to ten ring carbon atoms. For example, aryl can be phenyl or naphthyl, preferably phenyl. "Arylene" means a divalent radical derived from an aryl group. "Heteroaryl" is as defined for aryl where one or more of the ring members are a heteroatom. For example, C_{1-10}heteroaryl includes pyridyl, indolyl, indazolyl, quinoxalinyl, quinolinyl, benzofuranyl, benzopyranyl, benzothiopyranyl, benzo[1,3]dioxole, imidazolyl, benzo-imidazolyl, pyrimidinyl, furanyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazolyl, thienyl, 1H-pyridin-2-onyl, 6-oxo-1,6-dihydro-pyridin-3-yl, etc. "C_{6-10}arylC_{0-4}alkyl" means an aryl as described above connected via a alkylene grouping. For example, C_{6-10}arylC_{0-4}alkyl includes phenethyl, benzyl, etc. Heteroaryl also includes the N-oxide derivatives, for example, pyridine N-oxide derivatives with the following structure:



[0022] "Cycloalkyl" means a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing the number of ring atoms indicated. For example, C_{3-10}cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. "Heterocycloalkyl" means cycloalkyl, as defined in this application, provided that one or more of the ring carbons indicated, are replaced by a moiety selected from -O-, -N=, -NR-, -C(O) -, -S-, -S(O) - or -$S(O)_2$-, wherein R is hydrogen, C_{1-4}alkyl or a nitrogen protecting group. For example, C_{3-8}heterocycloalkyl as used in this application to describe compounds of the invention includes morpholino, pyrrolidinyl, piperazinyl, piperidinyl, piperidinylone, 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl, 2-oxo-pyrrolidin-1-yl, 2-oxo-piperidin-1-yl, etc.

[0023] GPR119 means G protein-coupled receptor 119 (GenBank® Accession No. AAP72125) is also referred to in the literature as RUP3 and GPR116. The term GPR119 as used herein includes the human sequences found in GeneBank accession number AY288416, naturally-occurring allelic variants, mammalian orthologs, and recombinant mutants thereof.

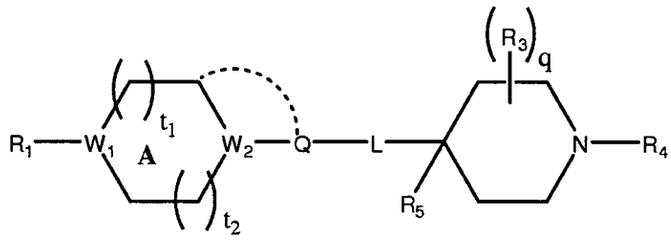
[0024] "Halogen" (or halo) preferably represents chloro or fluoro, but can also be bromo or iodo.

[0025] "Treat", "treating" and "treatment" refer to a method of alleviating or abating a disease and/or its attendant symptoms.

Description of the Preferred Embodiments

[0026] The present invention provides compounds, compositions and methods for the treatment of diseases in which modulation of GPR119 activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the diseases, which method comprises administering to the animal a therapeutically effective amount of a compound of Formula I.

[0027] In one embodiment, with reference to compounds of Formula I, are compounds of of Formula Ia:



[0028] in which:

[0029] Q is a divalent or trivalent radical selected from C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}cycloalkyl and C_{3-8}heterocycloalkyl; wherein said aryl, heteroaryl, cycloalkyl or heterocycloalkyl of Q is optionally substituted with up to 3 radicals independently selected from halo, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, $-C(O)R_{20}$ and $-C(O)OR_{20}$; wherein R_{20} is selected from hydrogen and C_{1-6}alkyl; and optionally connecting a carbon adjacent to W_2 through a CR_{31} or O with a carbon of Q (indicated by the dotted line in Formula Ia) to form a 5-membered ring fused to rings A and Q (such as the fused rings in examples V1-V5, *infra*); wherein R_{31} is selected from hydrogen and C_{1-6}alkyl;

[0030] W_1 and W_2 are independently selected from CR_{21} and N; wherein R_{21} is selected from hydrogen, cyano, C_{1-6}alkyl and $-C(O)OR_{25}$; wherein R_{25} is selected from hydrogen and C_{1-6}alkyl; ring A can have up to 2 ring carbons substituted with a group selected from –C(O)–, –C(S)– and $-C(=NOR_{30})-$ and can be partially unsaturated with up to 2 double bonds; wherein R_{30} is selected from hydrogen and C_{1-6}alkyl;

[0031] L is selected from C_{1-6}alkylene, C_{2-6}alkenylene, $-(CH_2)_nO-$, $-NR_{26}CH_2)_n-$, $-OC(O)(CH_2)_n-$, $-C(O)O(CH_2)_n-$ and $-O(CH_2)_n-$; wherein R_{26} is selected from hydrogen and C_{1-6}alkyl; wherein n is selected from 0, 1, 2, 3, 4 and 5; wherein any alkyl of L can be optionally substituted with 1 to 3 radicals independently selected from halo, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, $-C(O)R_{22}$ and $-C(O)OR_{22}$; wherein R_{22} is selected from hydrogen and C_{1-6}alkyl;

[0032] t_1 and t_2 are each independently selected from 0, 1 and 2;

[0033] q is selected from 0, 1, 2, 3 and 4;

[0034] R_1 is selected from $-X_1S(O)_{0-2}X_2R_{6a}$, $-X_1S(O)_{0-2}X_2OR_{6a}$, $-X_1S(O)_{0-2}X_2C(O)R_{6a}$, $-X_1S(O)_{0-2}X_2C(O)OR_{6a}$, $-X_1S(O)_{0-2}X_2OC(O)R_{6a}$ and $-X_1S(O)_{0-2}NR_{6a}R_{6b}$;

wherein X_1 is selected from a bond, O, $NR_{7a}R_{7b}$ and C_{1-4}alkylene; X_2 is selected from a bond and C_{1-4}alkylene; R_{6a} is selected from hydrogen, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}heterocycloalkyl and C_{3-8}cycloalkyl; wherein said aryl, heteroaryl, cycloalkyl and heterocycloalkyl of R_{6a} is optionally substituted with 1 to 3 radicals independently selected from hydroxy, halo, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, cyano-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy and C_{6-10}aryl-C_{1-4}alkoxy; R_{6b} is selected from hydrogen and C_{1-6}alkyl; and R_{7a} and R_{7b} are independently selected from hydrogen and C_{1-6}alkyl;

[0035] R_3 is selected from hydrogen, halo, hydroxy, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkoxy, $-C(O)R_{23}$, and $-C(O)OR_{23}$; wherein R_{23} is selected from hydrogen and C_{1-6}alkyl;

[0036] R_4 is selected from R_8 and $-C(O)OR_8$; wherein R_8 is selected from C_{1-6}alkyl, C_{6-10}aryl, C_{1-10}heteroaryl, C_{3-8}cycloalkyl and C_{3-8}heterocycloalkyl; wherein said aryl, heteroaryl, cycloalkyl or heterocycloalkyl of R_8 is optionally substituted with 1 to 3 radicals independently selected from halo, C_{1-6}alkyl, C_{3-12}cycloalkyl, C_{3-8}heterocycloalkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy and halo-substituted-C_{1-6}alkoxy;

[0037] R_5 is selected from hydrogen, C_{1-6}alkyl, halo-substituted-C_{1-6}alkyl, hydroxy-substituted-C_{1-6}alkyl, C_{1-6}alkoxy and halo-substituted-C_{1-6}alkoxy.

[0038] In a further embodiment, Q is a divalent or trivalent radical selected from phenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, 1,2,4-oxadiazolyl, and thiazolyl; wherein said phenyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl and thiazolyl of Q is optionally substituted with up to 3 radicals independently selected from halo, C_{1-6}alkyl, C_{1-6}alkoxy, halo-substituted-C_{1-6}alkyl, $-C(O)OR_{20}$ and $-C(O)R_{20}$; wherein R_{20} is selected from hydrogen and C_{1-6}alkyl; and optionally connecting a carbon adjacent to W_2 through a CR_{31} or O with a carbon of Q to form a 5-membered ring fused to rings A and Q; wherein R_{31} is selected from hydrogen and C_{1-6}alkyl.

[0039] In a further embodiment, W_1 and W_2 are independently selected from CR_{21} and N; wherein R_{21} is selected from hydrogen, cyano, C_{1-6}alkyl and $-C(O)OR_{25}$; wherein R_{25} is selected from hydrogen and C_{1-6}alkyl; ring A can have a ring carbon substituted with a group selected from $-C(O)-$, $-C(S)-$ and $-C(=NOR_{30})-$ and can be partially

unsaturated with a double bond; wherein R_{30} is selected from hydrogen and C_{1-6}alkyl; and L is selected from $-O(CH_2)_{0-4}-$, $-(CH=CH)-$, $-OC(O)-$, $-NH(CH_2)_{0-4}-$, $-NCH_3(CH_2)_{0-4}-$ and $-(CH_2)_{1-4}-$.

[0040] In another embodiment, $R_1$is selected from $-X_1S(O)_{0-2}X_2R_{6a}$, $-X_1S(O)_{0-2}X_2OR_{6a}$, $-X_1S(O)_{0-2}X_2C(O)OR_{6a}$, $-X_1S(O)_{0-2}X_2OC(O)R_{6a}$ and $-X_1S(O)_{0-2}NR_{6a}R_{6b}$; wherein X_1 is selected from a bond and O; X_2 is selected from a bond and C_{1-4}alkylene; R_{6a} is selected from hydrogen, halo, cyano, methyl, ethyl, propyl, isopropyl, ethenyl, pyridinyl, pyrrolidinyl, piperidinyl, morpholino, isoxazolyl, tetrazolyl, phenyl and imidazolyl; wherein said piperidinyl, pyridinyl, pyrrolidinyl, morpholino, isoxazolyl, tetrazolyl, phenyl or imidazolyl of R_{6a} is optionally substituted with 1 to 3 radicals independently selected from hydroxy, halo, C_{1-6}alkyl and benzoxy; and R_{6b} is selected from hydrogen, methyl and ethyl.

[0041] In another embodiment, R_4 is selected from R_8 and $-C(O)OR_8$; wherein R_8 is selected from isopropyl, cyclopropyl, t-butyl, 1,2,4-oxadiazolyl, pyrimidinyl, pyridinyl, pyridazinyl, tetrahydro-2H-pyranyl, tetrahydrofuranyl, oxetanyl, 2H-tetrazolyl and thiazolyl; wherein said cyclopropyl, 1,2,4-oxadiazolyl, pyrimidinyl, pyridinyl, pyridazinyl, tetrahydro-2H-pyranyl, tetrahydrofuranyl, oxetanyl, 2H-tetrazolyl or thiazolyl of R_8 is optionally substituted with 1 to 3 radicals independently selected from halo, trifluoromethyl, isopropyl, t-butyl, methyl, ethyl and cyclopropyl optionally substituted with methyl; and R_5 is selected from hydrogen and methoxy.

[0042] In another embodiment are compounds selected from: isopropyl 4-((4-((4-methanesulfonylpiperazin)-1-yl)phenoxy)methyl)piperidine-1-carboxylate, isopropyl 4-(2-(4-(4-(methylsulfonyl)piperazin-1-yl)phenoxy)ethyl)piperidine-1-carboxylate, isopropyl 4-(3-(4-(4-(methylsulfonyl)piperazin-1-yl)phenoxy)propyl)piperidine-1-carboxylate, isopropyl 4-(4-(4-(4-(methylsulfonyl)piperazin-1-yl)phenoxy)butyl)piperidine-1-carboxylate, Isopropyl 4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate, *tert*-Butyl 4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate, Isopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, *tert*-Butyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 3-Cyclopropyl-5-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, 5-

Cyclopropyl-3-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, 2-(4-(Methylsulfonyl)piperazin-1-yl)-5-((1-(5-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)methoxy)pyrazine, 5-Isopropyl-3-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, Tetrahydro-2H-pyran-4-yl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, (S)-Tetrahydrofuran-3-yl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, (R)-Tetrahydrofuran-3-yl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 2-Isopropyl-5-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)thiazole, 2-((1-(2-methyl-2H-tetrazol-5-yl)piperidin-4-yl)methoxy)-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazine, Oxetan-3-yl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, Isopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate, Isopropyl 4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridazin-3-yloxy)methyl)piperidine-1-carboxylate, Isopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrimidin-2-yloxy)methyl)piperidine-1-carboxylate, (E)-isopropyl 4-(2-(6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yl)vinyl)piperidine-1-carboxylate, Isopropyl 4-(2-(6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yl)ethyl)piperidine-1-carboxylate, (E)-Isopropyl 4-(2-(2-(4-(methylsulfonyl)piperazin-1-yl)pyrimidin-5-yl)vinyl)piperidine-1-carboxylate, 5-Ethyl-2-(4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)pyrimidine, 1-(Methylsulfonyl)-4-(5-((1-(5-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)methoxy)pyridin-2-yl)piperazine, 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 5-Ethyl-2-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)pyrimidine, 2-((1-(5-Methylpyridin-2-yl)piperidin-4-yl)methoxy)-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazine, 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate, 5-Ethyl-2-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyridin-2-yloxy)methyl)piperidin-1-yl)pyrimidine, 3-Isopropyl-5-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, 3-Isopropyl-5-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyridin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, 1-Methylcyclopropyl 4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate, 5-

Isopropyl-3-(4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, 2-((1-(5-Fluoropyridin-2-yl)piperidin-4-yl)methoxy)-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazine, 3-Isopropyl-5-(4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, *tert*-Butyl 4-((5-(4-(methylsulfonyl)-1,4-diazepan-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, *tert*-Butyl 4-((5-(4-(methylsulfonyl)-1,4-diazepan-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, *tert*-butyl 4-((5-(4-(methylsulfonyl)piperidin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)piperidin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, *tert*-Butyl 4-(2-(3-(4-(methylsulfonyl)piperazin-1-yl)-1,2,4-oxadiazol-5-yl)ethyl)piperidine-1-carboxylate, *tert*-Butyl 4-(3-(3-(4-(methylsulfonyl)piperazin-1-yl)-1,2,4-oxadiazol-5-yl)propyl)piperidine-1-carboxylate, 5-(3-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)propyl)-3-(4-(methylsulfonyl)piperazin-1-yl)-1,2,4-oxadiazole, Isopropyl 4-(3-(3-(4-(methylsulfonyl)piperazin-1-yl)-1,2,4-oxadiazol-5-yl)propyl)piperidine-1-carboxylate, 3-Isopropyl-5-(4-(2-(5-(4-(methylsulfonyl)piperazin-1-yl)thiazol-2-yl)ethyl)piperidin-1-yl)-1,2,4-oxadiazole, Isopropyl 4-((4-(1-methanesulfonyl-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)methyl)piperidine-1-carboxylate, isopropyl 4-(4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)piperidine-1-carboxylate, isopropyl 4-(2-(4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)ethyl)piperidine-1-carboxylate, isopropyl 4-(3-(4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)propyl)piperidine-1-carboxylate, isopropyl 4-(4-(4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)butyl)piperidine-1-carboxylate, 1-methylcyclopropyl 4-((4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)methyl)piperidine-1-carboxylate, 5-isopropyl-3-(4-((4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, Isopropyl 4-((4-(1-methanesulfonylpiperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate, isopropyl 4-(4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)piperidine-1-carboxylate, isopropyl 4-(2-(4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)ethyl)piperidine-1-carboxylate, isopropyl 4-(3-(4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)propyl)piperidine-1-carboxylate, isopropyl 4-(4-(4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)butyl)piperidine-1-carboxylate, 1-Methylcyclopropyl 4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-

carboxylate, 2-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)-5-(trifluoromethyl)pyridine, 5-isopropyl-3-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, 3-chloro-2-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)-5-(trifluoromethyl)pyridine, 5-chloro-2-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)pyridine, 3-chloro-6-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)pyridazine, 5-bromo-2-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)pyrimidine, 5-ethyl-2-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)pyrimidine, 5-fluoro-2-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)pyridine, 3-isopropyl-5-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole, 3-tert-butyl-6-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)pyridazine, 5-fluoro-2-(4-((4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)pyrimidine, Isopropyl 4-(2-(3-(1-methanesulfonyl-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)ethyl)piperidine-1-carboxylate, 1-Methylcyclopropyl 4-methoxy-4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 1-methylcyclopropyl 4-((6-formyl-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 1-Methylcyclopropyl 4-((6-chloro-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 1-Methylcyclopropyl 4-((5-(4-(3-methoxy-3-oxopropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate, 3-(4-(5-((1-((1-methylcyclopropoxy)carbonyl)-piperidin-4-yl)methoxy)pyrazin-2-yl)piperazin-1-ylsulfonyl)propanoic acid, 3-(4-(5-((1-((1-methylcyclopropoxy)carbonyl)piperidin-4-yl)methoxy)pyrazin-2-yl)piperazin-1-ylsulfonyl)propanoic acid, 3-(4-(5-((1-((1-methylcyclopropoxy)carbonyl)piperidin-4-yl)methoxy)pyrazin-2-yl)piperazin-1-ylsulfonyl)propanoic acid, 3-(4-(5-((1-((1-methylcyclopropoxy)carbonyl)piperidin-4-yl)methoxy)pyrazin-2-yl)piperazin-1-ylsulfonyl)propanoic acid, 3-(4-(5-((1-((1-methylcyclopropoxy)carbonyl)piperidin-4-yl)methoxy)pyrazin-2-yl)piperazin-1-ylsulfonyl)propanoic acid, 3-(4-(5-((1-((1-methylcyclopropoxy)carbonyl)piperidin-4-yl)methoxy)pyrazin-2-yl)piperazin-1-ylsulfonyl)propanoic acid; 1-methylcyclopropyl 4-((5-(4-(3-cyanopropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-(1H-

tetrazol-5-yl)propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(vinylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(2-(piperidin-1-yl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(2-morpholinoethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(2-(dimethylamino)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((5-(4-(3-chloropropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((5-(4-(3-acetoxypropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-aminopropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(2-ethoxyethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-(pyrrolidin-1-yl)propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-(2-methyl-1H-imidazol-1-yl)propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-(dimethylamino)propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(isopropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(isobutylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(sec-butylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-acetoxy-2,2-dimethylpropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-hydroxy-2,2-dimethylpropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-(2-(pyridin-3-yl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-(2-(pyridin-4-yl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-

Methylcyclopropyl 4-((5-(4-sulfamoylpiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; *tert*-Butyl 4-((5-(4-(morpholinosulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-fluoro-6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; tert-Butyl 4-((5-(4-(methylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(2-oxo-4-(propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-(isopropylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-(isopropylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(2-oxo-4-(propylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(isopropylsulfonyl)-2-oxopiperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-(5-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)pyrazin-2-yl)-4-(methylsulfonyl)piperazin-2-one; 1-(5-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)pyridin-2-yl)-4-(methylsulfonyl)piperazin-2-one; *tert*-Butyl 4-((2,6-difluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((3-methoxy-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2,6-dimethyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2,5-dimethyl-4-(1-

(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2-(methoxycarbonyl)-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2-chloro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((3-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2,3-dimethyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2-fluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((4-(1-(methylsulfonyl)piperidin-4-yl)-2-(trifluoromethyl)phenoxy)methyl)piperidine-1-carboxylate; 2-(4-((2,6-Difluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)-5-ethylpyrimidine; 1-Methylcyclopropyl 4-((2,6-difluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; 3-(4-(4-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-3,5-difluorophenyl)piperidin-1-ylsulfonyl)propyl acetate; 1-Methylcyclopropyl 4-((4-(1-(3-acetoxypropylsulfonyl)piperidin-4-yl)-2,6-difluorophenoxy)methyl)piperidine-1-carboxylate; 3-(4-(4-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-3,5-difluorophenyl)piperidin-1-ylsulfonyl)propan-1-ol; 1-Methylcyclopropyl 4-((2,6-difluoro-4-(1-(3-hydroxypropylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; Isopropyl 4-((5-(1,2,3,6-tetrahydro-1-methanesulfonylpyridin-4-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((6-(1,2,3,6-tetrahydro-1-methanesulfonylpyridin-4-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; Isopropyl 4-(2-(6-(1,2,3,6-tetrahydro-1-methanesulfonylpyridin-4-yl)pyridin-3-yloxy)ethyl)piperidine-1-carboxylate; 2-(4-((5-(1,2,3,6-Tetrahydro-1-methanesulfonylpyridin-4-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine; 2-(4-((6-(1,2,3,6-Tetrahydro-1-methanesulfonylpyridin-4-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine; 2-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-5-(1-methanesulfonylpiperidin-4-yl)pyrazine; 2-(4-((6-(1-Methanesulfonylpiperidin-4-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine; 3-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-6-(1-methanesulfonylpiperidin-4-yl)pyridazine; 2-(4-((5-(1-Methanesulfonylpiperidin-4-yl)pyridin-2-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine; 1-*tert*-Butyl 4-(4-(1-(methylsulfonyl)piperidin-4-yl)phenyl) piperazine-1,4-dicarboxylate; *N*-((1-(5-

Ethylpyrimidin-2-yl)piperidin-4-yl)methyl)-4-(1-(methylsulfonyl)piperidin-4-yl)aniline; *N*-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methyl)-*N*-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)aniline; 4-(4-((1-(5-fluoropyrimidin-2-yl)piperidin-4-yl)methoxy)phenyl)-1-(methylsulfonyl)piperidine-4-carboxylic acid; 2-[(2-{4-[5-({1-[(1-methylcyclopropoxy)carbonyl]piperidin-4-yl}methoxy)pyrazin-2-yl]-3-oxopiperazine-1-sulfonyl}ethyl)amino]acetic acid; 1-methylcyclopropyl 4-{[(5-{4-[(2-carbamimidamidoethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-methyl-3-nitrobutane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(1-benzylpyrrolidine-3-sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(carbamoylmethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(1-carbamoyl-1-methylethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(2-oxo-4-{[2-(pyrrolidin-1-yl)ethane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(morpholin-4-yl)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(dimethylamino)propane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(dimethylcarbamoyl)methane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[1-(2-methylpropyl)pyrrolidine-3-sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(2-oxo-4-{[3-(1H-pyrazol-1-yl)propane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[2-oxo-4-(pyrrolidine-3-sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(2-amino-2-methylpropane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-

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methylpyrrolidin-3-yl)methane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(azetidin-1-yl)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(2-oxo-4-{[2-(1H-pyrazol-1-yl)ethane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(1-methylpyrrolidine-3-sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[1-(dimethylcarbamoyl)-1-methylethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(3,3-difluoroazetidin-1-yl)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(dimethylamino)-3-methylbutane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(2-{[2-(tert-butoxy)-2-oxoethyl]amino}ethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(azetidine-3-sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(3,3-difluoroazetidin-1-yl)propane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(azetidin-1-yl)propane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(3S)-pyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3S)-1-methylpyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3R)-1-methylpyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3S)-pyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3R)-pyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(azetidine-3-sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(pyrrolidin-3-ylmethane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(1-

hydroxy-2-methylpropane-2-sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(2-hydroxyethane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(azetidin-3-ylmethane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-methylpyrrolidin-2-yl)methane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(3R)-pyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(1-methylazetidine-3-sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(1-methylazetidine-3-sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-methylazetidin-3-yl)methane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-methylazetidin-3-yl)methane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({3-[(3S,4S)-3,4-dihydroxypyrrolidin-1-yl]propane}sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({2-[(3S,4S)-3,4-dihydroxypyrrolidin-1-yl]ethane}sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(azetidin-3-ylmethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(pyrrolidin-2-ylmethane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-aminopropane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(2-aminoethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(3-methanesulfonamidoazetidin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(dimethylamino)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(2-oxo-4-{[3-(pyrrolidin-1-yl)propane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(morpholin-4-yl)propane]sulfonyl}-2-

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oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(3-methyloxetan-3-yl)methane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(acetyloxy)propane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3,3,3-trifluoropropane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[(2E)-2-(hydroxyimino)-4-methanesulfonylpiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-chloropropane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-hydroxypropane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({[1-(dimethylamino)cyclopropyl]methane}sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({[1-(dimethylamino)cyclopropyl]methane}sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-hydroxy-3-methylbutane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(3R)-oxolane-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(3S)-oxolane-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(acetyloxy)-3-methylbutane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({6-[4-({[1-(azetidin-1-yl)cyclopropyl]methane}sulfonyl)piperazin-1-yl]pyridin-3-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({[1-(benzylamino)cyclopropyl]methane}sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({[1-(azetidin-1-yl)cyclopropyl]methane}sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-hydroxycyclopropyl)methane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(1-

hydroxycyclopropyl)ethane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({2-[1-(acetyloxy)cyclopropyl]ethane}sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({[1-(benzyloxy)cyclopropyl]methane}sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-aminocyclopropyl)methane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(1-hydroxycyclopropyl)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{2,6-difluoro-4-[3-(N-methylmethanesulfonamido)azetidin-1-yl]phenoxymethyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[2,6-difluoro-4-(3-methanesulfonamidoazetidin-1-yl)phenoxymethyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{2,6-difluoro-4-[3-(2-methylpropane-1-sulfonamido)azetidin-1-yl]phenoxymethyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{4-[3-(N,2-dimethylpropane-1-sulfonamido)azetidin-1-yl]-2,6-difluorophenoxymethyl}piperidine-1-carboxylate; 5-ethyl-2-{4-[({2-methanesulfonyl-1H,2H,3H,4H-pyrazino[1,2-a]indol-8-yl}oxy)methyl]piperidin-1-yl}pyrimidine; 11-{[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]oxy}-5-methanesulfonyl-8-oxa-5-azatricyclo[7.4.0.0{2,7}]trideca-1(13),2(7),9,11-tetraene; 11-{[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]methoxy}-5-methanesulfonyl-8-oxa-5-azatricyclo[7.4.0.0{2,7}]trideca-1(13),2(7),9,11-tetraene; tert-butyl 4-[({2-methanesulfonyl-1H,2H,3H,4H-pyrazino[1,2-a]indol-8-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({2-methanesulfonyl-1H,2H,3H,4H-pyrazino[1,2-a]indol-8-yl}oxy)methyl]piperidine-1-carboxylate; propan-2-yl 4-{3-[3-(1-methanesulfonylpiperidin-4-yl)phenoxy]propyl}piperidine-1-carboxylate; propan-2-yl 4-{2-[3-(1-methanesulfonylpiperidin-4-yl)phenoxy]ethyl}piperidine-1-carboxylate; propan-2-yl 4-[3-(1-methanesulfonylpiperidin-4-yl)phenoxymethyl]piperidine-1-carboxylate; propan-2-yl 4-{3-[3-(1-methanesulfonyl-1,2,3,6-tetrahydropyridin-4-yl)phenoxy]propyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-methanesulfonyl-2-sulfanylidenepiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl (3S,4S)-3-hydroxy-4-{[(6-{4-[(2-

methylpropane)sulfonyl]piperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl (3R,4S)-3-hydroxy-4-{[(6-{4-[(2-methylpropane)sulfonyl]piperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-hydroxy-4-{[(6-{4-[(2-methylpropane)sulfonyl]piperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(6-{4-[(2-hydroxy-2-methylpropane)sulfonyl]piperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl (3S,4R)-3-methoxy-4-{[(6-{4-[(2-methylpropane)sulfonyl]piperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(3,3-difluoroazetidin-1-yl)propane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(azetidin-1-yl)propane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-methoxypropane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(6-{4-[(3-chloropropane)sulfonyl]-2-oxopiperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(azetidin-1-yl)ethane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[6-(4-{[3-(azetidin-1-yl)propane]sulfonyl}piperazin-1-yl)pyridin-3-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(pyrrolidine-3-sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(3,3-difluoroazetidin-1-yl)ethane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(6-{4-[(3-hydroxypropane)sulfonyl]-2-oxopiperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[6-(4-{[3-(azetidin-1-yl)propane]sulfonyl}-2-oxopiperazin-1-yl)pyridin-3-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[2,6-difluoro-4-(4-methanesulfonyl-2-oxopiperazin-1-yl)phenoxymethyl]piperidine-1-carboxylate; and 1-methylcyclopropyl 4-[({5-[4-(oxetane-3-sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate.

[0043] Further compounds of the invention are detailed in the Examples and Tables, *infra*.

[0044] The present invention includes all pharmaceutically acceptable isotopically-labeled compounds of the invention, i.e. compounds of formula (I), 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 usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the invention comprises 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.

[0045] Certain isotopically-labelled compounds of formula (I), 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.

[0046] 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.

[0047] Isotopically-labeled compounds of formula (I) 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.

Pharmacology and Utility

[0048] Compounds of the invention modulate the activity of GPR119 and, as such, are useful for treating diseases or disorders in which the activity of GPR119 contributes to the pathology and/or symptomology of the disease. This invention further provides compounds of this invention for use in the preparation of medicaments for the

treatment of diseases or disorders in which GPR119 activity contributes to the pathology and/or symptomology of the disease.

[0049] The resultant pathologies of Type II diabetes are impaired insulin signaling at its target tissues and failure of the insulin-producing cells of the pancreas to secrete an appropriate degree of insulin in response to a hyperglycemic signal. Current therapies to treat the latter include inhibitors of the β-cell ATP-sensitive potassium channel to trigger the release of endogenous insulin stores, or administration of exogenous insulin. Neither of these achieves accurate normalization of blood glucose levels and both carry the risk of inducing hypoglycemia. For these reasons, there has been intense interest in the development of pharmaceuticals that function in a glucose-dependent action, i.e. potentiators of glucose signaling. Physiological signaling systems which function in this manner are well-characterized and include the gut peptides GLP-1, GIP and PACAP. These hormones act via their cognate G-protein coupled receptor to stimulate the production of cAMP in pancreatic β-cells. The increased cAMP does not appear to result in stimulation of insulin release during the fasting or pre-prandial state. However, a series of biochemical targets of cAMP signaling, including the ATP-sensitive potassium channel, voltage-sensitive potassium channels and the exocytotic machinery, are modified in such a way that the insulin secretory response to a postprandial glucose stimulus is markedly enhanced. Accordingly, agonists of novel, similarly functioning, β-cell GPCRs, including GPR119, would also stimulate the release of endogenous insulin and consequently promote normoglycemia in Type II diabetes. It is also established that increased cAMP, for example as a result of GLP-1 stimulation, promotes β-cell proliferation, inhibits β-cell death and thus improves islet mass. This positive effect on β-cell mass is expected to be beneficial in both Type II diabetes, where insufficient insulin is produced, and Type I diabetes, where β-cells are destroyed by an inappropriate autoimmune response.

[0050] Some β-cell GPCRs, including GPR119, are also present in the hypothalamus where they modulate hunger, satiety, decrease food intake, controlling or decreasing weight and energy expenditure. Hence, given their function within the hypothalamic circuitry, agonists or inverse agonists of these receptors mitigate hunger, promote satiety and therefore modulate weight.

[0051] It is also well-established that metabolic diseases exert a negative influence on other physiological systems. Thus, there is often the codevelopment of multiple disease states (e.g. type I diabetes, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia, obesity or cardiovascular disease in "Syndrome X") or secondary diseases which clearly occur secondary to diabetes (e.g. kidney disease, peripheral neuropathy). Thus, it is expected that effective treatment of the diabetic condition will in turn be of benefit to such interconnected disease states.

[0052] In an embodiment of the invention is a method for treatment of a metabolic disease and/or a metabolic-related disorder in an individual comprising administering to the individual in need of such treatment a therapeutically effective amount of a compound of the invention or a pharmaceutical composition thereof. The metabolic diseases and metabolic-related disorders are selected from, but not limited to, hyperlipidemia, type 1 diabetes, type 2 diabetes mellitus, idiopathic type 1 diabetes (Type Ib), latent autoimmune diabetes in adults (LADA), early-onset type 2 diabetes (EOD), youth-onset atypical diabetes (YOAD), maturity onset diabetes of the young (MODY), malnutrition-related diabetes, gestational diabetes, coronary heart disease, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, myocardial infarction (e.g. necrosis and apoptosis), dyslipidemia, post-prandial lipemia, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity, osteoporosis, hypertension, congestive heart failure, left ventricular hypertrophy, peripheral arterial disease, diabetic retinopathy, macular degeneration, cataract, diabetic nephropathy, glomerulosclerosis, chronic renal failure, diabetic neuropathy, metabolic syndrome, syndrome X, premenstrual syndrome, coronary heart disease, angina pectoris, thrombosis, atherosclerosis, myocardial infarction, transient ischemic attacks, stroke, vascular restenosis, hyperglycemia, hyperinsulinemia, hyperlipidemia, hypertrygliceridemia, insulin resistance, impaired glucose metabolism, conditions of impaired glucose tolerance, conditions of impaired fasting plasma glucose, obesity, erectile dysfunction, skin and connective tissue disorders, foot ulcerations and ulcerative colitis, endothelial dysfunction and impaired vascular compliance.

[0053] In an embodiment of the invention are therapeutic benefits of GPR119 activity modulators derived from increasing levels of GIP and PPY. For example, neuroprotection, learning and memory, seizures and peripheral neuropathy.

[0054] GLP-1 and GLP-1 receptor agonists have been shown to be effective for treatment of neurodegenerative diseases and other neurological disorders. GLP-1 and exendin-4 have been shown to stimulate neurite outgrowth and enhance cell survival after growth factor withdrawal in PC12 cells. In a rodent model of neurodegeneration, GLP-1 and exendin-4 restore cholinergic marker activity in the basal forebrain. Central infusion of GLP-1 and exendin-4 also reduce the levels of amyloid-β peptide in mice and decrease amyloid precursor protein amount in cultured PC12 cells. GLP-1 receptor agonists have been shown to enhance learning in rats and the GLP-1 receptor knockout mice show deficiencies in learning behavior. The knockout mice also exhibit increased susceptibility to kainate-induced seizures which can be prevented by administration of GLP-1 receptor agonists. GLP-1 and exendin-4 has also been shown to be effective in treating pyridoxine-induced peripheral nerve degeneration, an experimental model of peripheral sensory neuropathy.

[0055] Glucose-dependent insulinotropic polypeptide (GIP) has also been shown to have effects on proliferation of hippocampal progenitor cells and in enhancing sensorimotor coordination and memory recognition.

[0056] In an embodiment of the invention are therapeutic benefits of GPR119 activity modulators. For example, GLP-2 and short bowel syndrome (SBS). Several studies in animals and from clinical trials have shown that GLP-2 is a trophic hormone that plays an important role in intestinal adaptation. Its role in regulation of cell proliferation, apoptosis, and nutrient absorption has been well documented. Short bowel syndrome is characterized by malabsorption of nutrients, water and vitamins as a result of disease or surgical removal of parts of the small intestine (eg. Crohn's disease). Therapies that improve intestinal adaptation are thought to be beneficial in treatment of this disease. In fact, phase II studies in SBS patients have shown that teduglutide, a GLP-2 analog, modestly increased fluid and nutrient absorption.

[0057] In an embodiment of the invention are therapeutic benefits of GPR119 activity modulators derived from increasing levels of GIP and PPY. For example, GLP-1, GIP and

osteoporosis. GLP-1 has been shown to increase calcitonin and calcitonin related gene peptide (CGRP) secretion and expression in a murine C-cell line (CA-77). Calcitonin inhibits bone resorption by osteoclasts and promotes mineralization of skeletal bone. Osteoporosis is a disease that is caharacterized by reduced bone mineral density and thus GLP-1 induced increase in calcitonin might be therapeutically beneficial.

[0058] GIP has been reported to be involved in upregulation of markers of new bone formation in osetoblasts including collagen type I mRNA and in increasing bone mineral density. Like GLP-1, GIP has also been shown to inhibit bone resorption.

[0059] In an embodiment of the invention are therapeutic benefits of GPR119 activity modulators derived from increasing levels of GIP and PPY. For example, PPY and gastric emptying. GPR119 located on the pancreatic polypeptide (PP) cells of the islets has been implicated in the secretion of PPY. PPY has been reported to have profound effects on various physiological processes including modulation of gastric emptying and gastrointestinal motility. These effects slow down the digestive process and nutrient uptake and thereby prevent the postprandial elevation of blood glucose. PPY can suppress food intake by changing the expression of hypothalamic feeding-regulatory peptides. PP-overexpressing mice exhibited the thin phenotype with decreased food intake and gastric emptying rate.

[0060] In accordance with the foregoing, the present invention further provides a method for preventing or ameliorating the symptamology of any of the diseases or disorders described above in a subject in need thereof, which method comprises administering to said subject a therapeutically effective amount (*See, "Administration and Pharmaceutical Compositions", infra*) of a compound of Formula I or a pharmaceutically acceptable salt thereof. For any of the above uses, the required dosage will vary depending on the mode of administration, the particular condition to be treated and the effect desired.

Administration and Pharmaceutical Compositions

[0061] In general, compounds of the invention will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in

the art, either singly or in combination with one or more therapeutic agents. A therapeutically effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5mg to about 100mg, conveniently administered, e.g. in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 50mg active ingredient.

[0062] Compounds of the invention can be administered as pharmaceutical compositions by any conventional route, in particular enterally, e.g., orally, e.g., in the form of tablets or capsules, or parenterally, e.g., in the form of injectable solutions or suspensions, topically, e.g., in the form of lotions, gels, ointments or creams, or in a nasal or suppository form. Pharmaceutical compositions comprising a compound of the present invention in free form or in a pharmaceutically acceptable salt form in association with at least one pharmaceutically acceptable carrier or diluent can be manufactured in a conventional manner by mixing, granulating or coating methods. For example, oral compositions can be tablets or gelatin capsules comprising the active ingredient together with a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrollidone; if desired d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions can be aqueous isotonic solutions or suspensions, and suppositories can be prepared from fatty emulsions or suspensions. The compositions can be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they can also contain other therapeutically valuable substances. Suitable formulations for transdermal applications include an effective amount of a compound of the present invention with a carrier. A

carrier can include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin. Matrix transdermal formulations can also be used. Suitable formulations for topical application, e.g., to the skin and eyes, are preferably aqueous solutions, ointments, creams or gels well-known in the art. Such can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[0063] Compounds of the invention can be administered in therapeutically effective amounts in combination with one or more therapeutic agents (pharmaceutical combinations).

[0064] For example, synergistic effects can occur with other anti-obesity agents, anorectic agents, appetite suppressant and related agents. Diet and/or exercise can also have synergistic effects. Anti-obesity agents include, but are not limited to, apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, MCR-4 agonists, cholescystokinin-A (CCK-A) agonists, serotonin and norepinephrine reuptake inhibitors (for example, sibutramine), sympathomimetic agents, β3 adrenergic receptor agonists, dopamine agonists (for example, bromocriptine), melanocyte-stimulating hormone receptor analogs, cannabinoid 1 receptor antagonists [for example, compounds described in WO2006/047516), melanin concentrating hormone antagonists, leptons (the OB protein), leptin analogues, leptin receptor agonists, galanin antagonists, lipase inhibitors (such as tetrahydrolipstatin, i.e., Orlistat), anorectic agents (such as a bombesin agonist), Neuropeptide-Y antagonists, thyromimetic agents, dehydroepiandrosterone or an analogue thereof, glucocorticoid receptor agonists or antagonists, orexin receptor antagonists, urocortin binding protein antagonists, glucagon-like peptide- 1 receptor agonists, ciliary neutrotrophic factors (such as Axokine™), human agouti-related proteins (AGRP), ghrelin receptor antagonists, histamine 3 receptor antagonists or reverse agonists, neuromedin U receptor agonists, noradrenergic anorectic agents (for example, phentermine, mazindol and the like) and appetite suppressants (for example, bupropion).

[0065] Where compounds of the invention are administered in conjunction with other therapies, dosages of the co-administered compounds will of course vary depending on the type of co-drug employed, on the specific drug employed, on the condition being treated and so forthours.

[0066] A combined preparation or pharmaceutical composition can comprise a compound of the invention as defined above or a pharmaceutical acceptable salt thereof and at least one active ingredient selected from:

[0067] a) anti-diabetic agents such as insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide, glyburide and Amaryl; insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide; insulin sensitizer such as protein tyrosine phosphatase-1B (PTP-1B) inhibitors such as PTP-112; GSK3 (glycogen synthase kinase-3) inhibitors such as SB-517955, SB-4195052, SB-216763, NN-57-05441 and NN-57-05445; RXR ligands such as GW-0791 and AGN-194204; sodium-dependent glucose co-transporter inhibitors such as T-1095; glycogen phosphorylase A inhibitors such as BAY R3401; biguanides such as metformin; alpha-glucosidase inhibitors such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs such as Exendin-4 and GLP-1 mimetics; DPPIV (dipeptidyl peptidase IV) inhibitors such as DPP728, LAF237 (vildagliptin - Example 1 of WO 00/34241), MK-0431, saxagliptin, GSK23A ; an AGE breaker; a thiazolidone derivative (glitazone) such as pioglitazone, rosiglitazone, or *(R)*-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonyl}-2,3-dihydro-1*H*-indole-2-carboxylic acid described in the patent application WO 03/043985, as compound 19 of Example 4, a non-glitazone type PPAR gamma agonist e.g. GI-262570; Diacylglycerol acetyltransferase (DGAT) inhibitors such as those disclosed in WO 2005044250, WO 2005013907, WO 2004094618 and WO 2004047755;

[0068] b) hypolipidemic agents such as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin and related compounds such as those disclosed in U.S. Pat. No. 4,231,938, pitavastatin, simvastatin and related compounds such as those disclosed in U.S. Pat. Nos. 4,448,784 and 4,450,171, pravastatin and related compounds such as those disclosed in U.S. Pat. No.4,346,227, cerivastatin, mevastatin and related compounds such as those disclosed in U.S. Pat. No. 3,983,140, velostatin,

fluvastatin, dalvastatin, atorvastatin, rosuvastatin and related statin compounds disclosed in U.S. Pat. No. 5,753,675, rivastatin, pyrazole analogs of mevalonolactone derivatives as disclosed in U.S. Pat. No. 4,613,610, indene analogs of mevalonolactone derivatives as disclosed in PCT application WO 86/03488, 6-[2- (substituted-pyrrol-1-yl)-alkyl)pyran-2-ones and derivatives thereof as disclosed in U.S. Pat. No. 4,647,576, Searle's SC-45355 (a 3- substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone as disclosed in PCT application WO 86/07054, 3- carboxy-2- hydroxy-propane-phosphonic acid derivatives as disclosed in French Patent No. 2,596,393, 2,3-disubstituted pyrrole, furan and thiophene derivatives as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone as disclosed in U.S. Pat. No. 4,686,237, octahydronaphthalenes such as disclosed in U.S. Pat. No. 4, 499,289, keto analogs of mevinolin (lovastatin) as disclosed in European Patent Application No.0,142,146 A2, and quinoline and pyridine derivatives disclosed in U.S. Pat. Nos. 5,506,219 and 5,691,322. In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase suitable for use herein are disclosed in GB 2205837; squalene synthase inhibitors; FXR (farnesoid X receptor) and LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid and aspirin;

[0069] c) an anti-obesity agent or appetite regulating agent such as a CB1 activity modulator, melanocortin receptor (MC4R) agonists, melanin-concentrating hormone receptor (MCHR) antagonists, growth hormone secretagogue receptor (GHSR) antagonists, galanin receptor modulators, orexin antagonists, CCK agonists, GLP-1 agonists, and other Pre-proglucagon-derived peptides; NPY1 or NPY5 antagonsist, NPY2 and NPY4 modulators, corticotropin releasing factor agonists, histamine receptor-3 (H3) modulators, aP2 inhibitors, PPAR gamma modulators, PPAR delta modulators, acetyl-CoA carboxylase (ACC) inihibitors, 11-β-HSD-1 inhibitors, adinopectin receptor modulators; beta 3 adrenergic agonists, such as AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) or other known beta 3 agonists as disclosed in U.S. Pat. Nos. 5,541,204, 5,770,615, 5, 491,134, 5,776,983 and 5,488,064, a thyroid receptor beta modulator, such as a thyroid receptor ligand as disclosed in WO 97/21993 (U. Cal SF), WO 99/00353 (KaroBio) and GB98/284425 (KaroBio), a SCD-1 inhibitor as disclosed in WO2005011655, a lipase inhibitor, such as orlistat or ATL-962 (Alizyme), serotonin

receptor agonists, (e.g., BVT- 933 (Biovitrum)), monoamine reuptake inhibitors or releasing agents, such as fenfluramine, dexfenfluramine, fluvoxamine, fluoxetine, paroxetine, sertraline, chlorphentermine, cloforex, clortermine, picilorex, sibutramine, dexamphetamine, phentermine, phenylpropanolamine or mazindol, anorectic agents such as topiramate (Johnson & Johnson), CNTF (ciliary neurotrophic factor)/Axokine® (Regeneron), BDNF (brain-derived neurotrophic factor), leptin and leptin receptor modulators, phentermine, leptin, bromocriptine, dexamphetamine, amphetamine, fenfluramine, dexfenfluramine, sibutramine, orlistat, dexfenfluramine, mazindol, phentermine, phendimetrazine, diethylpropion, fluoxetine, bupropion, topiramate, diethylpropion, benzphetamine, phenylpropanolamine or ecopipam, ephedrine, pseudoephedrine;

[0070] d) anti-hypertensive agents such as loop diuretics such as ethacrynic acid, furosemide and torsemide; diuretics such as thiazide derivatives, chlorithiazide, hydrochlorothiazide, amiloride; angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perinodopril, quinapril, ramipril and trandolapril; inhibitors of the Na-K-ATPase membrane pump such as digoxin; neutralendopeptidase (NEP) inhibitors e.g. thiorphan, terteo-thiorphan, SQ29072; ECE inhibitors e.g. SLV306; ACE/NEP inhibitors such as omapatrilat, sampatrilat and fasidotril; angiotensin II antagonists such as candesartan, eprosartan, irbesartan, losartan, telmisartan and valsartan, in particular valsartan; renin inhibitors such as aliskiren, terlakiren, ditekiren, RO 66-1132, RO-66-1168; beta-adrenergic receptor blockers such as acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol and timolol; inotropic agents such as digoxin, dobutamine and milrinone; calcium channel blockers such as amlodipine, bepridil, diltiazem, felodipine, nicardipine, nimodipine, nifedipine, nisoldipine and verapamil; aldosterone receptor antagonists; aldosterone synthase inhibitors; and dual ET/AII antagonist such as those disclosed in WO 00/01389.

[0071] e) a HDL increasing compound;

[0072] f) Cholesterol absorption modulator such as Zetia® and KT6-971;

[0073] g) Apo-A1 analogues and mimetics;

[0074] h) thrombin inhibitors such as Ximelagatran;

[0075] i) aldosterone inhibitors such as anastrazole, fadrazole, eplerenone;

[0076] j) Inhibitors of platelet aggregation such as aspirin, clopidogrel bisulfate;

[0077] k) estrogen, testosterone, a selective estrogen receptor modulator, a selective androgen receptor modulator;

[0078] l) a chemotherapeutic agent such as aromatase inhibitors e.g. femara, anti-estrogens, topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, alkylating agents, antineoplastic antimetabolites, platin compounds, compounds decreasing the protein kinase activity such as a PDGF receptor tyrosine kinase inhibitor preferably Imatinib ({ N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine }) described in the European patent application EP-A-0 564 409 as example 21 or 4-Methyl-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-benzamide described in the patent application WO 04/005281 as example 92; and

[0079] m) an agent interacting with a 5-HT_3 receptor and/or an agent interacting with 5-HT_4 receptor such as tegaserod described in the US patent No. 5510353 as example 13, tegaserod hydrogen maleate, cisapride, cilansetron;

[0080] n) an agent for treating tobacco abuse, e.g., nicotine receptor partial agonists, bupropion hypochloride (also known under the tradename Zyban®) and nicotine replacement therapies;

[0081] o) an agent for treating erectile dysfunction, e.g., dopaminergic agents, such as apomorphine), ADD/ADHD agents (e.g., Ritalin®, Strattera®, Concerta® and Adderall®);

[0082] p) an agent for treating alcoholism, such as opioid antagonists (e.g., naltrexone (also known under the tradename ReVia®) and nalmefene), disulfiram (also known under the tradename Antabuse®), and acamprosate (also known under the tradename Campral®)). In addition, agents for reducing alcohol withdrawal symptoms may also be co-administered, such as benzodiazepines, beta- blockers, clonidine, carbamazepine, pregabalin, and gabapentin (Neurontin®);

[0083] q) other agents that are useful including anti-inflammatory agents (e.g., COX-2 inhibitors) ; antidepressants (e.g., fluoxetine hydrochloride (Prozac®)); cognitive improvement agents (e.g., donepezil hydrochloride (Aircept®) and other

acetylcholinesterase inhibitors); neuroprotective agents (e.g., memantine) ; antipsychotic medications (e.g., ziprasidone (Geodon®), risperidone (Risperdal®), and olanzapine (Zyprexa®));

[0084] or, in each case a pharmaceutically acceptable salt thereof; and optionally a pharmaceutically acceptable carrier.

[0085] The invention also provides for a pharmaceutical combinations, e.g. a kit, comprising a) a first agent which is a compound of the invention as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent. The kit can comprise instructions for its administration.

[0086] The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

[0087] The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of Formula I and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of Formula I and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

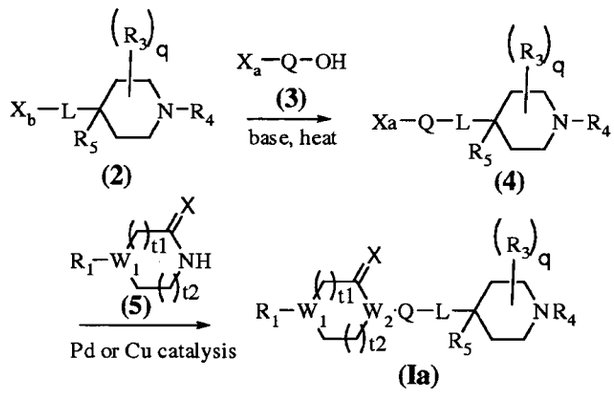
Processes for Making Compounds of the Invention

[0088] The present invention also includes processes for the preparation of compounds of the invention. In the reactions described, it can be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the

reactions. Conventional protecting groups can be used in accordance with standard practice, for example, see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry", John Wiley and Sons, 1991.

[0089] In the following schemes, several methods of preparing the compounds of the present invention are illustrative. One of skill in the art will appreciate that these methods are representative, and in no way inclusive of all methods for preparing the compounds of the present invention. The radicals in the schemes are as described in Formula I.

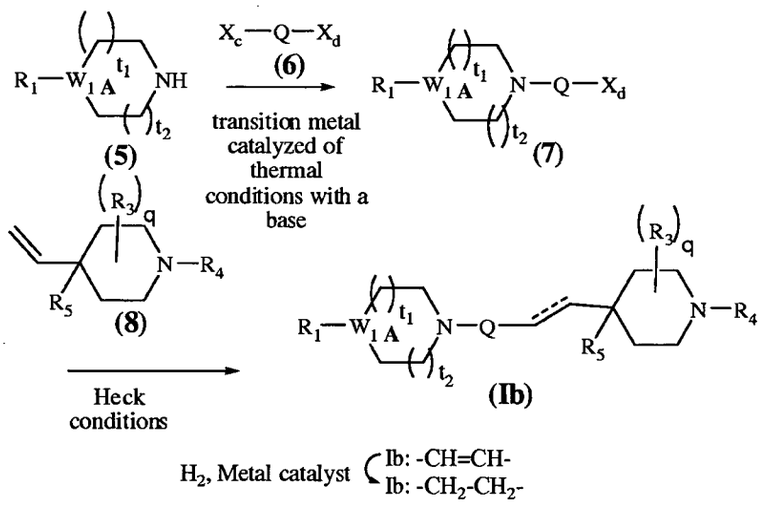
Reaction Scheme I



[0090] A compound of Formula Ia, where W_2 is nitrogen, can be prepared as in reaction scheme I by reacting a compound of formula 3 (where X_a refers to a chloride, bromide, iodide, triflate, nonaflate, or the like) with a compound of the formula 2 (where X_b refers to a leaving group such as an aryl- or alkylsulfonate ester, halide, epoxide where R_5 is the oxygen of the epoxide, or other appropriate group familiar to one skilled in the art) in a suitable solvent such as N,N-dimethylformamide, tetrahydrofuran and the like in the presence of a suitable base such as Cs_2CO_3, NaH or the like at an elevated temperature of up to about 80°C to generate an intermediate of the formula 4. A compound of the formula 5 (where C=X can be a C=O or CH_2) can be coupled with a compound of the formula 4 using the Pd or Cu methodology known in the art (for example, Shafir, A, Buchwald, S. F.; *J. Am Chem. Soc.* **2006**, 128, 8742 and references cited therein and Hartwig, J. F. *Handbook of Organopalladium Chemistry for Organic*

Synthesis, Negishi, E., Ed., Wiley-Interscience: Weinheim, 2002). In this scheme, it is understood that the groups may be protected versions of the radicals defined in the Summary of the Invention which may be deprotected and manipulated to a final compound of the invention after completion of this scheme or in the middle of the scheme.

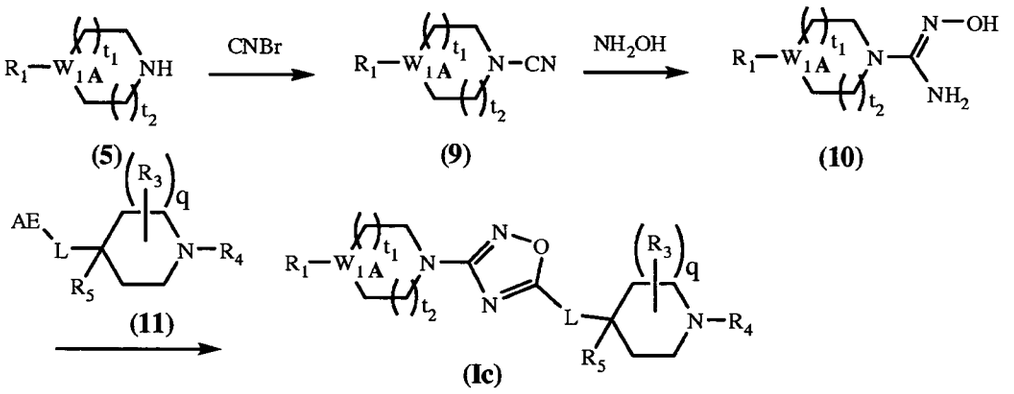
Reaction Scheme II



[0091] A compound of the Formula Ib, wherein W_2 is N and L can be –CH=CH- or -CH_2-CH_2-, can be prepared as in reaction scheme II. A compound of the formula 5 can be reacted with a compound of the formula 6 (where X_c and X_d both independently represent leaving groups such as F, Cl, Br, OTf, etc. with X_c being the more reactive group) using either the transition metal catalysis mentioned in scheme 1 or using a stoichiometric base such as K_2CO_3, triethylamine and the like in a suitable solvent such as N,N-dimethylformamide and the like at an elevated temperature to generate an intermediate of the formula 7. Intermediate 7 can then be reacted with an olefin of the formula 8 using heck reaction conditions (for example, Littke, A. F.; Fu, G. C, *J. Am. Chem. Soc.* **2001**, 123, 6989) to generate compounds where L is –(CH=CH)- which can subsequently be reduced using hydrogen and a catalytic amount of a transition metal

such as Pd/C and the like to compounds where L is $-(CH_2)_2-$. In this scheme, it is understood that the groups can be protected versions of the radicals defined in the Summary of the Invention which can be deprotected and manipulated to the final compound after completion of this scheme or in the middle of the scheme.

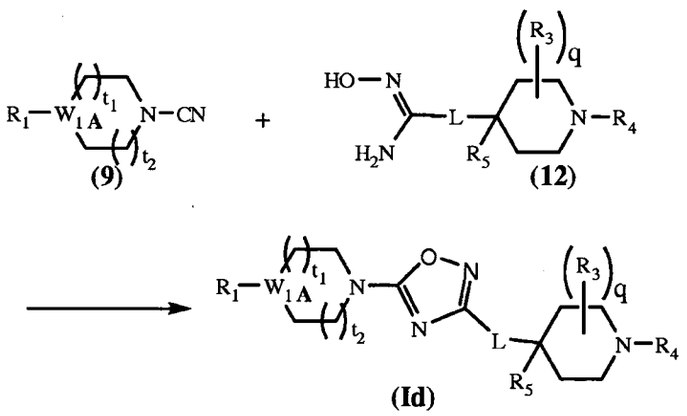
Reaction Scheme III



[0092] A compound of the Formula Ic, in which Q is a heteroaryl group such as 1,2,4-oxadiazolyl (as shown) and W_2 is N, can be prepared as in reaction scheme III by reacting a compound of the formula 5 with cyanogen bromide in a suitable solvent system such as aqueous Na_2CO_3 and dichloromethane and the to generate a compound of the formula 9. This intermediate can then be reacted with hydroxylamine in an appropriate solvent such as ethanol and the like at an elevated temperature such as 60 °C to furnish a compound of the formula 10. Intermediate 10 can then be reacted with a compound of the formula 11 (where AE stands for an acid equivalent such as a carboxylic acid, alkyl ester or activated ester such as an NHS ester and the like) using any of the protocols known in the literature (such as *Science of Synthesis* **2004**, *13*, 127, *Tetrahedron Lett.* **2006**, *47*, 3629 and *J. Med. Chem.* **2004**, *47*, 5821) to afford the desired compounds of the formula Ic. In this scheme, it is understood that the groups designated can be protected versions of the radicals defined in the Summary of the

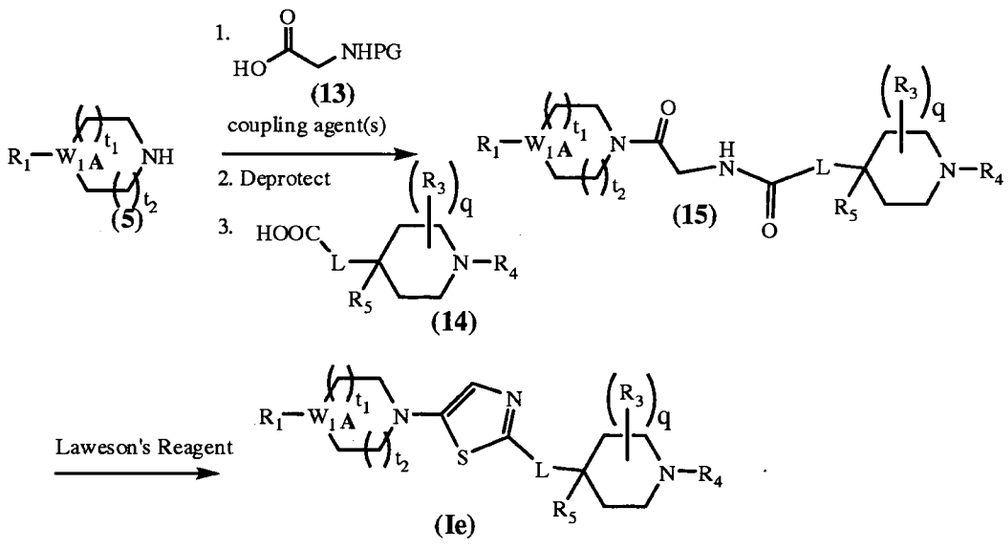
Invention which can be deprotected and manipulated to the final compound after completion of this scheme or in the middle of the scheme.

Reaction Scheme IV



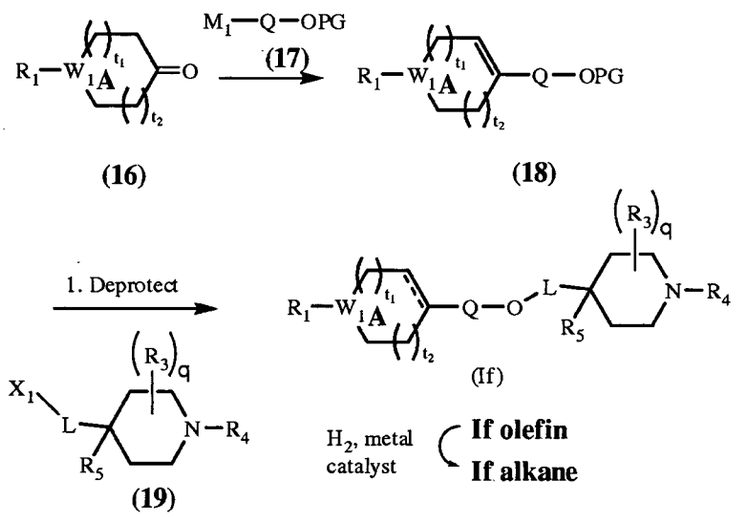
[0093] A compound of the Formula Id can be prepared as in reaction scheme IV by reacting a compound of the formula 9 with a compound of the formula 12 in a solvent such as tetrahydrofuran or the like in the presence of a Lewis acid such as $ZnCl_2$ and the like at an elevated temperature. In this scheme, it is understood that the groups designated can be protected versions of the radicals defined in the Summary of the Invention which can be deprotected and manipulated to the final compound after completion of this scheme or in the middle of the scheme.

Reaction Scheme V



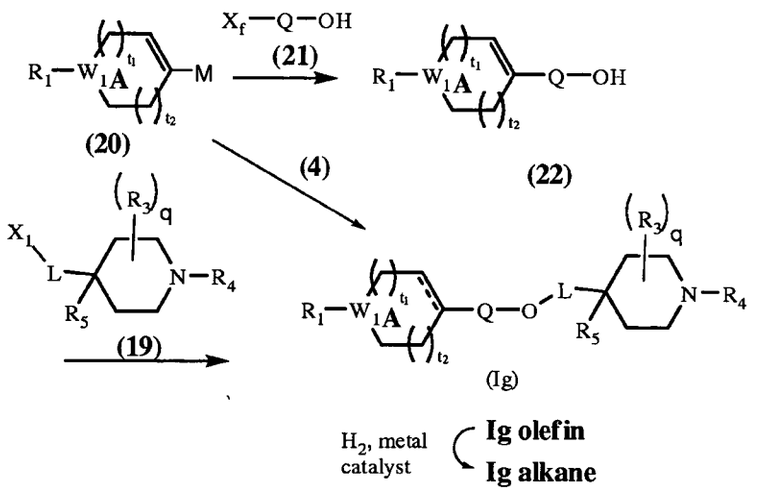
[0094] A compound of the Formula Ie, in which Q is thiazolyl (as sown above) and W_2 is N, can be prepared as in reaction scheme V by reacting a compound of the formula 5 with a protected glycine derivative of the formula 13 using appropriate coupling reagents followed by deprotection and coupling with a carboxylate of the formula 14 to generate an intermediate of the formula 15. This intermediate can then be cyclized using Lawesson's reagent or other thiotransfer/dehydrating agent in an appropriate solvent such as xylene at an elevated temperature such as 130 °C to generate the desired compound of the formula Ie. In this scheme, it is understood that the groups designated can be protected versions of the radicals defined in the Summary of the Invention which can be deprotected and manipulated to the final compound after completion of this scheme or in the middle of the scheme.

Reaction Scheme VI



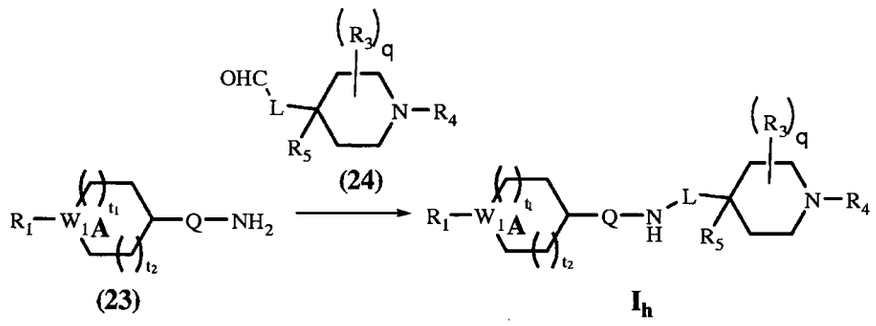
[0095] A compound of the Formula If, can be prepared as in reaction scheme VI. A ketone derivative of formula 16 can be reacted with an organometal reagent of formula 17 such as a Grignard reagent or the like to furnish after dehydration with an acid such as TFA and the like, an olefin of the formula 18. This material can be deprotected with the appropriate reagents followed by reaction with an electophile of the formula 19 where X_1 can be a leaving group such as mesylate, halide or the like in an appropriate solvent such as N,N-dimethylformamide or the like using a base such as Cs_2CO_3 or the like to afford If as the olefin. The olefin can then be reduced with a metal catalyst such as Pd/C or the like with hydrogen gas or the appropriate hydrogen transfer reagent to afford If as an alkane. In this scheme, it is understood that the groups designated can be protected versions of the radicals defined in the Summary of the Invention which can be deprotected and manipulated to the final compound after completion of this scheme or in the middle of the scheme.

Reaction Scheme VII



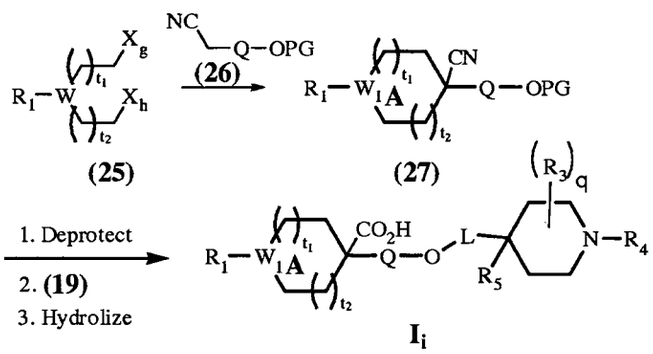
[0096] A compound of the Formula Ig, can be prepared as in reaction scheme VII. A vinyl metal derivative of formula 19 (where M is B, Sn, Si, Mg, Zn or other metals known to participate in metal catalyzed coupling reactions) can be reacted with a halide of formula 21 (where X_f refers to a chloride, bromide, iodide, triflate, nonaflate, or the like) using an appropriate metal catalyst such as Pd with an appropriate liand system such as familiar to those skilled in the art to generate an intermediate of formula 22. This intermediate can then be alkylated with an intermediate of formula 18 as outlined in scheme VI to afford Ig as an olefin. The olefin can then be reduced with a metal catalyst such as Pd/C or the like with hydrogen gas or the appropriate hydrogen transfer reagent to afford Ig as an alkane. Alternatively, Ig can be prepared by carrying out a metal mediated coupling on a compound of formula 20 with a compound of formula 4 and manipulating as before to get to the alkane. In this scheme, it is understood that the groups designated can be protected versions of the radicals defined in the Summary of the Invention which can be deprotected and manipulated to the final compound after completion of this scheme or in the middle of the scheme.

Reaction Scheme VIII



[0097] A compound of the Formula Ih, can be prepared as in reaction scheme VIII. A compound of formula 23 can be reductively aminated with a compound of formula 24 using the appropriate reductant such as $NaHB(OAc)_3$, $NaCNBH_3$ and the like in an appropriate solvent such as dichloromethane, methanol, ethanol and the like to afford I_h. The amine in I_h can then be further manipulated. In this scheme, it is understood that the groups designated can be protected versions of the radicals defined in the Summary of the Invention which can be deprotected and manipulated to the final compound after completion of this scheme or in the middle of the scheme.

Reaction Scheme IX

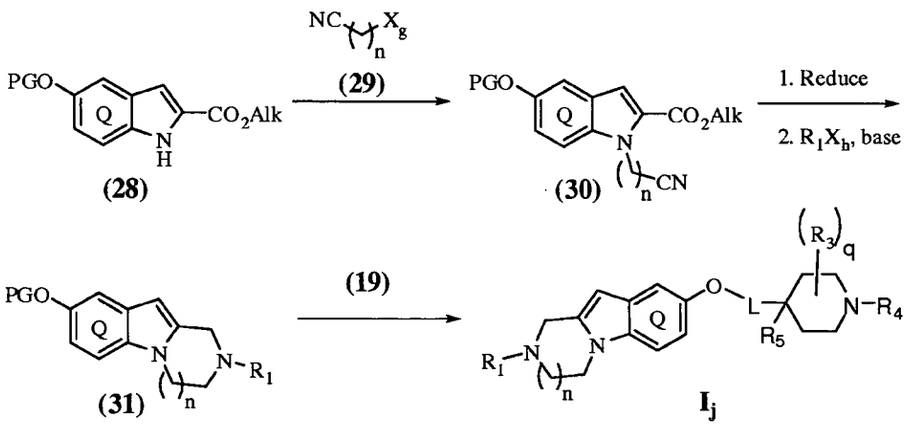


[0098] A compound of the Formula Ii, can be prepared as in reaction scheme IX. A compound of formula 25 (Where X_g and X_h can be chosen from chloro, bromo, iodo, mesylate, tosylate and the like) can be reacted with a compound of formula 26 using an

50

appropriate base such as sodium hydride, LDA and the like in an appropriate solvent such as N,N-dimethylformamide, N-methylpyrrolidinone, DMSO, tetrahydrofuran and the like at an elevated temperature such as 75 °C or similar to afford an intermediate of formula 27. This material can then be manipulated in a similar fashion to intermediate 18 in scheme VI to arrive at I_i. In this scheme, it is understood that the groups designated can be protected versions of the radicals defined in the Summary of the Invention which can be deprotected and manipulated to the final compound after completion of this scheme or in the middle of the scheme.

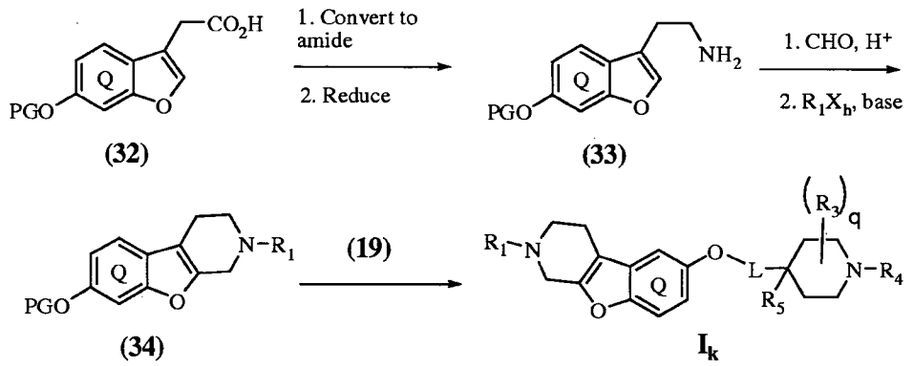
Reaction Scheme X



[0099] A compound of the Formula Ij, can be prepared as in reaction scheme X. A compound of formula 28 can be reacted with a compound of formula 29 (where X_g can be chosen from chloro, bromo, iodo, mesylate, tosylate and the like) using an appropriate base such as cesium carbonate, sodium hydride, LDA and the like in an appropriate solvent such as N,N-dimethylformamide, N-methylpyrrolidinone, DMSO, tetrahydrofuran and the like to afford an intermediate of formula 30. This material can then be reduced using an appropriate metal hydride such as LAH or BH_3 and then functionalized with the appropriate electrophile R_1X_h (where X_h can be chosen from chloro, bromo, succinate, p-nitrophenyl and the like) to afford an intermediate of the formula 31. This material can then be manipulated in a similar fashion to intermediate 18 in scheme VI to arrive at I_j. In this scheme, it is understood that the groups designated can be protected versions of the radicals defined in the Summary of the Invention which

can be deprotected and manipulated to the final compound after completion of this scheme or in the middle of the scheme.

Reaction Scheme XI



[00100] A compound of the Formula Ik, can be prepared as in reaction scheme XI. A compound of formula 32 can be converted to an amide by reacting with an activating agent such as oxlyl chloride or the like in an appropriate solvent such as dichloromethane or the like followed by reaction with ammonia or an equivalent followed by reduction with an appropriate reagent such as LAH or BH_3 to afford an intermediate of the formula 33. This material can then be cyclized with formaldehyde and acid such as acetic acid or the like followed by functionalization with an appropriate R_1X_h (where X_h can be chosen from chloro, bromo, succinate, p-nitrophenyl and the like) to afford an intermediate of the formula 34. This material can then be manipulated in a similar fashion to intermediate 18 in scheme VI to arrive at I_k. In this scheme, it is understood that the groups designated can be protected versions of the radicals defined in the Summary of the Invention which can be deprotected and manipulated to the final compound after completion of this scheme or in the middle of the scheme.

[00101] Detailed descriptions of the synthesis of compounds of the Invention are given in the Examples, *infra*.

Additional Processes for Making Compounds of the Invention

[00102] A compound of the invention can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of the invention can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Alternatively, the salt forms of the compounds of the invention can be prepared using salts of the starting materials or intermediates.

[00103] The free acid or free base forms of the compounds of the invention can be prepared from the corresponding base addition salt or acid addition salt from, respectively. For example a compound of the invention in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of the invention in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc.).

[00104] Compounds of the invention in unoxidized form can be prepared from N-oxides of compounds of the invention by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, or the like) in a suitable inert organic solvent (e.g. acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80 °C.

[00105] Prodrug derivatives of the compounds of the invention can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of the invention with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like).

[00106] Protected derivatives of the compounds of the invention can be made by means known to those of ordinary skill in the art. A detailed description of techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, "Protecting Groups in Organic Chemistry", 3rd edition, John Wiley and Sons, Inc., 1999.

[00107] Compounds of the present invention can be conveniently prepared, or formed during the process of the invention, as solvates (e.g., hydrates). Hydrates of compounds of the present invention can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

[00108] Compounds of the invention can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of the compounds of the invention, dissociable complexes are preferred (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981.

[00109] In summary, the compounds of Formula I can be made by a process, which involves:

(a) that of reaction schemes I to XI; and

(b) optionally converting a compound of the invention into a pharmaceutically acceptable salt;

(c) optionally converting a salt form of a compound of the invention to a non-salt form;

(d) optionally converting an unoxidized form of a compound of the invention into a pharmaceutically acceptable N-oxide;

(e) optionally converting an N-oxide form of a compound of the invention to its unoxidized form;

(f) optionally resolving an individual isomer of a compound of the invention from a mixture of isomers;

(g) optionally converting a non-derivatized compound of the invention into a pharmaceutically acceptable prodrug derivative; and

(h) optionally converting a prodrug derivative of a compound of the invention to its non-derivatized form.

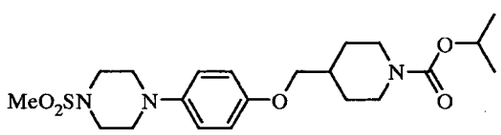
[00110] Insofar as the production of the starting materials is not particularly described, the compounds are known or can be prepared analogously to methods known in the art or as disclosed in the Examples hereinafter.

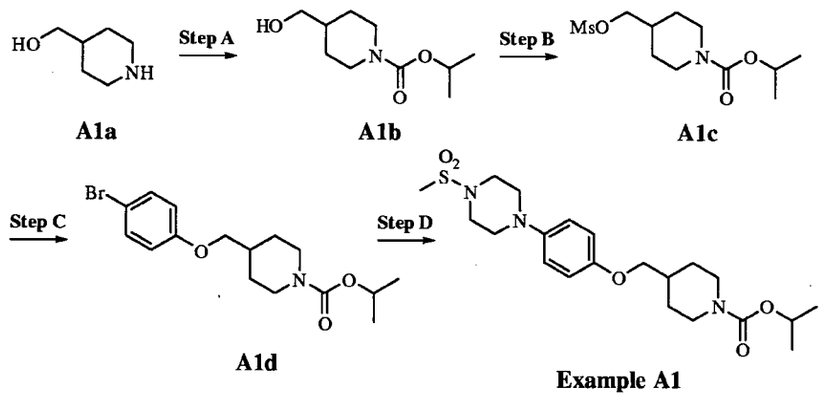
[00111] One of skill in the art will appreciate that the above transformations are only representative of methods for preparation of the compounds of the present invention, and that other well known methods can similarly be used.

Examples

[00112] The present invention is further exemplified, but not limited, by the following Examples that illustrate the preparation of compounds of the invention.

Example A1: Isopropyl 4-((4-((4-methanesulfonylpiperazin)-1-yl)phenoxy)methyl)piperidine-1-carboxylate.





A1a A1b A1c

A1d Example A1

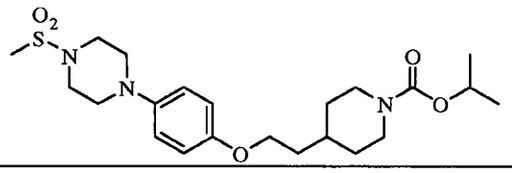
[00113] **Step A**: To a solution of **A1a** (5.26 g, 45.7 mmol) in dry dimethoxyethane (30 mL) is added triethylamine (8.0 g, 56.9 mmol). To the resulting mixture, a 1.0-M solution of isopropyl chloroformate in toluene (50 mL) is added dropwise, with vigorous stirring, over 10 min. A white precipitate forms. The suspension is stirred at room temperature for 4 hours; the white precipitate is filtered off, washed with more dimethoxyethane, and discarded. The resulting solution is concentrated to dryness to yield **A1b**; ^{1}H NMR (DMSO-d_6, 400.13 MHz): δ 4.75 (septet, J = 6.2 Hz, 1H), 4.49 (t, J = 5.3 Hz, 1H), 3.95 (dd, J = 5.6, 5.6 Hz, 2H), 3.24 (br, 2H), 1.63 (dd, J = 2.0, 12.9 Hz, 2H), 1.51 (m, 1H), 1.17 (d, J = 6.2 Hz, 6H), 0.98 (m, 2H); no mass spectrum could be obtained.

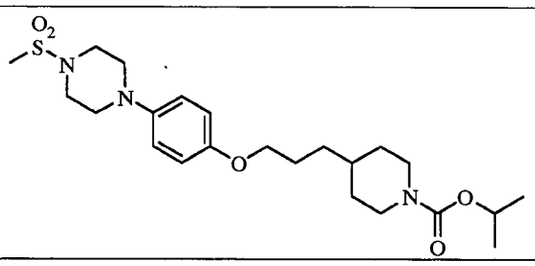
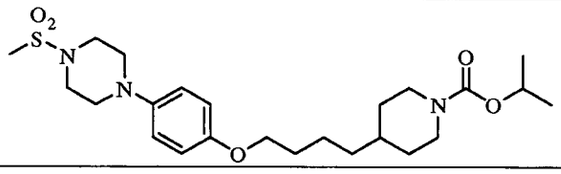
[00114] **Step B**: To a solution of **A1b** (4.25 g, 21.1 mmol) in dichloromethane (30mL) is added triethylamine (4.5 g, 32.0 mmol) in one portion. The resulting mixture is cooled in an ice/water bath and methanesulfonyl chloride (1.8 mL, 23.2 mmol) is added dropwise, with stirring, over 5 min. The bath is removed and the resulting solution is stirred at room temperature for 30 min. The reaction mixture is added to water (40 mL) and extracted with dichloromethane (2 x 40 mL). The combined organic extracts are washed with saturated ammonium chloride aqueous solution, dried over $MgSO_4$, and concentrated to yield **A1c**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 4.74 (septet, J = 6.2 Hz, 1H), 4.07 (d, J = 6.4 Hz, 2H), 3.99 (d, J = 11.0 Hz, 2H), 3.17 (s, 3H), 2.51 (br, 2H), 1.88 (dd, J = 1.6, 14.6 Hz, 2H), 1.68 (m, 1H), 1.18 (d, J = 6.2 Hz, 6H), 1.17 (m, 2H); ESIMS calcd. for $C_{11}H_{22}NO_5S$ ($M+H^+$) 280.11, found 280.2.

[00115] **Step C**: A solution of **A1c** (0.42 g, 1.50 mmol) and 4-bromophenol (0.26 g, 1.50 mmol) in acetonitrile (5.0 mL) is treated with powdered cesium carbonate (0.60 g, 1.84 mmol) and the mixture is stirred at 65 °C for 16 hours. Cooling to room temperature, filtration and concentration yields **A1d**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.36 (d, J = 9.0 Hz, 2H), 6.76 (d, J = 9.0 Hz, 2H), 4.91 (septet, J = 6.2 Hz, 1H), 4.19 (br, 2H), 3.76 (d, J = 6.4 Hz, 2H), 3.26 (br, 2H), 2.78 (m, 2H), 1.96 (m, 1H), 1.82 (dd, J = 1.6, 14.6 Hz, 2H), 1.30 (m, 2H), 1.28 (d, J = 6.2 Hz, 6H); ESIMS calcd. for $C_{16}H_{23}BrNO_3$ ($M+H^+$) 356.1, found 356.0.

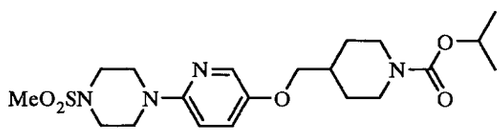
[00116] **Step D**: A solution of **A1d** (0.55 g, 1.50 mmol), 4-methanesulfonyl-piperazine (0.25 g, 1.52 mmol), and tri-*t*-butylphosphonium tetrafluoroborate (92.2 mg, 0.32 mmol) in dry dioxane (6mL) is treated with powdered cesium carbonate (1.03 g, 3.16 mmol) and the mixture is degassed using argon. Tris(dibenzylidene acetone)dipalladium(0) (0.15 g, 0.16 mmol) is added and the mixture is degassed again with argon. The suspension is stirred vigorously under argon at 110 °C for 18hours. Cooling, filtration and purification using mass-triggered reverse phase HPLC yields **A1**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 6.90 (d, J = 8.9 Hz, 2H), 6.84 (d, J = 8.9 Hz, 2H), 4.92 (septet, J = 6.2 Hz, 1H), 4.19 (br, 2H), 3.76 (d, J = 6.4 Hz, 2H), 3.39 (t, J = 3.9 Hz, 4H), 3.17 (t, J = 3.9 Hz, 4H), 2.83 (s, 1H), 2.77 (t, J = 11.2 Hz, 2H), 1.96 (m, 1H), 1.83 (dd, J = 1.4, 14.2 Hz, 2H), 1.27 (m, 2H), 1.24 (d, J = 6.2 Hz, 6H); ESIMS calcd. for $C_{21}H_{34}N_3O_5S$ ($M+H^+$) 440.2, found 440.2.

[00117] By following a similar procedure as the one used for preparing **A1** from **A1a** except substituting the appropriate alcohol for **A1a**, the following examples are obtained:

Example	Structure	Analytical data
A2		ESIMS calcd. for $C_{22}H_{36}N_3O_5S$ ($M+H^+$) 454.2, found 454.2.

A3		ESIMS calcd. for $C_{23}H_{38}N_3O_5S$ ($M+H^+$) 468.2, found 468.2.
A4		ESIMS calcd. for $C_{24}H_{40}N_3O_5S$ ($M+H^+$) 482.2, found 482.2.

Example B1: Isopropyl 4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate.

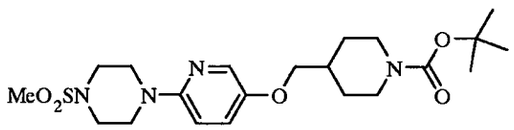


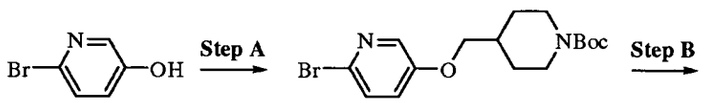
[00118] By following a similar procedure as the one used for preparing **A1** from **A1a** except substituting 2-chloro-5-hydroxypyridine for 4-bromophenol and performing step D as follows, **B1** is prepared;

[00119] A flask is charged with Pd_2dba_3 (6 mg, 0.006 mmol), xantphos (11 mg, 0.019 mmol), 1-(methylsulfonyl)piperazine (63 mg, 384 mmol), sodium *tert*-butoxide (46 mg, 0.48 mmol), and a solution of isopropyl 4-((6-chloropyridin-3-yloxy)methyl)piperidine-1-carboxylate (100 mg, 0.32 mmol) in toluene (1mL). The reaction is purged by bubbling nitrogen through the solution for 5 minutes and then sealed. The reaction is then dipped into a pre-heated 100 °C bath and stirred at this temperature for 3 hours. After cooling to room temperature, the reaction is treated with ethyl acetate and water and the aqueous phase is isolated, washed with ethyl acetate once more and discarded. The combined organics are dried over $MgSO_4$ and the solvent is removed. The residue is purified on a silica gel column using a linear gradient of 0-100% ethyl acetate in hexane as eluent to afford **B1**; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, J = 3.0, 1H), 7.18 (dd, J = 3.0, 9.1, 1H), 6.67 (d, J = 9.1, 1H), 4.91 (m, 1H), 4.20

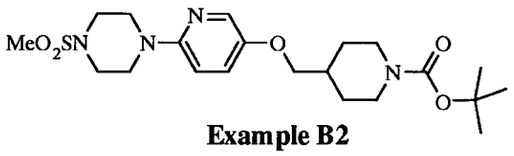
(m, 2H), 3.78 (d, J = 6.4, 2H), 3.56 (m, 4H), 3.34 (m, 4H), 2.81 (s, 3H), 2.76 (m, 2H), 1.94 (m, 1H), 1.81 (m, 2H), 1.29 (m, 2H), 1.24, d, J = 6.2, 6H); ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{33}N_4O_5S$ calcd.: 441.2, found: 441.3.

Example B2. *tert*-Butyl 4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate.





B2a **B2b**



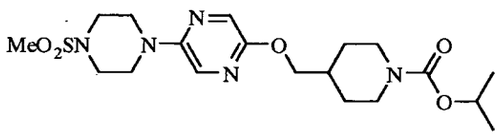
Example B2

[00120] **Step A:** A solution of **B2a** (4.00 g, 23 mmol) and tert-butyl 4-((methylsulfonyloxy)methyl)piperidine-1-carboxylate (7.08 g, 24 mmol) in N-methylpyrrolidinone (50 mL) is treated with Cs_2CO_3 (9.74 g, 30 mmol) and heated to 100 °C overnight. The reaction is then diluted with ethyl acetate, extracted with water 3 times, dried over $MgSO_4$, filtered, evaoparted and crystallized from toluene/hexane to afford **B2b**; ESIMS *m/z* for $(M-t\text{Bu}+H)^+$ $C_{12}H_{16}BrN_2O_3$ calcd.: 315.0, found: 315.0.

[00121] **Step B:** Following the procedure for the palladium coupling outlined for **B1** above, substituting **B2b** for isopropyl 4-((6-chloropyridin-3-yloxy)methyl)piperidine-1-carboxylate, **B2** is prepared; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.91 (d, J = 2.9, 1H), 7.15 (dd, J = 9.1, 3.1, 1H), 6.65 (d, J = 9.0, 1H), 4.15 (m, 2H), 3.78 (d, J = 6.4, 2H), 3.54 (m,

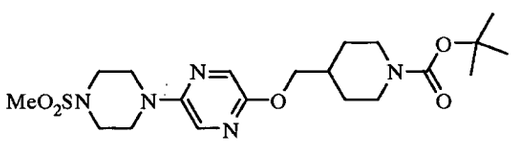
4H), 3.33 (m, 4H), 2.81 (s, 3H), 2.72 (m, 2H), 1.93 (m, 1H), 1.80 (m, 2H), 1.46 (s, 9H), 1.25 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{35}N_4O_5S$ calcd.: 455.2, found: 455.2.

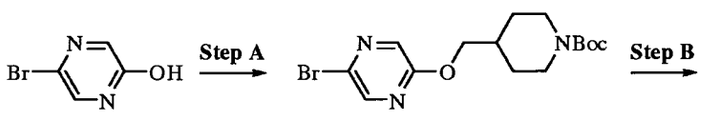
Example B3: Isopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



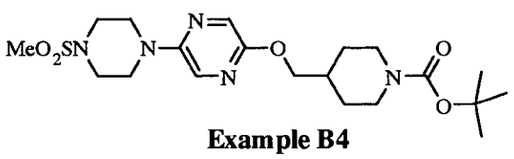
[00122] By following a similar procedure as the one used for preparing **B1** except using 2-bromo-5-hydroxypyrazine as the heterocycle, **B3** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, *J* = 1.4, 1H), 7.62 (d, *J* = 1.5, 1H), 4.92 (m, 1H), 4.18 (m, 2H), 4.08 (d, *J* = 6.5, 2H), 3.52 (m, 4H), 3.37 (m, 4H), 2.82 (s, 3H), 2.76 (m, 2H), 1.96 (m, 1H), 1.79 (m, 2H), 1.29 (m, 2H), 1.24, (d, *J* = 6.2, 6H); ESIMS *m/z* for $(M+H)^+$ $C_{19}H_{32}N_5O_5S$ calcd.: 442.2, found: 442.3.

Example B4: *tert*-Butyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





B4a **B4b**

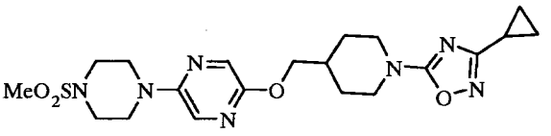


Example B4

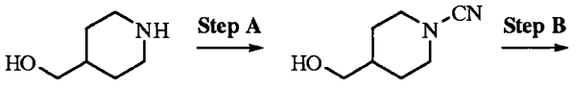
[00123] **Step A:** By following a similar procedure as the one used for preparing **B2b** from **B2a** except substituting **B4a** for **B2a, B4b** is prepared; ESIMS *m/z* for (M-*t*Bu+H$^+$)$^-$ $C_{11}H_{15}BrN_3O_3$ calcd.: 316.0, found: 316.0.

[00124] **Step B:** By following the procedure for the palladium coupling outlined for the preparation of **B1** except substituting **B4b** for isopropyl 4-((6-chloropyridin-3-yloxy)methyl)piperidine-1-carboxylate, **B4** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, *J* = 1.2, 1H), 7.62 (d, *J* = 1.2, 1H), 4.13 (m, 2H), 4.08 (d, *J* = 6.8, 2H), 3.52 (m, 4H), 3.37 (m, 4H), 2.82 (s, 3H), 2.72 (m, 2H), 1.93 (m, 1H), 1.46 (s, 9H), 1.26 (m, 2H); ESIMS *m/z* for (M+H)$^+$ $C_{20}H_{34}N_5O_5S$ calcd.: 456.2, found: 456.2.

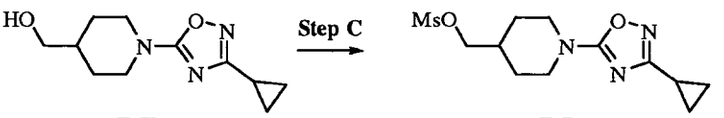
Example B5: 3-Cyclopropyl-5-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole.



[00125] By following a similar procedure as the one used for preparing **B3** from **B2a** except substituting **B5c** (see scheme below) for **B2a, B5** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (d, *J* = 1.3, 1H), 7.62 (d, *J* = 1.4, 1H), 4.16 (m, 2H), 4.10 (d, *J* = 6.8, 2H), 3.53 (m, 4H), 3.37 (m, 4H), 3.05 (ddd, *J* = 12.9, 12.9, 2.8, 2H), 2.82 (s, 3H), 2.02 (m, 1H), 1.88 (m, 4H), 1.41 (m, 2H), 0.94 (m, 4H); ESIMS *m/z* for (M+H)$^+$ $C_{20}H_{30}N_7O_4S$ calcd.: 464.2, found: 464.3.



A1a **B5a**



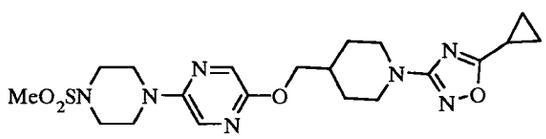
B5b **B5c**

[00126] **Step A:** A sample of **A1a** (10.19 g, 84.9 mmol) is treated with a solution of K_2CO_3 (24.5 g, 177 mmol) in water (100 mL). The reaction is cooled in an ice/water bath and treated with a solution of cyanogen bromide (10.31 g, 97.3 mmol) in dichloromethane (100 mL) dropwise. After stirring for an hour, the organic layer is isolated and the aqueous layer is extracted once more with dichloromethane. The combined organic extracts are dried over $MgSO_4$, filtered and evaporated to afford **B5a**; ESIMS *m/z* for $(M+H)^+$ $C_7H_{13}N_2O$ calcd.: 141.1, found: 141.1.

[00127] **Step B:** A solution of **B5a** (993 mg, 7.1 mmol), N'-hydroxycyclopropane carboximidamide (1.064 g, 10.6 mmol) and $ZnCl_2$ (1.448 g, 10.6 mmol) in dioxane (25 mL) is heated to 100 °C overnight. The reaction is then evaporated to dryness and partitioned between ethyl acetate and 1 M HCl. The organics are isolated, extracted with 1 M HCl once more, dried over $MgSO_4$, filtered, evaporated and purified by silica gel to afford **B5b**; ESIMS *m/z* for $(M+H)^+$ $C_{11}H_{18}N_3O_2$ calcd.: 224.1, found: 224.1.

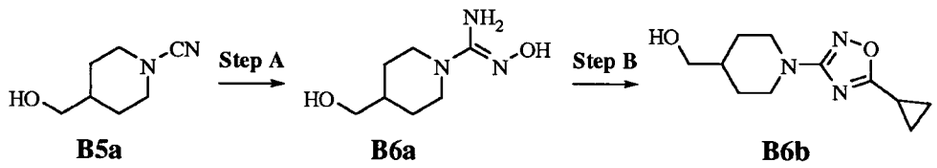
[00128] **Step C:** A solution of **B5b** (278.4 mg, 1.25 mmol) and triethylamine (131 mg, 130 mmol) in dichloromethane (1 mL) is cooled in an ice/water bath, treated with methanesulfonyl chloride (149 mg, 1.3 mmol) and stirred overnight. The reaction is diluted with water and extracted with dichloromethane. The organics are dried over $MgSO_4$, filtered, evaporated and purified on silica gel using a linear gradient of 0 to 100% ethyl acetate in hexane to afford **E5c**; ESIMS *m/z* for $(M+H)^+$ $C_{12}H_{20}N_3O_4S$ calcd.: 302.1, found: 302.1.

Example B6: 5-Cyclopropyl-3-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole.



[00129] By following a similar procedure as the one used for **B5** except substituting **B6b** (see scheme below) for **B5b**, **B6** is obtained; ^1H NMR ($CDCl_3$, 400

MHz): δ 7.87 (d, *J* = 1.5, 1H), 7.63 (d, *J* = 1.5, 1H), 4.10 (d, *J* = 6.8, 2H), 4.00 (m, 2H), 3.53 (m, 4H), 3.37 (m, 4H), 2.89 (ddd, *J* = 12.7, 12.7, 2.7, 2H), 2.82 (s, 3H), 2.00 (m, 1H), 1.86 (m, 4H), 1.40 (ddd, *J* = 25.0, 12.4, 4.3, 2H), 1.14 (m, 4H); ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{29}N_7O_4S$ calcd.: 464.2, found: 464.3.

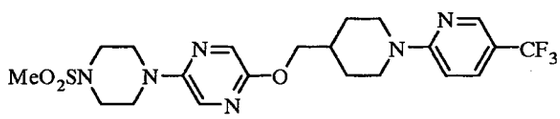


B5a **B6a** **B6b**

[00130] **Step A:** A solution of **B5a** (4.01 g, 28.6 mmol) and hydroxylamine (3.51 mL of a 50% by weight aqueous solution, 57.2 mmol) in ethanol (50 mL) is sealed and heated to 60 °C overnight. The solvent is then removed to **B6a**; ESIMS *m/z* for $(M+H)^+$ $C_7H_{16}N_3O_2$ calcd.: 174.1, found: 174.1.

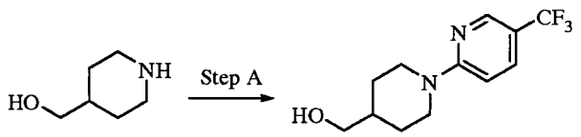
[00131] **Step B:** A solution of **B6a** (905 mg, 5.2 mmol) and 2,5-dioxopyrrolidin-1-yl cyclopropanecarboxylate (957 mg, 5.2 mmol) in dioxane (50 mL) is heated to 80 °C for 3 hours and then 70 °C overnight. The reaction is then cooled to room temperature, concentrated and purified on silica gel using a linear gradient of 0-80% ethyl acetate in hexane to afford **B6b**; ESIMS *m/z* for $(M+H)^+$ $C_{11}H_{18}N_3O_2$ calcd.: 224.1, found: 224.1.

Example B7: 2-(4-(Methylsulfonyl)piperazin-1-yl)-5-((1-(5-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)methoxy)pyrazine.



[00132] By following a similar procedure as the one used for preparing **B3** from **B2a** except substituting **B7a** (see scheme below) for **A1b, B7** is prepared; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.37 (m, 1H), 7.88 (d, *J* = 1.4, 1H), 7.63 (d, *J* = 1.4, 1H), 7.60 (dd, *J* = 9.1, 2.5, 1H), 6.65 (d, *J* = 9.1, 1H), 4.45 (m, 2H), 4.11 (d, *J* = 6.5, 1H), 3.53 (m, 4H),

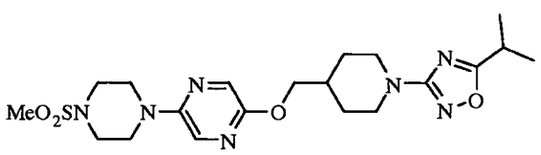
3.37 (m, 4H), 2.95 (m, 2H), 2.82 (s, 3H), 2.11 (m, 1H), 1.93 (m, 2H), 1.37 (ddd, J = 24.9, 12.5, 4.1, 2H); ESIMS m/z for $(M+H)^+$ $C_{21}H_{28}F_3N_6O_3S$ calcd.: 501.2, found: 501.3.



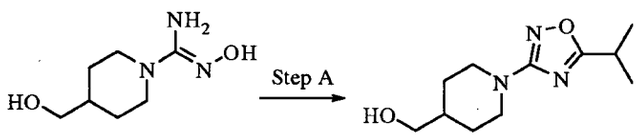
A1a **B7a**

[00133] **Step A:** A mixture of **A1a** (522.5 mg, 4.5 mmol), 2-chloro-5-trifluoromethylpyridine (1.19 g, 6.5 mmol) and K_2CO_3 (941 mg, 6.8 mmol) in N,N-dimethylformamide (8 mL) is heated to 160 °C for 10 minutes, cooled to room temperature and diluted with ethyl acetate and water. The organics are extracted with water, dried over MgSO4, filtered, evaporated and purified on silica gel using a linear gradient of 0 to 100% ethyl acetate in hexane to afford **B1a**; ESIMS m/z for $(M+H)^+$ $C_{12}H_{16}F_3N_2O$ calcd.: 261.1, found: 261.1.

Example B8: 5-Isopropyl-3-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole.



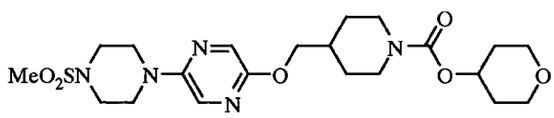
[00134] By following a similar procedure as the one used for preparing **B6** from **B6b** except substituting **B8a** (see scheme below) for **B6b, B8** is prepared; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.88 (d, J = 1.5, 1H), 7.63 (d, J = 1.5, 1H), 7.60 (dd, J = 9.1, 2.5, 1H), 4.11 (d, J = 6.6, 1H), 3.53 (m, 4H), 3.37 (m, 4H), 3.07 (m, 1H), 2.92 (ddd, J = 12.7, 12.7, 2.7, 2H), 2.82 (s, 3H), 2.01 (m, 1H), 1.88 (m, 2H), 1.42 (m, 2H), 1.35 (d, J = 7.0, 6H); ESIMS m/z for $(M+H)^+$ $C_{20}H_{32}N_7O_4S$ calcd.: 466.2, found: 466.2.



B6a **B8a**

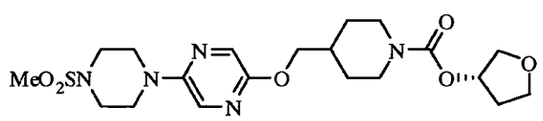
[00135] **Step A:** A solution of **B6a** (460.3 mg, 2.7 mmol) and isobutyric anhydride (420 mg, 2.7 mmol) in dioxane (3 mL) is heated to 150 °C for 5 minutes. The reaction is cooled to room temperature and diluted with ethyl acetate and water. The organics are isolated and washed once with water, dried over $MgSO_4$, filtered, evaporated and purified on silica using a linear gradient of ethyl acetate in hexane to afford **B8a**. A satisfactory mass spectal analysis could not be obtained.

Example B9: Tetrahydro-2H-pyran-4-yl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



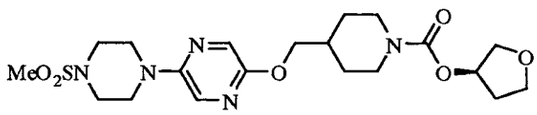
[00136] By following a similar procedure as the one used for preparing **B3** from **A1a** except substituting 4-nitrophenyl tetrahydro-2H-pyran-4-yl carbonate for isopropyl chloroformate in the first step, **B9** is prepared; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, J = 1.5, 1H), 7.62 (d, J = 1.5, 1H), 4.87 (m, 1H), 4.20 (m, 2H), 4.09 (d, J = 6.5, 1H), 3.89 (m, 2H), 3.57 (m, 2H), 3.54 (m, 4H), 3.46 (m, 4H), 2.82 (s, 3H), 2.80 (m, 2H), 1.95 (m, 3H), 1.82 (m, 2H), 1.67 (m, 3H), 1.28 (m, 2H); ESIMS m/z for $(M+H)^+$ $C_{21}H_{34}N_5O_6S$ calcd.: 484.2, found: 484.2.

Example B10: (S)-Tetrahydrofuran-3-yl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



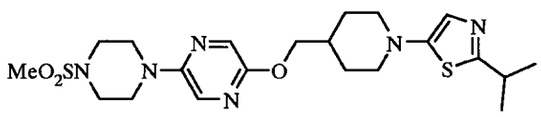
[00137] By following a similar procedure as the one used for preparing **B3** from **A1a** except substituting (S)-4-nitrophenyl tetrahydrofuran-3-yl carbonate for isopropyl chloroformate in the first step, **B10** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, J = 1.5, 1H), 7.62 (d, J = 1.5, 1H), 5.26 (m, 1H), 4.18 (m, 2H), 4.08 (d, J = 6.5, 1H), 3.89 (m, 4H), 3.53 (m, 4H), 3.47 (m, 4H), 2.82 (s, 3H), 2.80 (m, 2H), 2.17 (m, 1H), 2.00 (m, 2H), 1.82 (m, 2H), 1.27 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{31}N_5O_6S$ calcd.: 470.2, found: 470.2.

Example B11: (R)-Tetrahydrofuran-3-yl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



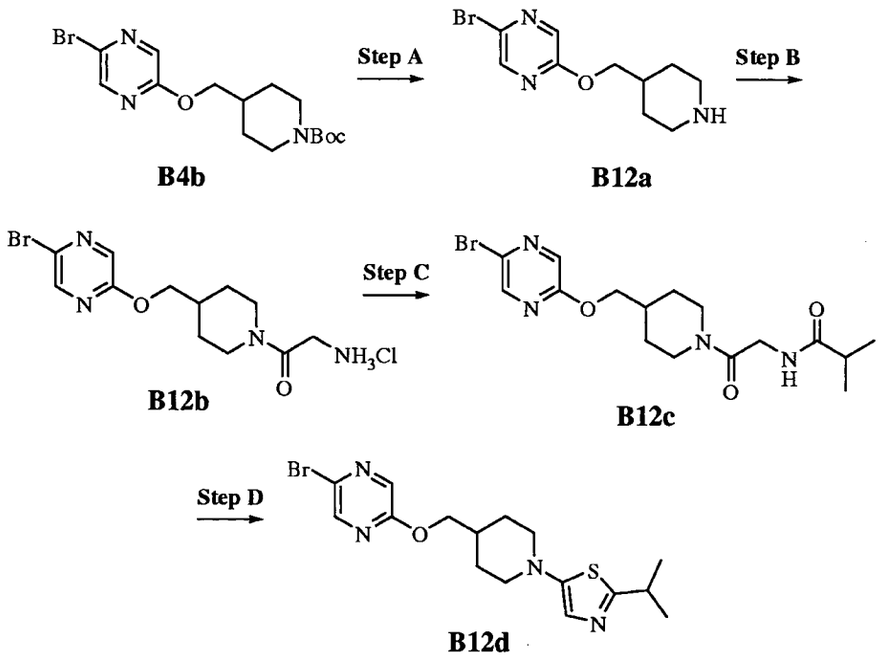
[00138] By following a similar procedure as the one used for preparing **B3** from **A1a** except substituting (R)-4-nitrophenyl tetrahydrofuran-3-yl carbonate for isopropyl chloroformate in the first step, **B11** is prepared with data identical to **B10**.

Example B12: 2-Isopropyl-5-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)thiazole.



[00139] By following a similar procedure as the one used for preparing **B3** from **A1d** except substituting **B12d** (see scheme below) for **A1d**, **B12** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (d, J = 1.5, 1H), 7.63 (d, J = 1.5, 1H), 7.60 (dd, J = 9.1, 2.5, 1H), 6.79 (s, 1H), 4.13 (d, J = 6.2, 1H), 3.53 (m, 4H), 3.46 (m, 2H), 3.37 (m, 4H), 3.14

(m, 1H), 2.82 (s, 3H), 2.79 (m, 2H), 1.91 (m, 3H), 1.53 (m, 2H), 1.34 (d, J = 6.9, 6H); ESIMS m/z for $(M+H)^+$ $C_{21}H_{33}N_6O_3S_2$ calcd.: 481.2, found: 481.2.



[00140] **Step A:** A sample of **B4b** (5.55 g, 14.9 mmol) is treated with 4 M HCl in dioxane (20 ml) and aged for 1 hour. The reaction is treated with water and the solvent is removed *in vacuo*. The residue is partitioned between ethyl acetate and 1 M NaOHOURS. The aqueous phase is isolated, extracted once more with ethyl acetate and discarded. The combined organics are dried over $MgSO_4$, filtered and evaporated to afford **B12a** which is used without further purification; ESIMS m/z for $(M+H)^+$ $C_{10}H_{15}BrN_3O$ calcd.: 272.0, found: 272.0.

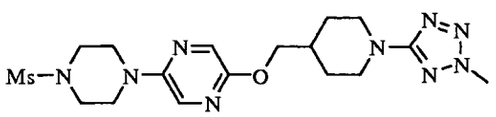
[00141] **Step B:** A solution of **B12a** (1 g, 3.7 mmol), Boc-gly (966 mg, 5.5 mmol) and HOBt (596 mg, 4.4 mmol) in N-methylpyrrolidinone (5 mL) is treated with EDC (845 mg, 845 mg, 4.4 mmol) and stirred for 1 hour. The reaction is then diluted with ethyl acetate and extracted with water and saturated aqueous sodium hydrogencarbonate twice. The organics are dried over $MgSO_4$, filtered and evaporated. The residue is treated with excess 4 M HCl in dioxane and aged for 1 hour. The mixture is slurried with

ether and the solid is collected to afford **B12b**; ESIMS *m/z* for $(M+H)^+$ $C_{12}H_{18}BrN_4O_2$ calcd.: 329.1, found: 329.1.

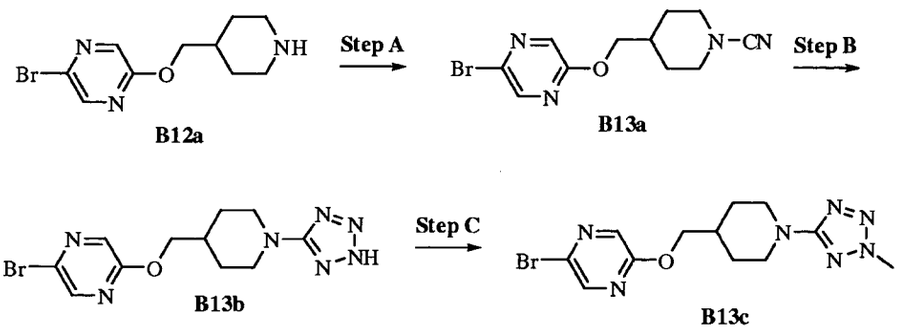
[00142] **Step C:** A suspension of **B12b** (400 mg, 1.1 mmol) in acetonitrile (8 mL) is treated with isobutyric anhydride (208 mg, 1.3 mmol) followed by triethylamine (360 mg, 3.6 mmol) and stirred for 1 hour. The solvent is removed and the residue is partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate. The aqueous phase is isolated, extracted once more with ethyl acetate and discarded. The combined organics are dried over $MgSO_4$, filtered and evaporated to afford **B12c** which is used without further purification; ESIMS *m/z* for $(M+H)^+$ $C_{16}H_{24}BrN_4O_3$ calcd.: 399.1, found: 399.1.

[00143] **Step D:** A solution of **B12c** (440 mg, 1.1 mmol) in *m*-xylene (2 mL) is treated with Laewesson's reagent (446 mmol, 1.1 mmol) and heated to 140 °C for 5 minutes and then purified on silica gel using a linear gradient of 0-100 % ethlyl acetate in hexane. The resulting material is further purified on preperative HPLC to afford **B12d**; ESIMS *m/z* for $(M+H)^+$ $C_{16}H_{22}BrN_4OS$ calcd.: 397.1, found: 397.1.

Example B13: 2-((1-(2-methyl-2H-tetrazol-5-yl)piperidin-4-yl)methoxy)-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazine.



[00144] By following a similar procedure as the one used for preparing **B3** from **A1d** except substituting **B13c** (see scheme below) for **A1d**, **B13** is prepared; ^1H NMR (400 MHz, CD_3CN) δ 7.84 (d, *J* = 0.9 Hz, 1H), 7.72 (d, *J* = 1.2 Hz, 1H), 4.10 (s, 3H), 4.10 (d, *J* = 4.8 Hz, 2H), 4.02 (m, 2H), 3.51 (t, *J* = 3.9 Hz, 4H), 3.27 (t, *J* = 3.9 Hz, 4H), 2.91 (dt, *J* = 2.1, 9.6 Hz, 2H), 2.79 (s, 3H), 1.39 (ddd, *J* = 3.3, 9.3, 16.8 Hz, 4H), 2.20 (t, *J* = 5.4 Hz, 2H), 0.88 (m, 2H); ESIMS $(M+H)^+$ $C_{17}H_{28}N_9O_3S$ cacld.: 438.2, found 438.2 (M+1).



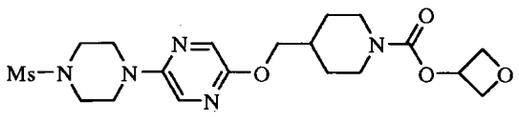
[00145] **Step A:** To a stirred suspension of **B12a** (200 mg, 0.74 mmol) and sodiumhydrogencarbonate (0.15 g, 1.78 mmol) in a mixed solvent of water (0.1 mL) and dichloromethane (1 mL) at 0 °C is added cyanogen bromide (93 mg, 0.89 mmol) in one portion. The reaction is then stirred at room temperature for 4 h and additional cyanogen bromide (93 mg, 0.89 mmol) is added. After stirring overnight, the reaction is diluted with dichloromethane (30 mL), dried over $MgSO_4$, and evaporated to give **B13a**; ESIMS $(M+H)^+$ $C_{11}H_{14}BrN_4O$ calcd.: 297.0, found 297.0.

[00146] **Step B:** The above crude **B13a** is stirred with sodium azide (143 mg, 2.2 mmol) and ammonium chloride (117 mg, 0.22 mmol) in anhydrous N,N-dimethylformamide (2 mL) at 110 °C for 2 hours. Additional sodium azide (143 mg, 2.2 mmol) and ammonium chloride (117 mg, 0.22) are added. After stirring overnight, water is added slowly to precipitate the product. The off white solid is collected by filtration, washed with water (10 mL) and dried *in vacuo* to afford **B13b**; ^1H NMR (400 MHz, DMSO-d_6) δ 8.41 (d, J = 1.2 Hz, 1H), 8.20 (d, J = 0.9 Hz, 1H), 4.18 (d, J = 5.1 Hz, 2H), 3.86 (m, 2H), 3.02 (dt, J = 2.1, 9.6 Hz, 2H), 2.03 (m, 1H), 1.81 (m, 2H), 1.34 (ddd, J = 3.3, 9.6, 18.9 Hz, 2H); ESIMS $(M+H)^+$ $C_{11}H_{15}BrN_7O$ calcd.: 340.0, found: 340.0.

[00147] **Step C:** A mixture of **B13b** (50 mg, 0.15 mmol), iodomethane (14 uL, 0.22 mmol) and K_2CO_3 (28 mg, 0.25 mmol) in anhydrous N,N-dimethylformamide (1 mL) is stirred at room temperature for 3 hours. The solvent is evaporated *in vacuo* and the crude **B13c** is used without purification: ESIMS $(M+H)^+$ $C_{12}H_{17}BrN_7O$ calcd.: 354.1, found 354.0 (M+1).

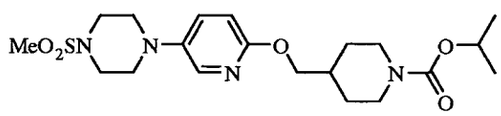
69

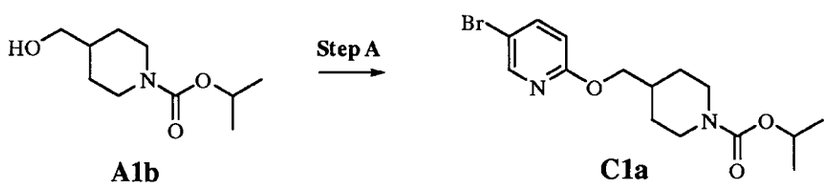
Example B14. Oxetan-3-yl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate



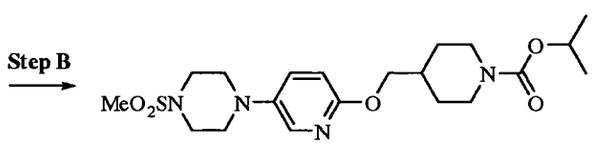
[00148] By following a similar procedure as the one used for preparing **B3** from **A1a** except substituting 4-nitrophenyl oxetan-3-yl carbonate for isopropyl chloroformate in the first step, **B14** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{19}H_{30}N_5O_6S$ calcd: 456.2, found: 456.0.

Example C1: Isopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate.





A1b **C1a**



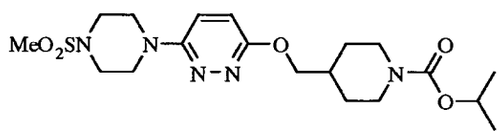
Example C1

[00149] **Step A:** A solution of 2-chloro-5-bromopyridine (344 mg, 1.8 mmol) and **A1b** (300 mg, 1.5 mmol) in dimethylformamide (3 mL) is treated with NaH (43 mg, 1.8 mmol) and the reaction is allowed to stir overnight. After quenching by addition of water, the reaction is diluted with ethyl acetate. The organics are isolated and extracted with water once more, dried over $MgSO_4$, filtered and evaporated. The residue is

purified on a silica gel column using a linear gradient of 0-50% ethyl acetate in hexane to afford **C1b**; ESIMS *m/z* for $(M+H)^+$ $C_{15}H_{22}ClN_2O_3$ calcd.: 313.1, found: 313.1.

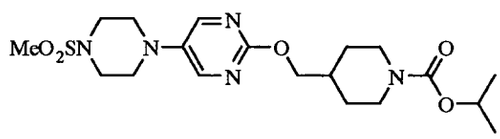
[00150] **Step B:** By following a similar Pd coupling procedure described for preparing **B1** except substituting **C1a** as the bromide coupling partner, **B14** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, *J* = 2.9, 1H), 7.18 (dd, *J* = 3.0, 8.9, 1H), 6.69 (d, *J* = 8.9, 1H), 4.91 (m, 1H), 4.18 (m, 2H), 4.09 (d, *J* = 6.4, 2H), 3.38 (m, 4H), 3.17 (m, 4H), 2.84 (s, 3H), 2.77 (m, 2H), 1.96 (m, 1H), 1.81 (m, 2H), 1.29 (m, 2H), 1.24, d, *J* = 6.3, 6H); ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{33}N_4O_5S$ calcd.: 441.2, found: 441.2.

Example C2: Isopropyl 4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridazin-3-yloxy)methyl)piperidine-1-carboxylate.



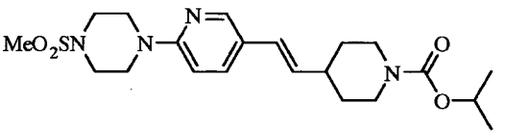
[00151] By following a similar procedure as the one used for preparing **C1** from **A1b** except substituting 2,5-dichloropyridazine for 2-chloro-5-bromopyridine in the first step, **C2** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.04 (d, *J* = 9.6, 1H), 6.88 (d, *J* = 9.6, 1H), 4.91 (m, 1H), 4.29 (m, 2H), 4.18 (m, 2H), 3.64 (m, 4H), 3.35 (m, 4H), 2.81 (s, 3H), 2.77 (m, 2H), 2.03 (m, 1H), 1.80 (m, 2H), 1.29 (m, 2H), 1.24, d, *J* = 6.4, 6H); ESIMS *m/z* for $(M+H)^+$ $C_{19}H_{32}N_5O_5S$ calcd.: 442.2, found: 442.3.

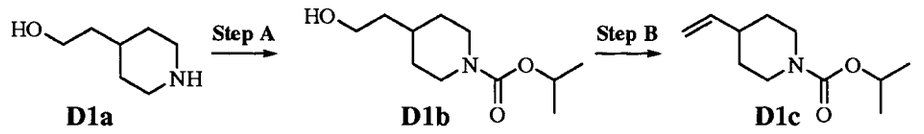
Example C3: Isopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrimidin-2-yloxy)methyl)piperidine-1-carboxylate.

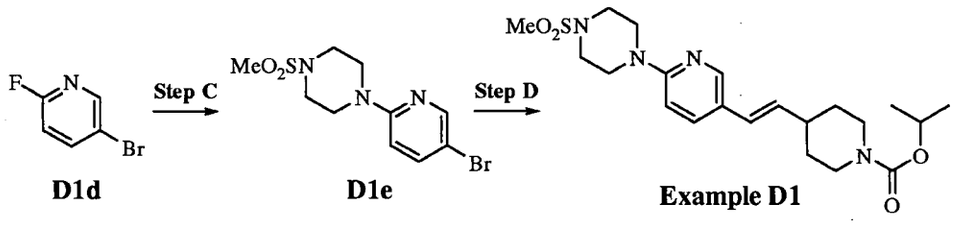


[00152] By following a similar procedure as the one used for preparing **C1** from **A1b** except substituting 2-chloro-5-bromopyrimidine for 2-chloro-5-bromopyridine in the first step, **C3** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.38 (s, 2H), 4.91 (sept., J = 6.3 Hz, 1H), 4.23 (m, 5H), 3.50 (m, 4H), 3.29 (m, 4H), 2.87 (s, 3H), 2.76 (m, 2H), 2.04 (m, 1H), 1.84 (m, 2H), 1.27 (m, 1H), 1.24 (d, J = 6.3 Hz, 6H).; ESIMS *m/z* for $(M+H)^+$ $C_{19}H_{32}N_5O_5S$ calcd.: 442.2, found: 442.3.

Example D1: (E)-isopropyl 4-(2-(6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yl)vinyl)piperidine-1-carboxylate.







[00153] **Step A:** A solution of **D1a** (10 g, 0.077 mol) in dichloromethane (100 mL) is treated with a solution of isopropyl chloroformate in toluene (93 mL of a 1M solution) dropwise. The reaction is then stirred at room temperature for 2.5 hours and quenched with saturated aqueous ammonium chloride solution. The phases are separated and the aqueous phase is extracted once more with dichloromethane and discarded. The combined organics are extracted once with 1M HCl, once with saturated aqueous sodiumhydrogencarbonate, dried over $MgSO_4$, filtered and evaporated to afford **D1b**; ESIMS *m/z* for $(M+H)^+$ $C_7H_{16}NO$ calcd.: 130.1, found: 130.1.

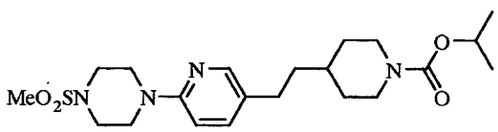
[00154] **Step B:** A cold (ice/water bath) solution of **D1b** (9.9 g, 0.046 mol) and triethylamine (6.7 mL, 0.048 mol) in dichloromethane is treated with the dropwise addition of methanesulfonyl chloride (3.7 mL, 0.048 mol) and stirred for 2 hours. The mixture is treated with water and extracted with dichloromethane. The organics are pooled, dried over $MgSO_4$, filtered and concentrated. The crude material is diluted in acetone (10 mL) and added dropwise to a slurry of lithium bromide (12 g, 0.138 mol) in acetone (50 mL). The reaction is heated to 35°C and maintained overnight. After cooling to room temperature, the reaction is concentrated, diluted with ethyl acetate and washed with water. The organic phase is collected, dried over $MgSO_4$, and concentrated. This residue is diluted in tetrahydrofuran (150 mL) and treated with the portionwise addition of potassium tert-butoxide (23.05 g, 0.2054 mol) every 30 min for 3 hours. Reaction is then heated to 40 °C and maintained overnight. Once the reaction had cooled to room temperature, saturated aqueous ammonium chloride is introduced and the reaction extracted with Et_2O. Organics are collected, dried over $MgSO_4$, concentrated, and purified *via* distillation (68°-70 °C, 180 mTorr) to afford **D1c**. ESIMS *m/z* for $(M+H)^+$ $C_{11}H_{20}NO_2$ calcd.: 198.3 found: 198.1.

[00155] **Step C:** A solution of **D1d** (321 mg, 1.8 mmol) and methanesulfonylpiperazine (300 mg, 1.8 mmol) in N-methylpyrrolidinone (2mL) is treated with K_2CO_3 (380 mg, 2.7 mmol) and heated to 160 °C for 5 minutes. The reaction is then partitioned between ethyl acetate and water and the organics are extracted with water again, dried over $MgSO_4$, filtered, evaporated and purified on silica gel using 0-100% ethyl acetate in hexane to afford **D1e**; ESIMS *m/z* for $(M+H)^+$ $C_{10}H_{15}BrN_3O_2S$ calcd.: 320.0, found: 320.1.

[00156] **Step D:** A solution of **D1e** (50 mg, 0.18 mmol), **D1c** (44 mg, 0.22 mmol) Pd_2dba_3 (5 mg, 0.006 mmol) and tri-*tert*-butylphosphonium tetrafluoroborate (3.2 mg, 0.011 mmol) and dicyclohexylmethylamine (72 mg, 0.37 mmol) in dioxane (1mL) is heated to 120 °C for 1 hour. The reaction is then partitioned between ethyl acetate and water and the organics are extracted with water once more, dried over $MgSO_4$, filtered, evaporated and purified on silica gel using a gradient of 0-100 % ethyl acetate in hexane to afford **D1**; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.11 (d, J = 2.3, 1H), 7.57 (dd, J = 8.8, 2.4, 1H), 6.63 (d, J = 8.8, 1H), 6.27 (d, J = 15.9, 1H), 5.99 (dd, J = 16.0, 6.9, 1H), 4.91 (m,

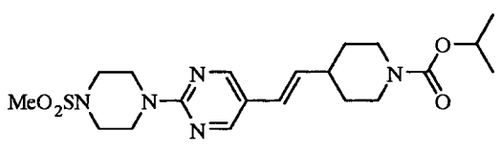
1H), 4.17 (m, 2H), 3.67 (m, 4H), 3.32 (m, 4H), 2.80 (m, 2H), 2.80 (s, 3H), 2.23 (m, 1H), 1.77 (m, 2H), 1.38 (m, 2H), 1.24, d, J = 6.2, 6H); ESIMS m/z for $(M+H)^+$ $C_{21}H_{33}N_4O_4S$ calcd.: 437.2, found: 437.2.

Example D2. Isopropyl 4-(2-(6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yl)ethyl)piperidine-1-carboxylate.



[00157] A solution of **D2** (25 mg, 0.057 mmol) in methanol (2 mL) is treated with 10% Pd/C (5 mg) and hydrogenated for 1 hour. The atmosphere is exchanged back for nitrogen and the reaction is filtered though a plug of Celite® and the solvent is removed to afford **D2**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (d, J = 2.2, 1H), 7.35 (dd, J = 8.6, 2.4, 1H), 6.63 (d, J = 8.6, 1H), 4.90 (m, 1H), 4.12 (m, 2H), 3.62 (m, 4H), 3.32 (m, 4H), 2.80 (s, 3H), 2.68 (m, 2H), 2.52 (m, 2H), 1.70 (m, 2H), 1.52 (m, 2H), 1.42 (m, 1H), 1.23 (d, J = 6.2, 6H), 1.12 (m, 2H); ESIMS m/z for $(M+H)^+$ $C_{21}H_{35}N_4O_4S$ calcd.: 439.2, found: 439.3.

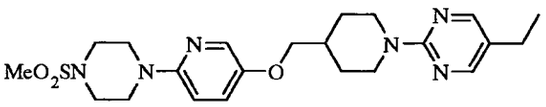
Example D3. (E)-Isopropyl 4-(2-(2-(4-(methylsulfonyl)piperazin-1-yl)pyrimidin-5-yl)vinyl)piperidine-1-carboxylate.

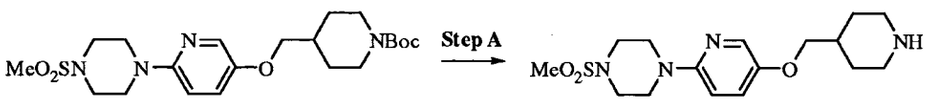


[00158] By following a similar procedure as the one used for preparing **D1** from **D1a** except substituting 2-chloro-5-bromopyrimidine for **D1d**, **D3** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.38 (s, 2H), 6.18 (d, J = 16.2 Hz, 1H), 6.05 (dd, J = 16.1, 6.6 Hz, 1H), 4.92 (m, 1H), 4.18 (m, 2H), 3.98 (m, 4H), 3.30 (m, 4H), 2.80 (s, 3H), 2.80 (m, 2H),

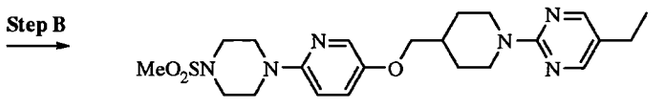
2.29 (m, 1H), 1.76 (m, 2H), 1.38 (m, 2H), 1.24 (d, J = 6.2 Hz, 6H); ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{32}N_5O_4S$ calcd.: 438.2, found: 438.3.

Example E1. 5-Ethyl-2-(4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)pyrimidine.





B2 **E1a**



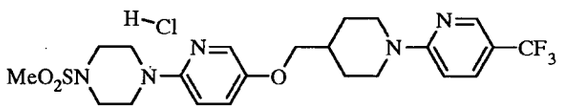
Example E1

[00159] **Step A:** A sample of **B2** (202 mg, 0.445 mmol) is treated with 4 M HCl in dioxane (3 mL) and aged for 1 hour. The solvent is then removed and the residue is partitioned between ethyl acetate and 1 M NaOH. The aqueous phase is isolated, extracted once more with ethyl acetate and discarded. The combined organics are dried over $MgSO_4$, filtered and evaporated to afford **E1a**; ESIMS *m/z* for $(M+H)^+$ $C_{16}H_{27}N_4O_3S$ calcd.: 355.2, found: 355.2.

[00160] **Step B:** The resulting material is treated with 2-chloro-5-ethylpyrimidine (121 mg, 0.85 mmol), CuI (12 mg, 0.063 mmol), diisopropylethylamine (176 mg, 1.4 mmol) and N-methylpyrrolidinone (2 mL). The resulting solution is sealed in a reaction vial and heated to 160 °C for 10 minutes using a microwave reactor. The reaction is then diluted with ethyl acetate and extracted with water once, 1 M HCl once and saturated aqueous sodiumhydrogencarbonate once, dried over $MgSO_4$, filtered, evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane followed

by lyophilization from 1 M HCl to afford **E1** as the HCl salt; ^{1}H NMR (DMSO-d6, 400 MHz): δ 8.27 (s, 2H), 7.82 (d, *J* = 2.9, 1H), 7.50 (m, 1H), 7.05 (m, 1H), 4.63 (m, 2H), 3.86 (d, *J* = 6.4, 2H), 3.57 (m, 4H), 3.22 (m, 4H), 2.91 (s, 3H), 2.91 (m, 2H), 2.43 (dd, *J* = 15.1, 7.6, 2H), 2.03 (s, 1H), 1.82 (m, 2H), 1.22 (m, 2H), 1.13 (dd, *J* = 7.6, 7.6, 36H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{33}N_6O_3S$ calcd.: 461.2, found: 461.2.

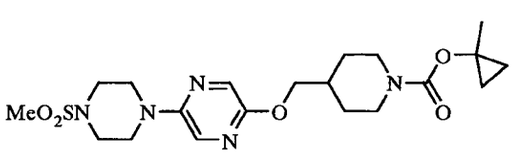
Example E2. 1-(Methylsulfonyl)-4-(5-((1-(5-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)methoxy)pyridin-2-yl)piperazine.

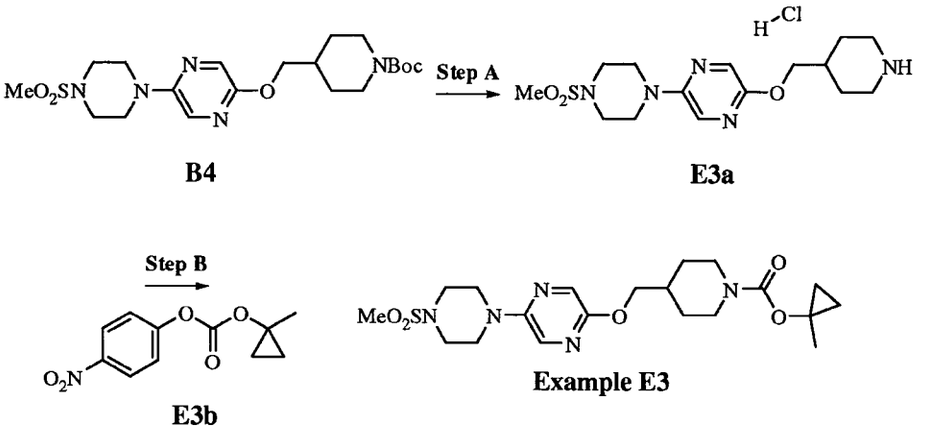


[00161] By following a similar procedure as the one used for preparing **E1** from **B2** except substituting the following procedure for **Step B**, **E2** is prepared;

[00162] A sample of **E1a** hydrochloride (900 mg, 2.3 mmol) is treated with 2-chloro-3-trifluoromethylpyridine (501 mg, 2.76 mmol), K_2CO_3 (795 mg, 5.8 mmol), N-methylpyrrolidinone (10 mL) and water (8 mL) and heated in a sealed vessel in a microwave reactor at 160 °C for 10 minutes. The resulting suspension is treated with ethyl acetate and water and filtered. The resulting solid is washed with water and ethyl acetate, dissolved in 1 M HCl and lyophilized to afford **E2** ; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22 (m, 1H), 8.10 (dd, *J* = 9.8, 2.3, 1H), 7.86 (dd, *J* = 9.9, 2.9, 1H), 7.60 (d, *J* = 2.9, 1H), 7.53 (d, *J* = 9.8, 1H), 7.42 (d, *J* = 9.1, 1H), 4.30 (m, 2H), 3.94 (d, *J* = 6.2, 1H), 3.71 (m, 4H), 3.37 (m, 4H), 2.86 (s, 3H), 2.28 (m, 1H), 2.06 (m, 2H), 1.57 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{29}F_3N_5O_3S$ calcd.: 500.2, found: 500.2.

Example E3. 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





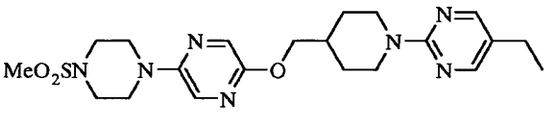
B4 E3a

E3b Example E3

[00163] **Step A:** A sample of **B4** (745 mg, 0.16 mmol) is treated with 4 M HCl in dioxane and stirred for 3 hours. The solvent is decanted and the residue is lyophilized from water to afford **E3a**; ESIMS *m/z* for $(M+H)^+$ $C_{15}H_{26}N_5O_3S$ calcd.: 356.2, found: 356.2.

[00164] **Step B:** A sample of **E3a** (181.8 mg, 0.46 mmol) is treated with N, N-dimethylformamide (1.5 mL), **E3b** (110 mg, 0.46 mmol) and diisopropylethylamine (242 µL, 1.4 mmol) and stirred overnight. The reaction is then partitioned between ethyl acetate and water and the organics are isolated, extracted with 1 M NaOH three times, dried over $MgSO_4$, filtered, evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **E3**; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, J = 1.5, 1H), 7.62 (d, J = 1.4, 1H), 4.18 (m, 2H), 4.08 (d, J = 6.5, 2H), 3.52 (m, 4H), 3.36 (m, 4H), 2.82 (s, 3H), 2.72 (m, 2H), 1.93 (m, 1H), 1.80 (m, 2H), 1.56 (d, J = 9.9, 3H), 1.23 (m, 2H), 0.87 (m, 2H), 0.62 (m,2H); ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{32}N_5O_5S$ calcd.: 454.2, found: 454.2.

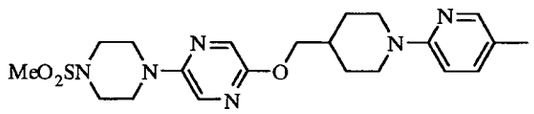
Example E4. 5-Ethyl-2-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)pyrimidine.



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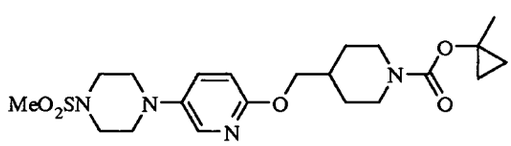
[00165] By following a similar procedure as the one used for preparing **E1** from **E1a** except substituting **E3a** for **E1a**, **E4** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (s, 2H), 7.88 (d, *J* = 1.4, 1H), 7.63 (d, *J* = 1.5, 1H), 4.76 (m, 2H), 4.11 (d, *J* = 6.6, 2H), 3.52 (m, 4H), 3.37 (m, 4H), 2.90 (m, 2H), 2.82 (s, 3H), 2.45 (dd, *J* = 15.2, 7.6, 2H), 2.08 (m, 2H), 1.90 (m, 2H), 1.33 (ddd, *J* = 24.9, 12.4, 4.2, 2H), 1.18 (dd, *J* = 7.6, 7.6, 3H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{32}N_7O_3S$ calcd.: 462.2, found: 462.3.

Example E5. 2-((1-(5-Methylpyridin-2-yl)piperidin-4-yl)methoxy)-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazine.



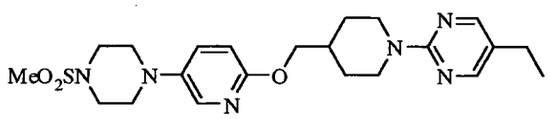
[00166] A mixture of **E3a** (103 mg, 0.26 mmol), 2-bromo-5-methylpyridine (45.3 mg, 0.26 mmol), Pd_2dba_3 (4.8 mg, 0.005 mmol), xantphos (9.1 mg, 0.016 mmol), sodium *tert*-butoxide (78 mg, 0.815 mmol) and toluene (1.5 mL) is purged with nitrogen for 5 minutes and heated in an oil bath at 100 °C overnight. The reaction is cooled to room temperature and diluted with water and ethyl acetate. The organics are dried over $MgSO_4$, filtered, evaporated and purified by silica gel column chromatography using a linear gradient of 0-100 % ethyl acetate in hexane to afford **E5**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (m, 1H), 7.88 (d, *J* = 1.4, 1H), 7.30 (m, 1H), 6.62 (d, *J* = 8.6, 1H), 4.27 (m, 2H), 4.11 (d, *J* = 6.6, 1H), 3.53 (m, 4H), 3.37 (m, 4H), 2.82 (m, 2H), 2.82 (s, 3H), 2.19 (s, 3H), 2.02 (m, 1H), 1.91 (m, 2H), 1.42 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{31}N_6O_3S$ calcd.: 447.2, found: 447.3.

Example E6. 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate.



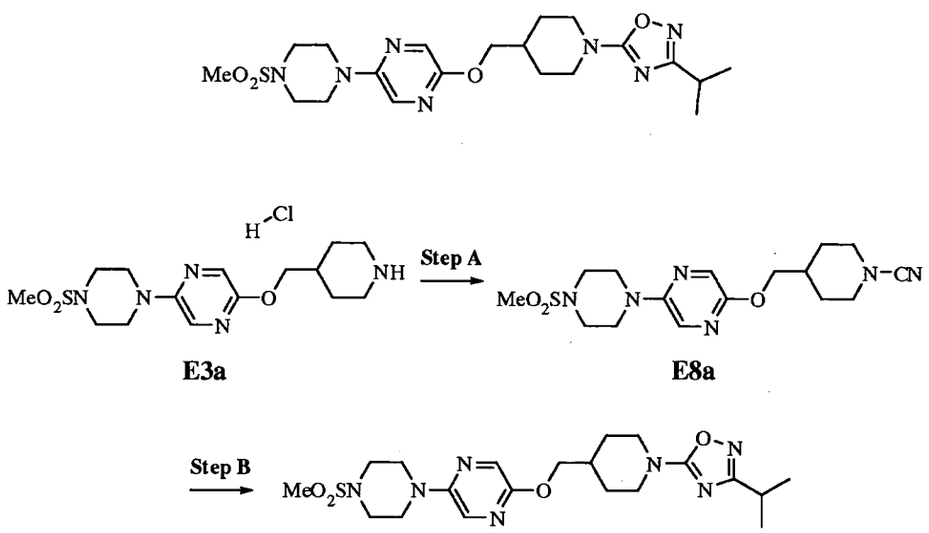
[00167] By following a similar procedure as the one used for preparing **E3** from **B4** except substituting *tert*-butyl 4-((5-(4-(methylsulfonyl) piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate for **B4**, **E6** is prepared; *tert*-Butyl 4-((5-(4-(methylsulfonyl) piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate is prepared in an analogous fashion to **B4** except using 2-fluoro-5-bromopyridine instead of **A1d**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, J = 2.9, 1H), 7.28 (dd, J = 8.9, 3.0, 1H), 6.68 (d, J = 8.9, 1H), 4.18 (m, 2H), 4.08 (d, J = 6.5, 2H), 3.38 (m, 4H), 3.14 (m, 4H), 2.83 (s, 3H), 2.73 (m, 2H), 1.93 (m, 1H), 1.79 (m, 2H), 1.54 (s, 3H), 1.23 (m, 2H), 0.86 (m, 2H), 0.61 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{33}N_4O_5S$ calcd: 453.2, found: 453.3.

Example E7. 5-Ethyl-2-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyridin-2-yloxy)methyl)piperidin-1-yl)pyrimidine.



[00168] By following a similar procedure as the one used for preparing **E1** from **E1a** except substituting *tert*-butyl 4-((5-(4-(methylsulfonyl) piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate for **E1a**, **E7** is prepared; *tert*-Butyl 4-((5-(4-(methylsulfonyl) piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate is prepared in an analogous fashion to **B4** except using 2-fluoro-5-bromopyridine instead of **A1d**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (s, 2H), 7.78 (d, J = 2.9, 1H), 7.28 (dd, J = 8.9, 3.0, 1H), 6.69 (d, J = 9.0, 1H), 4.73 (m, 2H), 4.11 (d, J = 6.6, 1H), 3.38 (m, 4H), 3.14 (m, 4H), 2.89 (m, 2H), 2.83 (s, 3H), 2.44 (dd, J = 15.2, 7.6, 2H), 2.08 (m, 1H), 1.90 (m, 2H), 1.34 (ddd, J = 24.8, 12.4, 4.1, 2H), 1.73 (dd, J = 7.6, 7.6, 3H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{33}N_6O_3S$ calcd.: 461.2, found: 461.3.

Example E8. 3-Isopropyl-5-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole.



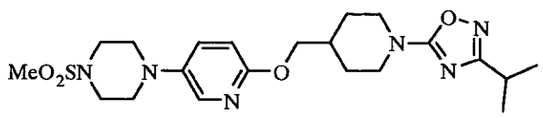
Example E8

[00169] **Step A:** A cold (ice/water bath) solution of **E3a** (256 mg, 0.65 mmol) in dichloromethane (5 mL) is treated with a solution of K_2CO_3 (298 mg, 2.2 mmol) in water (5 mL). The vigorously stirred solution is treated with a solution of cyanogen bromide (76.1 mg, 0.72 mmol) in dichloromethane (2 mL) and the reaction is allowed to stir cold for 3 hours. The phases are then separated and the organic phase is dried over $MgSO_4$, filtered and evaporated to afford **E8a** which is used without further purification; ESIMS *m/z* for $(M+H)^+$ $C_{16}H_{25}N_6O_3S$ calcd.: 381.2, found: 381.1.

[00170] **Step B:** A solution of **E3a** (215.5 mg, 0.57 mmol) in dioxane (2 mL) is treated with N'-hydroxyisobutyrimidamide (86.8 mg, 0.85 mmol) and $ZnCl_2$ (115.8 mgL, 0.85 mmol) and stirred at 100 °C overnight. The reaction is then partitioned between ethyl acetate and 1 M NaOH and the organics are isolated, dried over $MgSO_4$, filtered, evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **E8**; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.88 (d, J = 1.4, 1H), 7.62 (d, J = 1.4, 1H), 4.19 (m, 2H), 4.11 (d, J = 6.5, 2H), 3.53 (m, 4H), 3.37 (m, 4H), 3.08 (ddd, J = 12.9, 12.9, 2.8, 2H), 2.87 (m, 1H), 2.82 (s, 3H), 2.03 (m, 1H), 1.91 (m, 2H), 1.43 (ddd, J = 25.2, 12.5, 4.4, 2H), 1.28 (d, J = 7.0, 3H); ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{32}N_7O_4S$ calcd.: 466.2, found: 466.3.

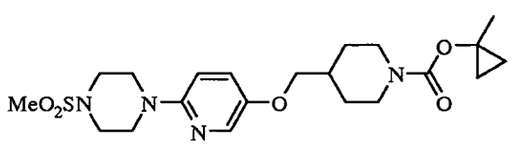
86

Example E9. 3-Isopropyl-5-(4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyridin-2-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole.



[00171] By following a similar procedure as the one used for preparing **E8** from **B4** except substituting *tert*-butyl 4-((5-(4-(methylsulfonyl) piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate for **B4**, **E9** is prepared; *tert*-Butyl 4-((5-(4-(methylsulfonyl) piperazin-1-yl)pyridin-2-yloxy)methyl)piperidine-1-carboxylate is prepared in an analogous fashion to **B4** except using 2-fluoro-5-bromopyridine instead of **A1d**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, *J* = 2.9, 1H), 7.29 (dd, *J* = 8.9, 3.0, 1H), 6.69 (d, *J* = 8.9, 1H), 4.17 (m, 2H), 4.13 (d, *J* = 6.5, 1H), 3.40 (m, 4H), 3.17 (m, 4H), 3.08 (ddd, *J* = 12.9, 12.9, 2.8, 2H), 2.88 (m, 1H), 2.84 (s, 3H), 2.03 (m, 1H), 1.91 (m, 2H), 1.34 (ddd, *J* = 25.1, 12.5, 4.4, 2H), 1.28 (d, *J* = 7.0, 3H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{33}N_6O_4S$ calcd.: 465.2, found: 465.3.

Example E10. 1-Methylcyclopropyl 4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate.

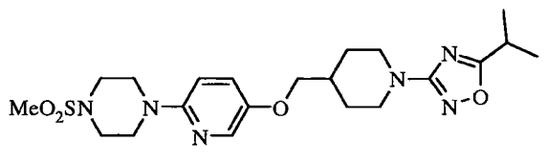


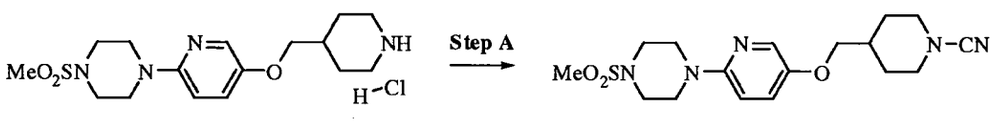
[00172] By following a similar procedure as the one used for preparing **E3** from **B4** except substituting **B2** for **B4**, **E10** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90 (d, *J* = 2.9, 1H), 7.14 (dd, *J* = 9.1, 3.0, 1H), 6.65 (d, *J* = 9.0, 1H), 4.12 (m, 2H), 3.77 (d, *J* = 6.3, 1H), 3.54 (m, 4H), 3.33 (m, 4H), 2.80 (s, 3H), 2.73 (m, 2H), 1.92 (m, 1H), 1.89 (m, 2H), 1.54 (s, 3H), 1.23 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{33}N_4O_5S$ calcd.: 453.2, found: 453.2.

[00173]

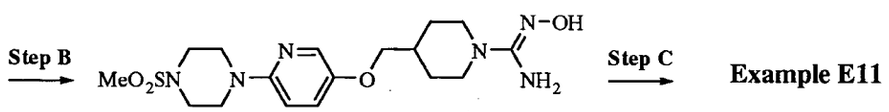
81

Example E11. 5-Isopropyl-3-(4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole.





E1a·HCl **E11a**



E11b

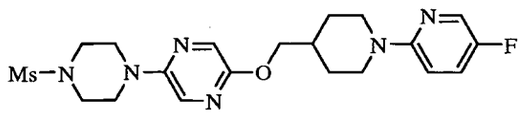
[00174] **Step A:** A mixture of **E1a·HCl** (202.3 mg, 0.52 mmol) and K_2CO_3 (143 mg, 1.0 mmol) in water (3 mL) is cooled to ice/water bath temperature and treated dropwise with a solution of cyanogen bromide (60.3 mg, 0.57 mmol) in dichlormethane (3 mL) and stirred for 2 hours while cooled. The reaction is then diluted with dichloromethane, extracted with water, dried over $MgSO_4$, filtered and evaporated to afford **E11a** which is used without further purification; ESIMS *m/z* for $(M+H)^+$ $C_{17}H_{26}N_5O_3S$ calcd.: 380.2, found: 380.2.

[00175] **Step B:** A solution of **E11a** (152.4 mg, 0.40 mmol) and hydroxylamine (492 µL of a 50% aqueous solution, 0.80 mmol) in ethanol (2 mL) is heated to 60 °C in a sealed vessel overnight. The reaction is cooled to room temperature and the resulting sample of **E11b**; ESIMS *m/z* for $(M+H)^+$ $C_{17}H_{29}N_6O_4S$ calcd.: 413.2, found: 413.2.

[00176] **Step C:** A solution of **E11b** (134.2 mg, 0.32 mmol) and isobutyric anhydride (50 mg, 0.32 mmol) in dioxane is heated at 400 W in a microwave reactor for 10 minutes (~120 °C). The reaction is cooled to room temperature, evaporated and

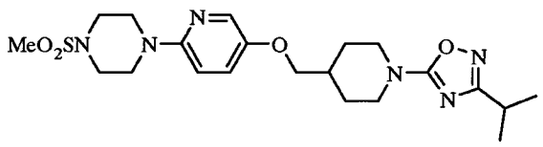
partitioned between ethyl acetate and saturated aqueous sodium hydrogencarbonate. The organics are isolated, dried over $MgSO_4$, filtered, evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane and lyophilized from 1 M HCl to afford **E11** as an HCl salt; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, J = 3.0, 1H), 7.16 (dd, J = 9.1, 3.0, 1H), 6.65 (d, J = 9.1, 1H), 4.06 (m, 2H), 3.80 (d, J = 6.4, 1H), 3.54 (m, 4H), 3.33 (m, 4H), 3.07 (m, 1H), 2.92 (ddd, J = 12.7, 12.7, 2.7, 1H), 2.80 (s, 3H), 2.73 (m, 2H), 1.99 (m, 1H), 1.88 (m, 2H), 1.42 (m, 2H), 1.34 (d, J = 7.0, 6H); ESIMS m/z for $(M+H)^+$ $C_{21}H_{33}N_6O_4S$ calcd.: 465.2, found: 453.3.

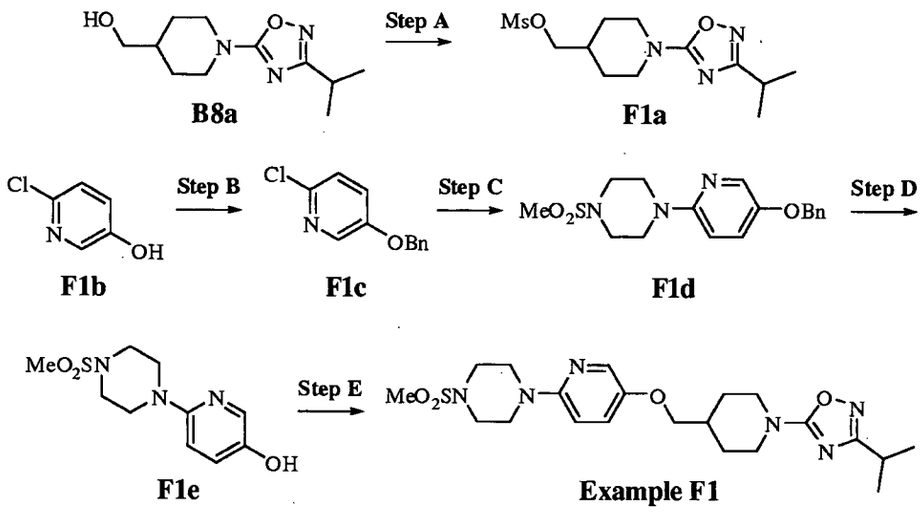
Example E12. 2-((1-(5-Fluoropyridin-2-yl)piperidin-4-yl)methoxy)-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazine.



[00177] By following a similar procedure as the one used for preparing **E5** from **E3a** except substituting 2-bromo-5-fluoropyridine for 2-bromo-5-methylpyridine and dicyclohexyl(2',6'-dimethoxybiphenyl-4-yl)phosphine for xantphos, **E12** is prepared; ESIMS m/z for $(M+H)^+$ $C_{20}H_{28}FN_6O_3S$ calcd: 451.2, found: 451.2.

Example F1. 3-Isopropyl-5-(4-((6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole





[00178] **Step A:** By following a similar procedure as the one used for preparing **B5c** from **B5b** except substituting **B8a** for **B5b**, **F1a** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{12}H_{22}N_3O_4S$ calcd: 304.1, found: 304.1.

[00179] **Step B:** A solution of **F1b** (3.00 g, 23.0 mmol) and benzyl chloride (2.93 mL, 25.5 mmol) in acetonitrile (50 mL) is treated with Cs_2CO_3 (15.0 g, 46.0 mmol) and the reaction mixture is heated at 90 °C for 2hours, cooled and filtered. The solvents are evaporated and the crude compound purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **F1c**; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, J = 0.8, 2.8 Hz, 1H), 7.42 (m, 4H), 7.39 (m, 1H), 7.25 (m, 2H), 5.12 (s, 2H); ESIMS calcd. for $[M+H]^+$ $C_{12}H_{11}ClNO$: 220.1 found: 220.1.

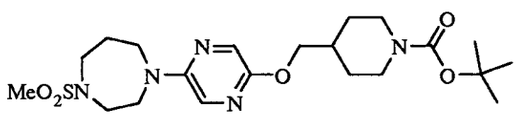
[00180] **Step C: F1c** (2.67 g, 12.2 mmol), 1-methanesulfonyl piperazine (3 g, 18.3 mmol), $Pd(OAc)_2$ (548 mg, 2.4 mmol), ((2-dicyclohexyl)phosphino)biphenyl (1.7 g, 4.8 mmol), NaO*t*Bu (3.5 g, 36.6 mmol) and toluene (20 mL) are charged to a sealed flask and degassed with bubbling Ar for 30 minutes. The mixture is heated at 120 °C for 18h, then is hot filtered to remove particulates. The filter cake is washed with ethyl acetate (10 mL) and water (20 mL) and the filtrates are combined and extracted with ethyl acetate (20 mL). The organic layer is extracted with 1N HCl (3 x 20 mL) and discarded. The acidic layer is then basified with NaOH and extracted with ethyl acetate (3 x 20 mL). The remaining organic layers are combined, dried ($MgSO_4$), filtered and

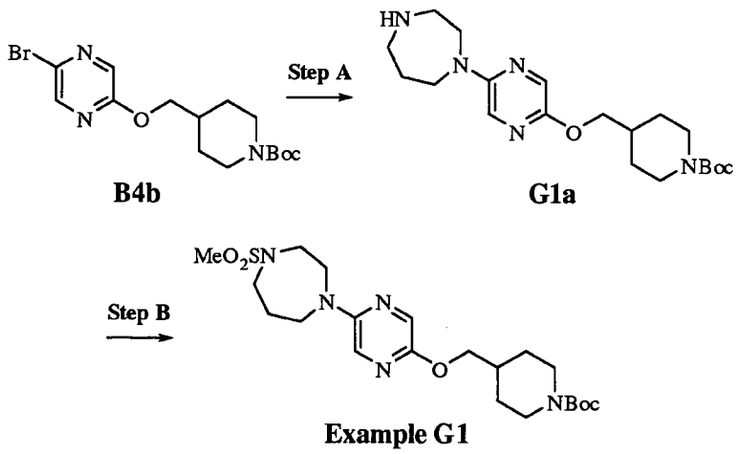
concentrated. The residue is recrystallized from ethyl acetate /Hexane to provide **F1d**; ESIMS calcd. for $[M+H]^+$ $C_{17}H_{22}N_3O_3S$: 348.1 found: 348.1.

[00181] **Step D:** A solution of **F1d** (1.3 g, 3.88 mmol) in EtOH is treated with Pd/C (0.2 g of 10%, wet). The reaction is stirred under H_2 (1 atmosphere) for 12 hours. The mixture is filtered and concentrated to provide **F1e** which is used without further purification: ESIMS calcd. for $[M+H]^+$ $C_{10}H_{16}N_3O_3S$: 258.1 found: 258.1.

[00182] **Step E:** A solution of **F1e** (97.7 mg, 0.38 mmol) and **F1a** (115.2 mg, 0.38 mmol) in N, N-dimethylformamide (1.5 mL) is treated with Cs_2CO_3 (185.6 mg, 0.57 mmol) and heated to 60 °C overnight. The reaction is cooled to room temperature, diluted with ethyl acetate, extracted with water, dried over $MgSO_4$, filtered, evaporated and purified by silica gel column chromatography using a linear gradient of 0 to 100% ethyl acetate in hexane and then lyophilized from HCl to afford **F1** as an HCl salt; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.01 (m, 0.5H), 7.92 (d, J = 2.8, 1H), 7.16 (dd, J = 9.1, 3.1, 1H), 6.66 (d, J = 9.1, 1H), 4.20 (m, 2H), 3.81 (d, J = 6.3, 1H), 3.54 (m, 4H), 3.33 (m, 4H), 3.09 (m, 2H), 2.88 (m, 1H), 2.81 (s, 3H), 2.00 (m, 1H), 1.92 (m, 2H), 1.44 (m, 2H), 1.28 (d, J = 7.0, 3H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{33}N_6O_4S$ calcd.: 465.2, found: 465.3.

Example G1. *tert*-Butyl 4-((5-(4-(methylsulfonyl)-1,4-diazepan-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



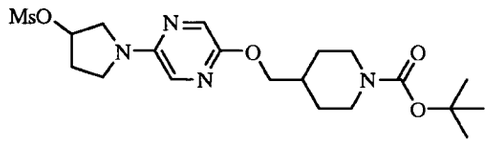


Example G1

[00183] **Step A:** A mixture of **B4b** (307.5 mg, 0.83 mmol), homopiperazine (248.2 mg, 2.5 mmol), xantphos (28.7 mg, 0.050 mmol), sodium *tert*-butoxide 119 mg, 1.2 mmol) and toluene (5 mL) is sparged with nitrogen for 5 minutes and treated with Pd_2dba_3 (15.1 mg, 0.017 mmol). The reaction is then sealed and dipped into a pre-heated oil bath at 100 °C. The reaction is stirred at this temperature for 4 hours, cooled to room temperature, diluted with ethyl acetate and extracted with water twice. The organics are dried over $MgSO_4$, filtered, evaporated and purified on a silica gel column using 0-10% methanol in dichloromethane to afford **G1a**; ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{35}N_4O_3$ calcd.: 391.3, found: 391.3.

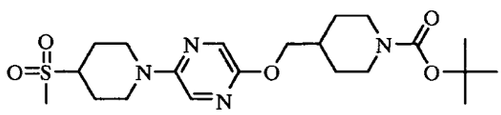
[00184] **Step B:** A solution of **G1a** (139 mg, 3.6 mmol) in dichloromethane (0.25 m L) is cooled to ice/water bath temperature and treated with triethylamine (37.4 mg, 0.37 mmol) followed by methanesulfonyl chloride (42.3 mg, 0.37 mmol) and stirred overnight. The reaction is then poured into water and extracted with dichloromethane twice. The combined organics are dried over $MgSO_4$, filtered, evaporated and purified on a silica gel column using 0-100% ethyl acetate in hexane to afford **G1**; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.79 (d, J = 2.9, 1H), 7.49 (d, J = 1.5, 1H), 4.13 (m, 2H), 4.14 (d, J = 6.5, 1H), 3.82 (m, 2H), 3.74 (dd, J = 6.3,6.3, 2H), 3.49 (m, 2H), 3.26 (m, 2H), 2.78 (s, 3H), 2.73 (m, 2H), 2.07 (m, 2H), 1.94 (m, 1H), 1.79 (m, 1H), 1.46 (s, 9H), 1.25 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{36}N_5O_5S$ calcd.: 470.2, found: 370.2 (M-Boc+H^+).

Example G2 *tert*-Butyl 4-((5-(3-(methylsulfonyloxy)pyrrolidin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



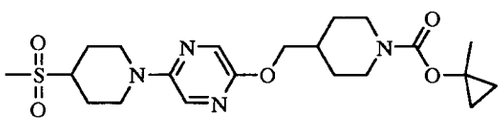
[00185] By following a similar procedure as the one used for preparing **G1** from **B4b** except substituting pyrrolidin-3-ol for homopiperazine, **G2** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, J = 1.5, 1H), 7.38 (d, J = 1.5, 1H), 5.43 (m, 1H), 4.03 (m, 2H), 4.06 (d, J = 6.6, 1H), 3.82 (m, 21H), 3.74 (dd, J = 12.4, 4.4, 1H), 3.58 (m, 2H), 3.05 (s, 3H), 2.72 (m, 2H), 2.47 (m, 1H), 2.33 (m, 1H), 1.93 (m, 1H), 1.79 (m, 2H), 1.46 (s, 9H), 1.26 (m, 2H); ESIMS *m/z* for $(M\text{-Boc}+H)^+$ $C_{15}H_{25}N_4O_4S$ calcd.: 357.2, found: 357.2.

Example G3. *Tert*-butyl 4-((5-(4-(methylsulfonyl)piperidin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



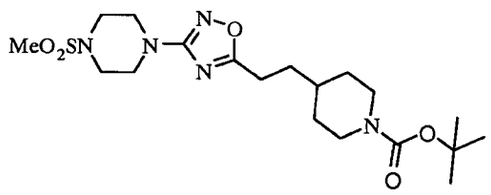
[00186] By following a similar procedure as the one used for preparing **G1a** from **B4b** except substituting 4-(methylsulfonyl)piperidine for homopiperazine, **G3** is prepared; ESIMS *m/z* for $(M\text{-}^t\text{Bu}+H)^+$ $C_{16}H_{27}N_4O_3S$ calcd: 355.2, found: 355.2

Example G4. 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)piperidin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



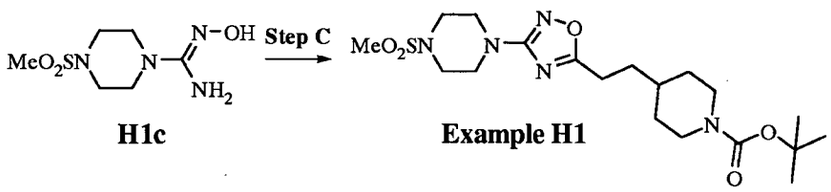
[00187] By following a similar procedure as the one used for preparing **E3** from **B4** except substituting **G3** for **B4**, **G4** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{34}N_4O_5S$ calcd: 454.2, found: 454.2.

Example H1. *tert*-Butyl 4-(2-(3-(4-(methylsulfonyl)piperazin-1-yl)-1,2,4-oxadiazol-5-yl)ethyl)piperidine-1-carboxylate.





H1a **H1b**



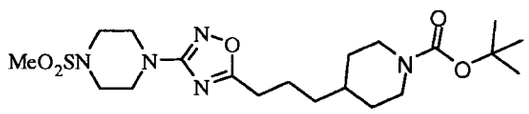
H1c **Example H1**

[00188] **Step A:** To a stirred a solution of potassium carbonate (2.78 g, 20.0 mmol) in water (20 mL) is added **H1a** (3.0 g, 18.3 mmol). The solution is cooled to 10 °C, then a solution of cyanogen bromide (2.12 g, 20.0 mmol) in dichloromethane (20 mL) is added dropwise over 30 min. The reaction is warmed to room temperature and stirred for 2 hours, then extracted into dichloromethane. The organic layer is washed with 1N HCl (30 mL), dried over $MgSO_4$, filtered and concentrated. The product is used without further purification.

[00189] **Step B:** A solution of **H1b** (2.6 g, 13.7 mmol) and hydroxylamine (1 mL, 15.1 mmol) in EtOH (10 mL) is heated in a sealed vial at 90 °C for 12 hours. The mixture is concentrated *in vacuo* to provide **H1c**, which is used without further purification.

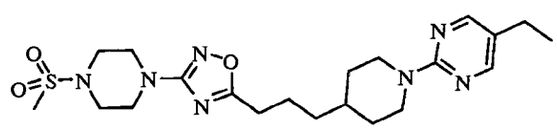
[00190] **Step C:** A solution of 1-Boc-piperidin-4-yl propionic acid acid (112 mg, 0.44 mmol) and N,N-carbonyl dimidazole (71 mg, 0.44 mmol) in N,N-dimethylformamide (0.5 mL) is stirred at room temperature for 30 min. **H1c** (107 mg, 0.48 mmol) is added, the tube is sealed and heated at 115 °C for 18 hours. The reaction mixture is cooled, extracted into ethyl acetate (10 mL), washed with water (2 x 10 mL), then brine (10 mL). The organic layer is dried over $MgSO_4$, filtered, concentrated, and purified by mass triggered reverse phase HPLC to provide **H1**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.10 (br.s, 2H), 3.59 (m, 4H), 3.32 (m, 4H), 2.82 (s, 3H), 2.79 (t, J = 8.0 Hz, 2H), 2.68 (m, 2H), 1.71 (m, 4H), 1.46 (s, 9H), 1.15 (m, 2H) ; ESIMS *m/z* for $(M+H+Na)^+$ $C_{19}H_{33}N_5O_5SNa$ calcd.: 466.2, found: 466.2.

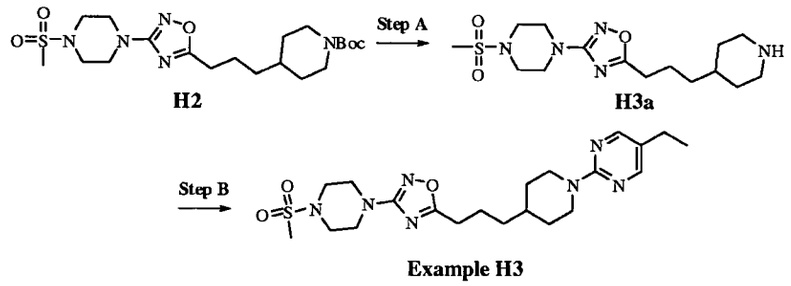
Example H2. *tert*-Butyl 4-(3-(3-(4-(methylsulfonyl)piperazin-1-yl)-1,2,4-oxadiazol-5-yl)propyl)piperidine-1-carboxylate.



[00191] By following a similar procedure as the one used for preparing **H1** from **H1a** except substituting 4-(1-Boc-piperidin-4-yl) butanoic acid for 1-Boc-piperidin-4-yl propionic acid acid, **H2** is prepared; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.08 (d, J = 13.2 Hz, 2H), 3.59 (m, 4H), 3.32 (m, 4H), 2.82 (s, 3H), 2.75 (t, J = 7.6 Hz, 2H), 2.68 (dt, J = 2.4, 13.2 Hz, 2H), 1.80 (m, 2H), 1.68 (s, 1H), 1.65 (s, 1H), 1.46 (s, 9H), 1.42 (m, 1H), 1.34 (s, 2H), 1.11 (m, 2H) ; ESIMS *m/z* for $(M+H+Na)^+$ $C_{20}H_{35}N_5O_5SNa$ calcd.: 480.2, found: 480.3.

Example H3. 5-(3-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)propyl)-3-(4-(methylsulfonyl)piperazin-1-yl)-1,2,4-oxadiazole.





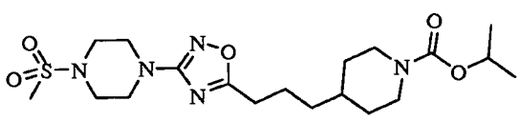
H2 H3a

Example H3

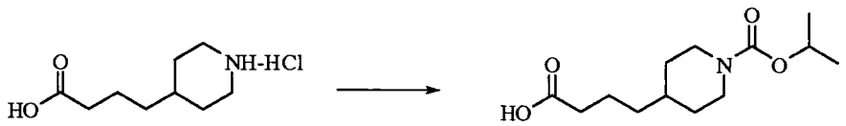
[00192] **Step A: A** solution of **H2** (261 mg, 0.57 mmol) in tetrahydrofuran (5 mL) is treated with HCl (5 mL of 4N in dioxane) and stirred at room temperature for 1 hour. The reaction is concentrated, dissolved in dichloromethane (5 mL) and concentrated *in vacuo* to remove traces of acid and provide **H3a**, which is used without further purification; ESIMS *m/z* for $(M+H)^+$ $C_{15}H_{28}N_5O_3S$ calcd.: 358.2, found: 358.2.

[00193] **Step B: H3a** (53 mg, 0.15 mmol) and 2-chloro-5-ethyl-pyrimidine (22 μL, 0.18 mmol) are dissolved in 1, 4-dioxane (1 mL). Cesium carbonate (120 mg, 0.37 mmol) is added and the tube is sealed and heated at 150 °C for 2 hours. The reaction mixture is cooled, filtered, and purified by mass triggered reverse phase HPLC to provide **H3**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27 (s, 2H), 4.70 (d, J = 13.2 Hz, 2H), 3.60 (m, 4H), 3.33 (m, 4H), 2.93 (dt, J = 2.0, 13.2 Hz, 2H), 2.83 (s, 3H), 2.77 (t, J = 7.6 Hz, 2H), 2.51 (q, J = 7.6 Hz, 2H), 1.84 (m, 4H), 1.58 (m, 1H), 1.37 (m, 3H), 1.22 (t, J = 7.6 Hz, 3H; ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{34}N_7O_3S$ calcd.: 464.2, found: 464.2.

Example H4. Isopropyl 4-(3-(3-(4-(methylsulfonyl)piperazin-1-yl)-1,2,4-oxadiazol-5-yl)propyl)piperidine-1-carboxylate.



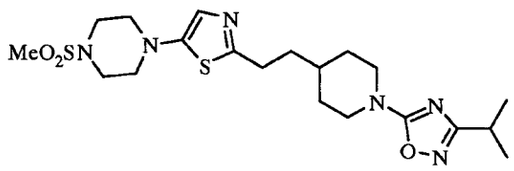
[00194] By following a similar procedure as the one used for preparing **H1** from **H1a** except substituting **H4b** (see scheme below) for 1-Boc-piperidin-4-yl propionic acid acid, **H4** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{19}H_{34}N_5O_5S$ calcd.: 444.2, found: 480.3.

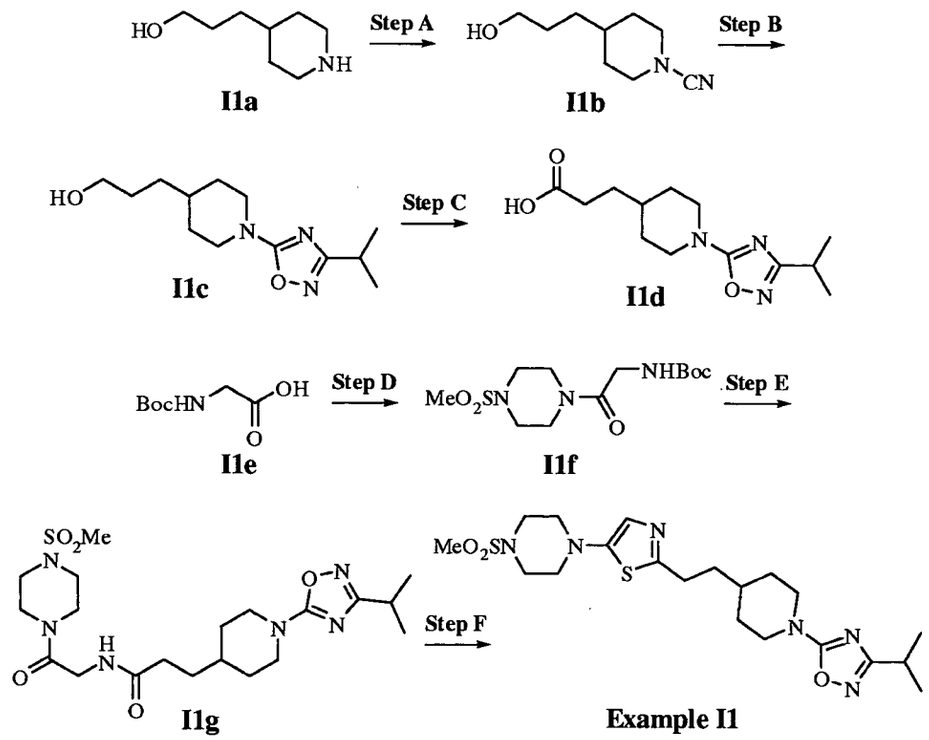


H4a **H4b**

[00195] Commercially available **H4a** (20 g, 96 mmol) is suspended in dry dimethylacetamide (100 mL). Triethylamine (34 mL, 240 mmol) is added and the resulting mixture is cooled in an ice/water bath. A solution of isopropyl chloroformate in toluene (1.0M, 150 mL) is added dropwise, forming a white precipitate. The suspension is stirred at room temperature for 18 hours, then the white precipitate is filtered, washed with ethyl acetate, and discarded. The filtrate is concentrated *in vacuo* to yield **H4b**.

Example I1. 3-Isopropyl-5-(4-(2-(5-(4-(methylsulfonyl)piperazin-1-yl)thiazol-2-yl)ethyl)piperidin-1-yl)-1,2,4-oxadiazole.





[00196] **Step A:** To a stirred a suspension of sodiumhydrogencarbonate (2.80 g, 33.3 mmol) in water (1.5 mL) is added **I1a** hydrochloride salt (2.00 g, 11.1 mmol) and dichloromethane (2 mL). The mixture is cooled in ice/water bath and stirred. A solution of cyanogen bromide (1.42 g, 13.4 mmol) in dichloromethane (3 mL) is added over a period of 1 hour. The cold bath is removed and the reaction is stirred overnight. 0.33 g of Na_2CO_3 is added to ensure the reaction is basic. The reaction is diluted with dichloromethane (20 mL), dried with $MgSO_4$. The mixture is filtered, washed with dichloromethane, and evaporated to give **I1b**; ESIMS *m/z* for $(M+H)^+$ $C_9H_{17}N_2O$ calcd.: 169.1, found: 169.1.

[00197] **Step B:** A solution of **I1b** (1.87 g, 11.1 mmol) and N'-hydroxy isobutyrimidamide (1.70 g, 16.7 mmol) in ethyl acetate (40 mL) is treated with a solution of $ZnCl_2$ (16.7mL, 1N in ether) dropwise. A white precipitate is formed. After stirring at room temperature for 15 minutes, the precipitate stuck on the flask and made stirring difficult. The solid is triturated with ether (40 mL) and stirred for 4 hours until a yellow suspension is obtained. The solid is collected by filtration, washed with ether (30 mL) and dried to give a yellow solid which is used without purification for the next step;

ESIMS *m/z* for $(M+H)^+$ $C_{13}H_{27}N_4O_2$ calcd.: 271.2, found: 271.2. The intermediate material (422 mg) is treated with dioxane (10 mL) and 4M HCl in dioxane (0.5 mL) and heated to 100 °C for 1 hour. The reaction is then cooled to room temperature and the solvent is removed. The residue is diluted with ethyl acetate and extracted with 1 M HCl twice, dried over $MgSO_4$, filtered and evaporated to afford **I1c**; ESIMS *m/z* for $(M+H)^+$ $C_{13}H_{24}N_3O_2$ calcd.: 254.2, found: 254.2.

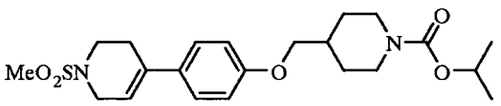
[00198] **Step C:** A solution of **I1c** (368 mg, 1.45 mmol) in acetonitrile (8 mL) is treated with NaH_2PO_4 (218 mg, 1.8 mmol), Na_2HPO_4 (258 mg, 1.8 mmol), TEMPO free radical (16 mg, 0.1 mmol), $NaClO_2$ (328 mg of an 80% pure sample, 2.91 mmol) and water (8mL). After all the reagents went into solution, 10% bleach (22 μL, 0.03 mmol) is added and the reaction is stirred overnight. The acetonitrile is removed *in vacuo* and the resulting solution is extracted with ethyl acetate once and the organics are discarded. The aqueous phase is made acidic (pH<1) with concentrated HCl and extracted twice with ethyl acetate and discarded. The combined organics are dried over $MgSO_4$ and the solvent is removed to afford **I1d**; ESIMS *m/z* for $(M+H)^+$ $C_{13}H_{22}N_3O_3$ calcd.: 268.2, found: 268.1.

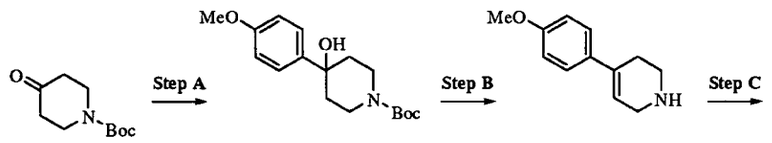
[00199] **Step D.** A solution of **I1e** (250 mg, 1.4 mol) and methanesulfonyl piperazine (258 mg, 1.6 mmol) in dichloromethane (4 mL) is treated with HOBt hydrate (328 mg, 2.1 mmol) followed by EDC (356 mg, 1.9 mmol). After stirring for 3 hours, the reaction is diluted with ethyl acetate and extracted with water, 1M HCl and 1 M NaOH, dried over $MgSO_4$, filtered and evaporated to afford **I2f** ; ESIMS *m/z* for $(M+H)^+$ $C_{12}H_{24}N_3O_5S$ calcd.: 322.1, found: 322.2.

[00200] **Step E.** A sample of **I1f** (388 mg, 1.2 mmol) is treated with 4 M HCl in dioxane (4 mL) and aged for 1 hour. The solvent is removed and the residue is treated with **I1d** (298 mg, 1.1 mmol), HATU (502 mg, 1.3 mmol) and N-methylpyrrolidinone (4 mL). The solution is then treated with triethylamine (0.39 mL, 2.8 mmol) and stirred for 2 hours. The reaction is then diluted with 1M NaOH and saturated with NaCl. The resulting solution is extracted 4 times with ethyl acetate and discarded. The combined organics are dried over MgSO4, filtered, evaporated and further purified on a UV triggered HPLC to afford **I1g**; ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{35}N_6O_5S$ calcd.: 471.2, found: 471.1.

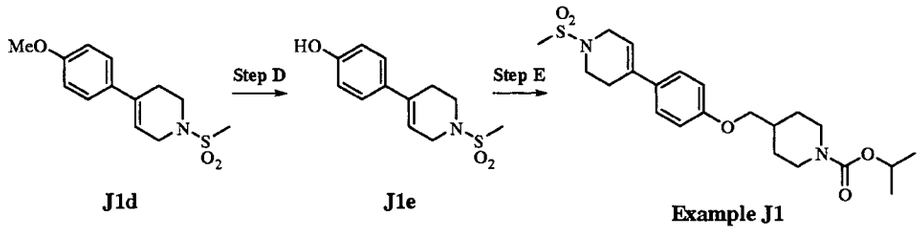
[00201] **Step F.** A suspension of **I1g** (354 mg, 0.75 mmol) and Lawesson's reagent (304 mg, 0.75 mmol) in *m*-xylene (3 mL) is dipped into an oil bath which is preheated to 140 °C and stirred for 5 minutes. The reaction is then cooled to room temperature and loaded onto silica gel and purified using a linear gradient of 0-100% ethyl acetate to afford **F1**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.86 (s, 1H), 4.12, (2, 2H), 3.38 (m, 4H), 3.19 (m, 4H), 3.02 (m, 2H), 2.99 (m, 3H), 2.83 (s, 3H), 1.80 (m, 2H), 1.73 (dd, J = 15.3, 7.1, 21H), 1.40 (m, 1H), 1.24 (m, 2H), 1.28 (d, J = 7.0, 6H); ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{33}N_6O_3S_2$ calcd.: 469.2, found: 469.1.

Example J1: Isopropyl 4-((4-(1-methanesulfonyl-1,2,3,6-tetrahydropyridin-4-yl)phenoxy)methyl)piperidine-1-carboxylate.





J1a **J1b** **J1c**



J1d **J1e** **Example J1**

[00202] **Step A**: 4-Bromoanisole (4.5 mL, 36.0 mmol) is dissolved in dry tetrahydrofuran (50 mL) and cooled to –78 °C under nitrogen. A solution of *n*-butyllithium (1.6 M in hexane (22.0 mL, 35.2 mmol) is slowly added with stirring. The mixture is stirred at –78 °C for 2 hours. A solution of **J1a** (7.28 g, 36.5 mmol) in dry tetrahydrofuran (80 mL) under nitrogen is cooled to –78 °C. The suspension of organolithium prepared above is slowly cannulated with stirring into the solution of **J1a**,

using a 20-mL tetrahydrofuran rinse. The resulting mixture is stirred at –78 °C for 30 minutes, then at 0 °C for 15 min. Addition of saturated ammonium chloride solution (60 mL) and extraction with ethyl acetate, washing with brine and concentration in vacuo yield an oil. The residue is purified using a linear gradient of 10-80% ethyl acetate in hexane to afford **J1b**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.39 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 3.99 (br., 2H), 3.81 (s, 3H), 1.96 (br, 2H), 1.71 (m, 4H), 1.49 (s, 9H); no mass spectrum could be obtained.

[00203] **Step B**: To a solution of **J1b** (6.29 g, 20 mmol) in dichloromethane (120mL) is added trifluoroacetic acid (20 mL), slowly, with stirring. The resulting solution is stirred at room temperature for 3 hours. Concentration, dilution with dichloromethane (50 mL), washing with saturated aqueous sodiumhydrogencarbonate solution, drying over $MgSO_4$ and concentration yields **J1c**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.30 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.93 (m, 1H), 3.82 (s, 5H), 3.40 (t, J = 6.0 Hz, 2H), 2.77 (m, 2H); ESIMS calcd. for $C_{12}H_{16}NO$ ($M+H^+$) 190.1, found 190.0.

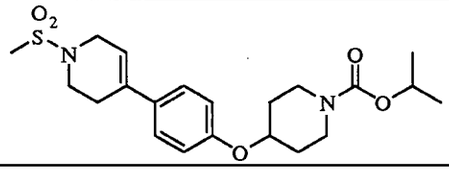
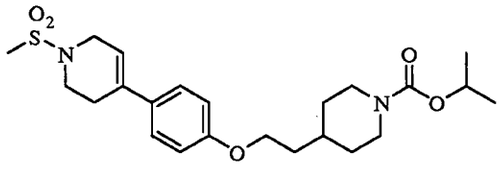
[00204] **Step C**: To a solution of **J1c** (3.41 g, 18 mmol) in dichloromethane (80 mL) is added triethylamine (4.5 mL, 32.0 mmol) in one portion. The resulting mixture is cooled in an ice/water bath and methanesulfonyl chloride (1.75 mL, 22.5 mmol) is added dropwise, with stirring, over 5 minutes. The resulting solution is stirred at room temperature for 30 min. The reaction mixture is added to water (40 mL) and extracted with dichloromethane (2 x 40 mL). The combined organic extracts are washed with saturated ammonium chloride aqueous solution, dried over $MgSO_4$, and concentrated to yield **J1d**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.31 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.98 (m, 1H), 3.96 (q, J = 3.2 Hz, 2H), 3.82 (s, 3H), 3.52 (t, J = 5.7 Hz, 2H), 2.86 (s, 3H), 2.64 (m, 2H); ESIMS calcd. for $C_{13}H_{18}NO_3S$ ($M+H^+$) 268.1, found 268.1.

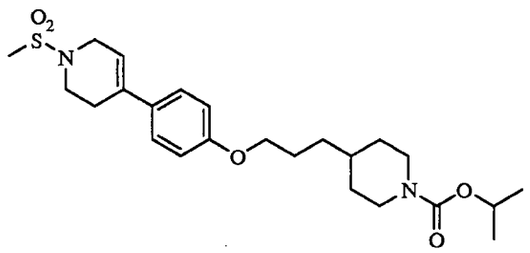
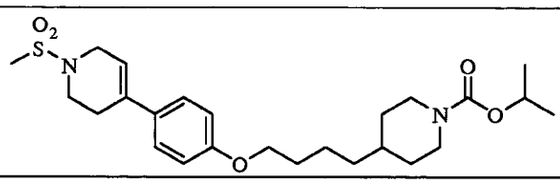
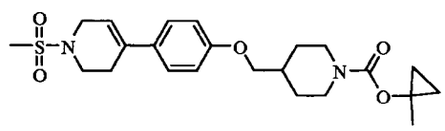
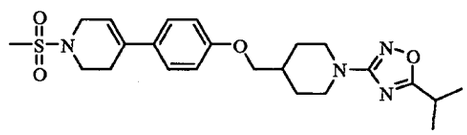
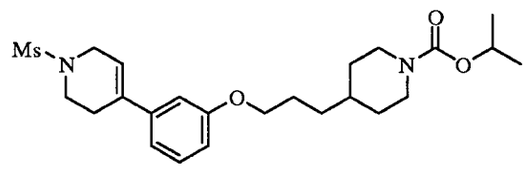
[00205] **Step D**: A solution of **J1d** (3.71 g, 13.9 mmol) in dichloromethane (100 mL) is treated with boron tribromide (5.0 mL, 51.9 mmol) slowly and stirred at room temperature for 3 hours. The mixture is poured over crushed ice and, after the ice melts, it is extracted with dichloromethane. Washing with saturated aqueous sodiumhydrogencarbonate solution, water, and saturated ammonium chloride, drying over $MgSO_4$ and concentration yield **J1e**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.27 (d, J

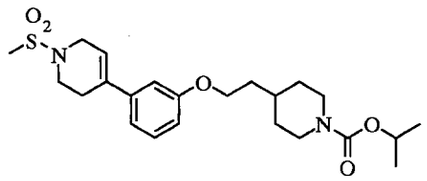
= 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.97 (m, 1H), 4.85 (s, 1H), 3.95 (q, J = 3.2 Hz, 2H), 3.52 (t, J = 5.7 Hz, 2H), 2.86 (s, 3H), 2.63 (m, 2H); ESIMS calcd. for $C_{12}H_{16}NO_3S$ ($M+H^+$) 254.1, found 254.1.

[00206] **Step E**: A solution of **J1e** (0.12 g, 0.47 mmol) in acetonitrile (3 mL) is treated with **A1c**,(0.16 g, 0.57 mmol) followed by powdered cesium carbonate (0.20 g, 0.6 mmol) and stirred at 60 °C for 5 hours. Cooling, filtration and purification using mass-triggered reverse phase HPLC affords **J1**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.30 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.97 (m, 1H), 4.92 (septet, J = 6.2 Hz, 1H), 4.19 (br, 2H), 3.95 (dd, J = 2.6, 5.9 Hz, 2H), 3.81 (d, J = 6.3 Hz, 2H), 3.52 (t, J = 5.8 Hz, 2H), 2.85 (s, 3H), 2.78 (m, 2H), 2.63 (m, 2H), 1.97 (m, 1H), 1.83 (dd, J = 1.0, 13.4 Hz, 2H), 1.25 (m, 2H), 1.24 (d, J = 6.2 Hz, 6H); ESIMS calcd. for $C_{22}H_{33}N_2O_5S$ ($M+H^+$) 437.2, found 437.1.

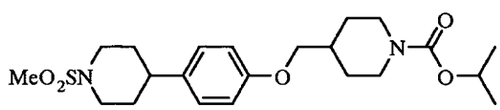
[00207] By following a similar procedure as the one used for preparing **J1** from **HJ1a** except substituting the appropriate methanesulfonate for intermediate **A1c** in **Step E** and/or 3-bromoanisole for 4-bromoanisole, the following examples are prepared;

Example	Structure	Analytical data
J2		ESIMS calcd. for $C_{21}H_{31}N_2O_5S$ ($M+H^+$) 423.2, found 423.1.
J3		^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.30 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.97 (m, 1H), 4.92 (septet, J = 6.2 Hz, 1H), 4.12 (br, 2H), 4.02 (t, J = 5.8, 2H), 3.95 (dd, J = 2.6, 5.9 Hz, 2H), 3.52 (t, J = 5.8 Hz, 2H), 2.85 (s, 3H), 2.74 (m, 2H), 2.64 (m, 2H), 1.85 (m, 1H), 1.73 (dd, J = 1.0, 13.4 Hz, 2H), 1.24 (d, J = 6.2 Hz, 6H), 1.18 (m, 2H); ESIMS calcd. for $C_{23}H_{35}N_2O_5S$ ($M+H^+$) 451.2, found 451.2.

J4		^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.97 (m, 1H), 4.91 (septet, *J* = 6.2 Hz, 1H), 4.13 (br, 2H), 3.52 (t, *J* = 5.8 Hz, 2H), 2.85 (s, 3H), 2.71 (m, 2H), 2.63 (m, 2H), 1.81 (m, 2H), 1.70 (m, 5H), 1.42 (m, 4H), 1.24 (d, *J* = 6.2 Hz, 6H), 1.12 (m, 2H); ESIMS calcd. for $C_{24}H_{37}N_2O_5S$ ($M+H^+$) 465.2, found 465.1.
J5		ESIMS calcd. for $C_{25}H_{39}N_2O_5S$ ($M+H^+$) 479.3, found 479.1.
J6		^{1}H-NMR (400MHz, DMSO-d6) δ 7.37 (m, 2H), 6.90 (m, 2H), 6.08 (m, 1H), 3.70-4.05 (m, 6H), 2.92 (s, 3H), 2.75 (m, 2H), 2.56 (m, 2H), 1.91 (m, 1H), 1.73 (m, 2H), 1.46 (s, 3H), 1.13 (m, 2H), 0.76 (m, 2H), 0.59 (m, 2H); ESIMS calcd. for $C_{23}H_{33}N_2O_5S$ ($M+H^+$) 449.2, found 448.8.
J7		^{1}H-NMR (400MHz, DMSO-d6) δ 7.38 (m, 2H), 6.92 (m, 2H), 6.08 (m, 1H), 3.86 (m, 6H), 3.10 (h, 1H, J = 7.0 Hz), 2.92 (s, 3H), 2.91 (m, 2H), 2.56 (m, 2H), 1.97 (m, 1H), 1.82 (m, 2H), 1.30 (m, 2H), 1.26 (d, 6H, J = 7.0 Hz); ESIMS calcd. for $C_{23}H_{33}N_4O_4S$ ($M+H^+$) 461.2, found 460.8.
J8		^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.25 (dd, *J* = 7.8, 8.2 Hz, 1H), 6.95 (dd, *J* = 2.2, 7.8 Hz, 1H), 6.89 (dd, *J* = 1.9, 2.2 Hz, 1H), 6.81 (dd, *J* = 1.9, 8.2 Hz, 1H), 6.07 (tt, *J* = 1.5, 3.5 Hz, 1H), 4.91 (septet, *J* = 6.2 Hz, 1H), 4.13 (br. s, 2H), 3.96 (m, 4H), 3.52 (t, *J* = 5.7 Hz, 2H), 2.86 (s, 3H), 2.73 (t, *J* = 12.4 Hz, 2H), 2.65 (m, 2H), 1.81 (m, 2H), 1.71 (d, *J* = 12.7 Hz, 2H), 1.46 (m, 1H), 1.41 (m, 2H), 1.24 (d, J = 6.3

		Hz, 6H), 1.12 (ddd, J = 4.2, 12.7, 13.0 Hz, 2H); ESIMS calcd. for $C_{24}H_{37}N_2O_5S$ ($M+H^+$) 465.2, found 465.2.
J9		^1H NMR ($CDCl_3$, 400.13 MHz): δ 7.26 (dd, J = 7.9, 8.1 Hz, 1H), 6.96 (d, J = 7.8 Hz, 1H), 6.89 (dd, J = 1.8, 2.2 Hz, 1H), 6.82 (dd, J = 2.0, 7.8 Hz, 1H), 6.07 (m, 1H), 4.91 (septet, J = 6.2 Hz, 1H), 4.13 (br, 2H), 4.02 (t, J = 5.8 Hz, 2H), 3.97 (dd, J = 2.7, 6.0 Hz, 2H), 3.52 (t, J = 5.7 Hz, 2H), 2.86 (s, 3H), 2.74 (t, J = 12.4 Hz, 2H), 2.66 (m, 2H), 1.80 (m, 2H), 1.74 (m, 3H), 1.24 (d, J = 6.2 Hz, 6H), 1.20 (m, 2H); ESIMS calcd. for $C_{23}H_{35}N_2O_5S$ ($M+H^+$) 451.2, found 451.2.

Example J10: Isopropyl 4-((4-(1-methanesulfonylpiperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate.

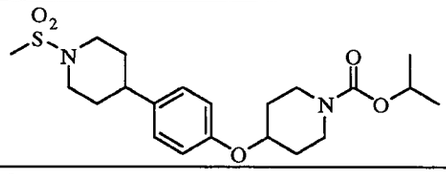
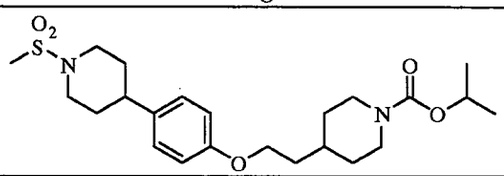
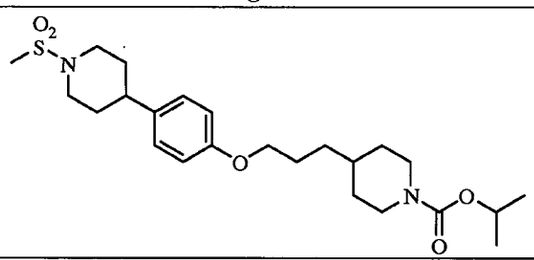
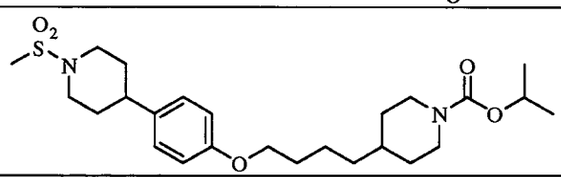
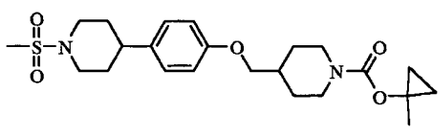
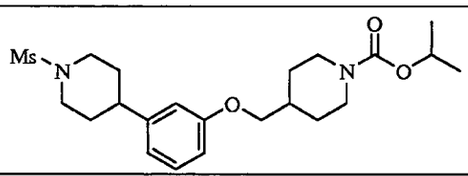


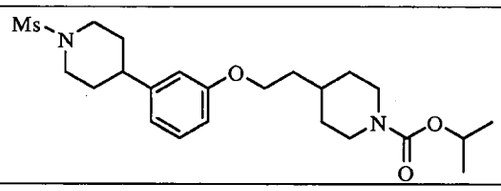
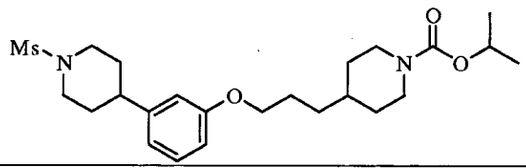
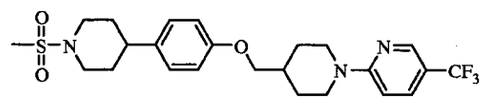
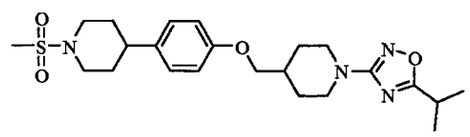
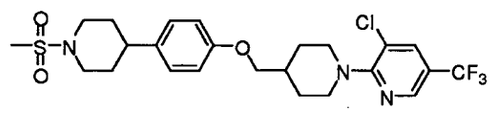
[00208] A solution of **J1** (0.18 g, 0.4 mmol) in ethanol (10 mL) and ethyl acetate (2 mL) is treated with palladium(0) on charcoal (5%, 0.12 g). The mixture is stirred under 1 atm hydrogen for 18 hours. Filtration, concentration, and purification using mass-triggered reverse phase HPLC yields **J9**; ^1H NMR (CD_3CN, 400.13 MHz): δ 7.19 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 4.95 (septet, J = 6.2 Hz, 1H), 4.16 (br, 2H), 3.83 (d, J = 6.4 Hz, 2H), 3.78 (m, 2H), 2.81 (s, 3H), 2.78 (m, 4H), 2.61 (tt, J = 3.6, 12.1 Hz, 1H), 2.01 (m, 1H), 1.90 (m, 2H), 1.81 (m, 2H), 1.71 (m, 2H), 1.23 (d, J = 6.2 Hz, 6H), 1.22 (m, 2H); ESIMS calcd. for $C_{22}H_{35}N_2O_5S$ ($M+H^+$) 439.2, found 439.2.

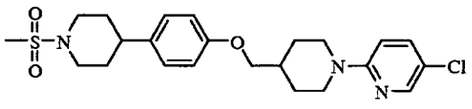
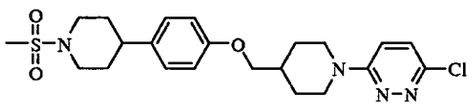
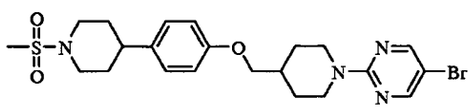
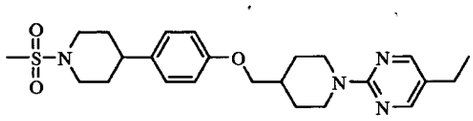
[00209] By following a similar procedure as the one used for preparing **J10** from **J1** except substituting the olefin for intermediate **J1** or by following a similar procedure

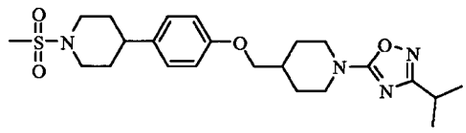
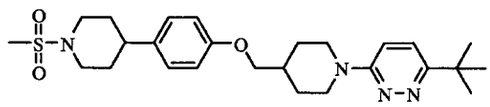
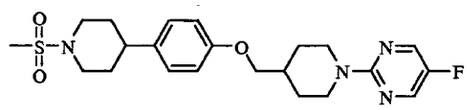
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as the one used for preparing **J1** from **J1a** except substituting 4-(4-methoxyphenyl)piperidine or 4-(3-methoxyphenyl)piperidine for **J1c**, the following examples are prepared;

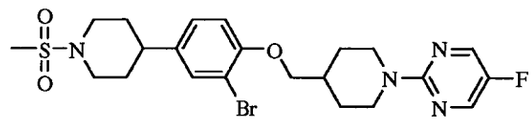
Example	Structure	Analytical data
J11		ESIMS calcd. for $C_{21}H_{33}N_2O_5S$ ($M+H^+$) 425.2, found 425.0.
J12		ESIMS calcd. for $C_{23}H_{37}N_2O_5S$ ($M+H^+$) 453.2, found 453.2.
J13		ESIMS calcd. for $C_{24}H_{39}N_2O_5S$ ($M+H^+$) 467.3, found 467.2.
J14		ESIMS calcd. for $C_{25}H_{41}N_2O_5S$ ($M+H^+$) 481.3, found 481.1.
J15		^{1}H-NMR (400MHz, $CDCl_3$) δ 7.11 (m, 2H), 6.83 (m, 2H), 4.12 (m, 2H), 3.93 (m, 2H), 3.77 (d, 2H, J = 6.3 Hz), 2.81 (s, 3H), 2.75 (m, 2H), 2.55 (tt, 1H, J = 3.5, 12.1 Hz), 1.93 (m, 2H), 1.81 (m, 4H), 1.55 (s, 3H), 1.26 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H). ESIMS calcd. for $C_{23}H_{35}N_2O_5S$ ($M+H^+$) 451.2, found 451.2.
J16		ESIMS calcd. for $C_{22}H_{35}N_2O_5S$ ($M+H^+$) 439.2, found 439.1.

J17		ESIMS calcd. for $C_{23}H_{37}N_2O_5S$ ($M+H^+$) 453.2, found 453.1.
J18		ESIMS calcd. for $C_{24}H_{39}N_2O_5S$ ($M+H^+$) 467.3, found 467.1.
J19		^{1}H-NMR (400MHz, DMSO-d6) δ 8.38 (m, 1H), 7.75 (dd, 1H, J = 2.5, 9.2 Hz), 7.16 (m, 2H), 6.96 (d, 1H, J = 9.2 Hz), 6.86 (m, 2H), 4.46 (m, 2H), 3.82 (d, 2H, J = 6.4 Hz), 3.65 (m, 2H), 2.95 (m, 2H), 2.88 (s, 3H), 2.78 (m, 2H), 2.56 (tt, 1H, J = 3.5, 12.3 Hz), 2.07 (m, 1H), 1.83 (m, 4H), 1.62 (m, 2H), 1.24 (m, 2H). ESIMS calcd. for $C_{24}H_{31}F_3N_3O_3S$ ($M+H^+$) 498.2, found 497.8.
J20		^{1}H-NMR (400MHz, DMSO-d6) δ 7.16 (m, 2H), 6.86 (m, 2H), 3.87 (m, 2H), 3.82 (d, 2H, J = 6.5 Hz), 3.65 (m, 2H), 3.10(h, 1H, J = 7.0Hz), 2.90 (m, 2H), 2.89 (s, 3H), 2.78 (m, 3H), 2.56 (tt, 1H, J = 3.4, 12.2 Hz), 1.95 (m, 1H), 1.82 (m, 4H), 1.62 (m, 2H), 1.29 (m, 2H), 1.26 (d, 6H, J = 7.0 Hz). ESIMS calcd. for $C_{23}H_{35}N_4O_4S$ ($M+H^+$) 463.2, found 463.2.
J21		^{1}H-NMR (400MHz, DMSO-d6) δ 8.54 (m, 1H), 8.16 (d, 1H, J = 2.0 Hz), 7.17 (m, 2H), 6.88 (m, 2H), 4.04 (m, 2H), 3.86 (d, 2H, J = 6.4 Hz), 3.65 (m, 2H), 2.93 (m, 2H), 2.89 (s, 3H), 2.78 (m, 2H), 2.56 (tt, 1H, J = 3.5, 12.2 Hz), 2.01 (m, 1H), 1.86 (m, 4H), 1.62 (m, 2H), 1.43 (m, 2H). ESIMS calcd. for $C_{24}H_{30}ClF_3N_3O_3S$ ($M+H^+$) 532.2, found 531.9.

J22		^{1}H-NMR (400MHz, DMSO-d6) δ 8.08 (d, 1H, J =2.5 Hz), 7.56 (dd, 1H, J = 2.7, 9.1 Hz), 7.16 (m, 2H), 6.87 (m, 3H), 4.29 (m, 2H), 3.81 (d, 2H, J = 6.4 Hz), 3.65 (m, 2H), 2.88 (s, 3H), 2.81 (m, 4H), 2.56 (tt, 1H, J = 3.4, 11.9 Hz), 2.00 (m, 1H), 1.82 (m, 4H), 1.62 (m, 2H), 1.25 (m, 2H). ESIMS calcd. for $C_{23}H_{31}ClN_3O_3S$ (M+H$^+$) 464.2, found 464.2.
J23		^{1}H-NMR (400MHz, DMSO-d6) δ 7.50 (d, 1H, J =9.6 Hz), 7.41 (d, 1H, J = 9.7 Hz), 7.16 (m, 2H), 6.87 (m, 2H), 4.37 (m, 2H), 3.82 (d, 2H, J = 6.4 Hz), 3.64 (m, 2H), 2.96 (m, 2H), 2.88 (s, 3H), 2.78 (m, 2H), 2.56 (tt, 1H, J = 3.4, 11.9 Hz), 2.06 (m, 1H), 1.84 (m, 4H), 1.62 (m, 2H), 1.29 (m, 2H). ESIMS calcd. for $C_{22}H_{30}ClN_4O_3S$ (M+H$^+$) 465.2, found 465.2.
J24		^{1}H-NMR (400MHz, DMSO-d6) δ 8.43 (s, 2H), 7.16 (m, 2H), 6.86 (m, 2H), 4.61 (m, 2H), 3.81 (d, 2H, J = 6.6 Hz), 3.65 (m, 2H), 2.93 (m, 2H), 2.88 (s, 3H), 2.78 (m, 2H), 2.55 (m, 1H), 2.05 (m, 1H), 1.82 (m, 4H), 1.62 (m, 2H), 1.22 (m, 2H). ESIMS calcd. for $C_{22}H_{30}BrN_4O_3S$ (M+H$^+$) 509.1, found 508.9.
J25		^{1}H-NMR (400MHz, DMSO-d6) δ 8.24 (s, 2H), 7.16 (m, 2H), 6.86 (m, 2H), 4.65 (m, 2H), 3.81 (d, 2H, J = 6.4 Hz), 3.65 (m, 2H), 2.87 (m, 2H), 2.89 (s, 3H), 2.78 (m, 2H), 2.56 (tt, 1H, J = 3.5, 11.9 Hz), 2.42 (q, 2H, J = 7.6 Hz), 2.03 (m, 1H), 1.82 (m, 4H), 1.62 (m, 2H), 1.20 (m, 2H), 1.12 (t, 3H, J = 7.6). ESIMS calcd. for $C_{24}H_{35}N_4O_3S$ (M+H$^+$) 459.2, found 459.2.
J26		^{1}H-NMR (400MHz, DMSO-d6) δ 8.07 (d, 1H, J = 3.1 Hz), 7.49 (ddd, 1H, J = 3.1, 8.4,9.2 Hz), 7.16 (m, 2H), 6.88 (m, 3H), 4.23 (m, 2H), 3.82 (d,

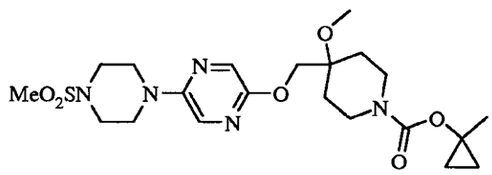
		2H, J = 6.4 Hz), 3.65 (m, 2H), 2.89 (s, 3H), 2.79 (m, 4H), 2.57 (tt, 1H, J = 3.5, 12.0 Hz), 1.98 (m, 1H), 1.82 (m, 4H), 1.62 (m, 2H), 1.27 (m, 2H). ESIMS calcd. for $C_{23}H_{31}FN_3O_3S$ ($M+H^+$) 448.2, found 448.2.
J27		^{1}H-NMR (400MHz, DMSO-d6) δ 7.16 (m, 2H), 6.87 (m, 2H), 3.99 (m, 2H), 3.83 (d, 2H, J = 6.4 Hz), 3.65 (m, 2H), 3.12(m, 2H), 2.89 (s, 3H), 2.79 (m, 3H), 2.56 (tt, 1H, J = 3.5, 11.9 Hz), 1.99 (m, 1H), 1.84 (m, 4H), 1.62 (m, 2H), 1.31 (m, 2H), 1.18 (d, 6H, J = 6.9 Hz). ESIMS calcd. for $C_{23}H_{35}N_4O_4S$ ($M+H^+$) 463.2, found 463.2.
J28		^{1}H-NMR (400MHz, DMSO-d6) δ 8.10 (d, 1H, J = 10.0 Hz), 8.01 (d, 1H, J = 10.0 Hz), 7.17 (m, 2H), 6.87 (m, 2H), 4.31 (m, 2H), 3.84 (d, 2H, J = 6.4 Hz), 3.66 (m, 2H), 3.25 (m, 2H), 2.89 (s, 3H), 2.78 (m, 2H), 2.56 (tt, 1H, J = 3.4, 12.3 Hz), 2.16 (m, 1H), 1.92 (m, 2H), 1.82 (m, 2H), 1.62 (m, 2H), 1.41 (m, 2H), 1.32 (s, 9H). ESIMS calcd. for $C_{26}H_{39}N_4O_3S$ ($M+H^+$) 486.3, found 486.3.
J29		^{1}H-NMR (400MHz, DMSO-d6) δ 8.42 (d, 2H, J = 0.8 Hz), 7.16 (m, 2H), 6.86 (m, 2H), 4.60 (m, 2H), 3.82 (d, 2H, J = 6.4 Hz), 3.65 (m, 2H), 2.91 (m, 2H), 2.88 (s, 3H), 2.78 (m, 2H), 2.56 (tt, 1H, J = 3.5, 11.9 Hz), 2.03 (m, 1H), 1.82 (m, 4H), 1.62 (m, 2H), 1.21 (m, 2H). ESIMS calcd. for $C_{22}H_{30}FN_4O_3S$ ($M+H^+$) 449.2, found 448.8.

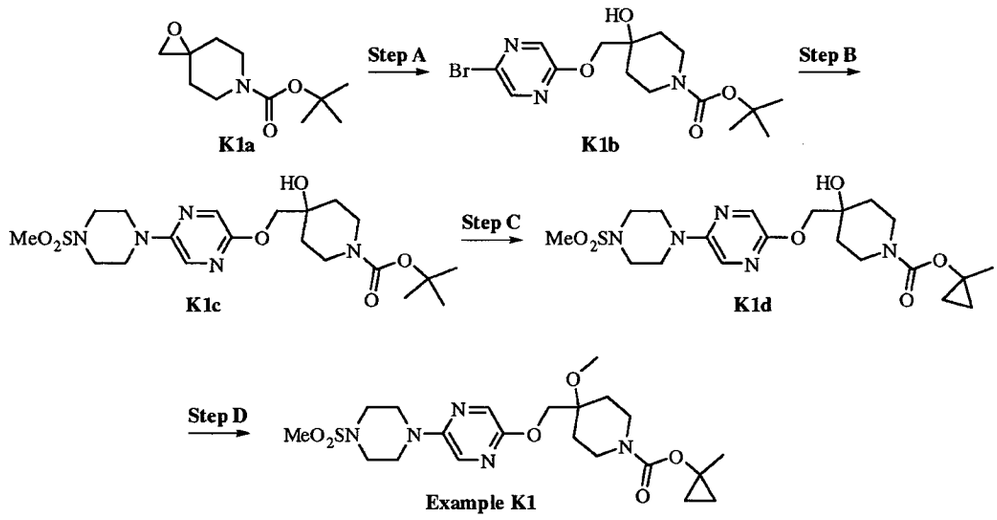
Example J30: 2-(4-((2-Bromo-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)-5-fluoropyrimidine



[00210] This material is prepared when a large scale preparation of **J28** from 4-(4-methoxyphenyl)piperidine in place of **J1c** following the scheme outlined for **J1** yielded a brominated byproduct in **step D:** ^{1}H-NMR (400MHz, DMSO-d6) δ 8.43 (d, 2H, J = 0.8 Hz), 7.45 (d, 1H, J = 2.1 Hz), 7.21 (dd, 1H, J = 2.1, 8.6 Hz), 7.04 (d, 1H, J = 8.6 Hz), 4.61 (m, 2H), 3.91 (d, 2H, J = 6.3 Hz), 3.65 (m, 2H), 2.93 (m, 2H), 2.89 (s, 3H), 2.77 (m, 2H), 2.59 (tt, 1H, J = 3.5, 12.0 Hz), 2.07 (m, 1H), 1.84 (m, 4H), 1.62 (m, 2H), 1.27 (m, 2H). ESIMS calcd. for $C_{22}H_{29}BrFN_4O_3S$ ($M+H^+$) 527.1, found 527.1.

Example K1: 1-Methylcyclopropyl 4-methoxy-4-((5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





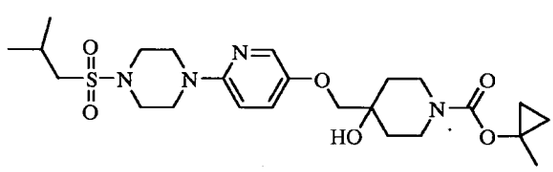
[00211] **Step A:** A solution of **K1a** (2.22 g, 10.4 mmol) and 2-bromo-5-hydroxypyrazine (2 g, 11.4 mmol) in N-methylpyrrolidinone (10 mL) is treated with K_2CO_3 (2.37 g, 17.1 mmol) and heated to 80 °C overnight. After cooling to room temperature, the reaction is diluted with ethyl acetate and extracted with water twice. The organics are dried over $MgSO_4$, filtered evaporated and purified by silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **K1b**; ESIMS *m/z* for ($M+H^+$) $C_{15}H_{23}BrN_3O_4$ calcd.: 388.1, found: 388.2.

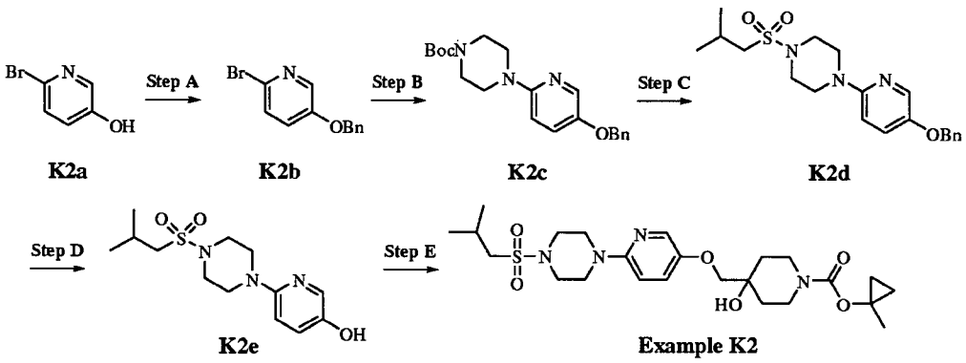
[00212] **Step B:** By following a similar procedure as the one used for preparing **B1** from isopropyl 4-((6-chloropyridin-3-yloxy)methyl)piperidine-1-carboxylate except substituting **K1b** for isopropyl 4-((6-chloropyridin-3-yloxy)methyl)piperidine-1-carboxylate, **K1c** is prepared; ESIMS *m/z* for ($M+H^+$) $C_{20}H_{34}N_5O_6S$ calcd.: 472.2, found: 472.2.

[00213] **Step C: :** By following a similar procedure as the one used for preparing **E3** from **B4** except substituting **K1c B4, K1d** is prepared; ESIMS *m/z* for ($M+H^+$) $C_{20}H_{32}N_5O_6S$ calcd.: 470.2, found: 470.2.

[00214] **Step D:** A solution of **K1d** (75 mg, 0.16 mmol) in N, N-dimethylformamide is treated with dimethylsulfate (80 mg, 0.63 mmol) followed by NaH (30 mg, 1.25 mmol). After stirring at room temperature for 1 hour, the reaction is treated with water and ethyl acetate. The organics are isolated, washed with water, dried over $MgSO_4$, filtered evaporated and purified by silica gel using a linear gradient of 50-100% ethyl acetate in hexane to afford **K1**; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 7.94 (d, J = 1.5 Hz, 1H), 7.61 (d, J = 1.4 Hz, 1H), 4.20 (m, 2H), 3.91 (m, 2H), 3.54 (m, 4H), 3.37 (m, 4H), 3.29 (s, 3H), 3.13 (m, 2H), 2.82 (s, 3H), 1.89 (m, 2H), 1.55 (m, 2H), 1.55 s, 3H), 0.87 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{21}H_{34}N_5O_6S$ ($M+H^+$) 484.2, found 484.1.

Example K2: 1-methylcyclopropyl 4-hydroxy-4-((6-(4-(isobutylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate.





[00215] **Step A**: A solution of **K2a** (2.0 g, 11.5 mmol) and benzyl bromide (2.36 g, 13.8 mmol) in N-methylpyrrolidinone (15 mL) is treated with K_2CO_3 (2.38 g, 17.2 mmol) and stirred at 60 °C overnight. The reaction is cooled to room temperature, diluted with ethyl acetate and extracted with water twice. The organics are then dried over $MgSO_4$, filtered evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **K2b**; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 8.13 (d, J = 3.1 Hz, 1H), 7.38 (m, 6H), 7.15 (dd, J = 3.2, 8.7 Hz, 1H), 5.09 (s, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{12}H_{11}BrNO$ calcd: 264.0, found: 264.0.

[00216] **Step B**: A roundbottom flask is charged with **K2b** (2.55 g, 9.65 mmol), Pd_2dba_3 (177 mg, 0.19 mmol), xantphos (335 mg, 0.58 mmol) and tert-butyl piperazine-1-carboxylate (2.16 g, 11.6 mmol) followed by dry toluene (30 mL). The flask is sparged with dry nitrogen, treated with NaO*t*Bu (1.39 g, 14.5 mmol), sealed, dipped into a pre heated 100 °C oil bath and stirred for 2 hours. The reaction is then cooled to room temperature, diluted with ethyl acetate and extracted with water twice. The organics are then dried over $MgSO_4$, filtered evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **K2c**; ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{28}N_3O_3$ calcd: 370.2, found: 370.1.

[00217] **Step C**: A solution of **K2c** (970 mg, 2.2 mmol) in 1:1 TFA/ dichloromethane (10 mL) is aged for 1 hour and the solvent is removed. The resulting residue is partitioned between ethyl acetate and 1 M HCl. The aqueous phase is collected and the organics are extracted once more with 1 M HCl and discarded. The combined

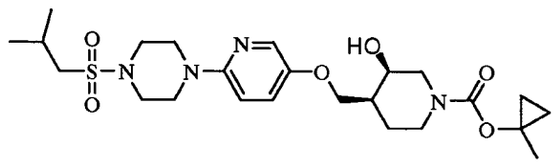
aqueous extracts are made basic with solid Na_2CO_3 and extracted three times with dichloromethane. The combined organics are dried over $MgSO_4$, filtered, evaporated, dissolved in dichloromethane (10 mL) and treated with triethylamine (337 mg, 3.33 mmol) followed by isobutanesulfonyl chloride (452 mg, 2.89 mmol). After stirring for 30 minutes, the reaction is diluted with ethyl acetate, extracted with saturated aqueous sodiumhydrogencarbonate twice, dried over $MgSO_4$, filtered and evaporated to afford **K2d**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.99 (d, J = 2.8 Hz, 1H), 7.38 (m, 5H), 7.22 (dd, J = 3.2, 9.1 Hz, 1H), 6.64 (d, J = 9.0 Hz, 1H), 5.04 (s, 2H), 3.52 (m, 4H), 3.37 (m, 4H), 2.76 (d, J = 6.6 Hz, 2H), 1.12 (d, J = 6.7 Hz, 6H); ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{28}N_3O_3S$ calcd: 390.2, found: 390.2.

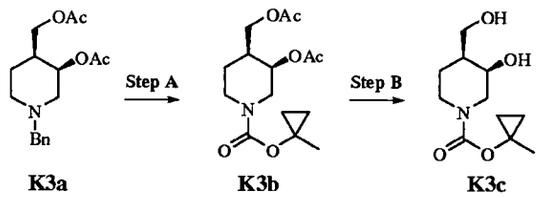
[00218] **Step D**: A solution of **K2d** (0.80 g, 2.0 mmol) in ethanol (10 mL) is treated with $Pd(OH)_2$ (50 mg) and hydrogenated overnight. The catalyst is removed by filtration through Celite® and resubjected to hydrogenation with 100 mg of 10% Pd/C overnight. The catalyst is removed by filtration through Celite® and the solvent is removed. The resulting material is slurried in hexane, collected and dried to afford **K2e**; ESIMS *m/z* for $(M+H)^+$ $C_{13}H_{22}N_3O_3S$ calcd: 300.1, found: 300.1.

[00219] **Step E**: A solution of **K2e** (75 mg, 0.25 mmol) and **K1a** (64 mg, 0.30 mmol) in N-methylpyrrolidinone (2 mL) is treated with K_2CO_3 (52 mg, 0.38 mmol) and stirred at 80 °C overnight. The reaction is then cooled to room temperature, partitioned between ethyl acetate and water and extracted with water once more. The organics are dried over $MgSO_4$, filtered, evaporated, dissolved in dichloromethane (2 mL) and treated with TFA (2 mL). After stirring for 1 hour, the solvent is removed and the residue is dissolved in dichloromethane, treated with **E3b** (59 mg, 0.25 mmol) and excess triethylamine and stirred overnight. The reaction is then partitioned between ethyl acetate and water and extracted with water once more. The organics are dried over $MgSO_4$, filtered, evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **K2;** ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.93 (d, J = 3.0 Hz, 1H), 7.18 (dd, J = 3.1, 9.1 Hz, 1H), 6.65 (d, J = 9.2 Hz, 1H), 3.99 (m, 2H), 3.77 (s, 2H), 3.52 (m, 4H), 3.37 (m, 4H), 3.20 (m, 2H), 2.77 (d, J = 6.6 Hz, 2H), 2.32 (m, 1 H), 2.12 (s, 1H), 1.72 (m, 2H), 1.55 (m, 3H), 1.12 (d, J = 6.7 Hz, 6H), 0.87 (m, 2H), 0.63 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{38}N_4O_6S$ calcd: 510.3, found: 511.5.

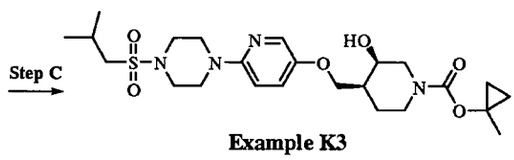
[00220]

Example K3: (+/-)-(cis)-1-methylcyclopropyl 3-hydroxy-4-((6-(4-(isobutylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate





K3a K3b K3c



Example K3

[00221] **Step A**: A solution of **K3a** (420 mg, 1.4 mmol) (Helv. Chim. Acta **2004**, 87, 2629) in EtOH containing 1% by volume TFA (150 mL) is hydrogenated in an H-Cube apparatus at 50 atmospheres of H_2 and 70 °C. The solvent is then removed and the residue is co-evaporated twice with toluene, dissolved in dichloromethane (10 mL) and treated with **E3b** (342 mg, 1.4 mmol), excess triethylamine and a few crystals of DMAP. The reaction is stirred overnight, partitioned between ethyl acetate and saturated aqueous sodiumhydrogencarbonate and extracted with satutated aqueous sodium carbonate twice. The organics are then dried over $MgSO_4$, filtered evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **K3b**; ESIMS *m/z* for $(M+H)^+$ $C_{15}H_{24}NO_6$ calcd: 314.2, found: 314.1.

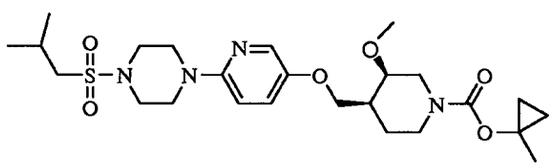
[00222] **Step B**: A solution of **K3b** (333 mg, 1.1 mmol) in MeOH is treated with a solution of $Mg(OMe)_2$ (5.6 mL of a 0.57 M solution, 3.2 mmol) and stirred for 1 hour. The reaction is then quenched with excess prewashed Amberlite IR-120 H^+ resin and

filtered. The solvent is removed to afford **K3c**; ESIMS *m/z* for $(M+H)^+$ $C_{11}H_{20}NO_4$ calcd: 230.1, found: 230.1.

[00223] **Step C**: A solution of DIAD (88 mg, 0.22 mmol) in dichloromethane (0.5 mL) is cooled in an ice bath and treated with a solution of PPh_3 (114 mg, 0.44 mmol) in dichloromethane (1 mL). The solution is stirred for 15 minutes and treated with a solution of **K3c** (50 mg, 0.22 mmol) and **K2d** (65 mg, 0.22 mmol) in dichloromethane (1.5 mL). The reaction is sealed and heated to 50 °C overnight. The reaction is cooled to room temperature and loaded onto a silica gel column and purified using a linear gradient of 0-100% ethyl acetate in hexane. The product fractions are partitioned between ethyl acetate and 1 M HCl. The aqueous phase is collected and the organics are extracted once more with 1 M HCl and discarded. The combined aqueous extracts are made basic with solid Na_2CO_3 and extracted three times with ethyl acetate. The combined organics are dried over $MgSO_4$, filtered and evaporated to afford **K3**; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 7.93 (d, *J* = 2.9 Hz, 1H), 7.17 (dd, *J* = 3.1, 9.1 Hz, 1H), 6.64 (d, *J* = 9.1 Hz, 1H), 4.19 (m, 2H), 4.09 (m, 1H), 4.03 (dd, *J* = 7.6, 9.1 Hz, 1H), 3.84 (dd, *J* = 6.0, 9.1 Hz, 1H), 3.51 (m, 4H), 3.37 (m, 4H), 2.91 (m, 1H), 2.78 (m, 1H), 2.76 (d, *J* = 6.6 Hz, 2H), 2.32 (m, 1H), 2.00 (m, 1H), 1.86 (m, 1H), 1.68 (m, 1H), 1.55 (s, 3H), 1.12 (d, *J* = 6.7 Hz, 6H), 0.88 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{39}N_4O_6S$ calcd: 511.3, found: 511.4.

[00224]

Example K4: (+/-)-(cis)-1-Methylcyclopropyl 4-((6-(4-(isobutylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)-3-methoxypiperidine-1-carboxylate

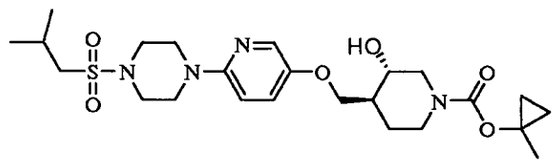


[00225] A solution of **K3** (25 mg, 0.22 mmol) in N, N-dimethylformamide (2 mL) is treated with excess (~100 uL) dimethylsulfate and excess (~40 mg) of NaH. The reaction is stirred for 1 hour and then diluted with ethyl acetate and water. The organics

are isolated and washed once more with water, dried over MgSO4, filtered, evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **K4**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.93 (d, J = 2.9 Hz, 1H), 7.16 (dd, J = 3.0, 9.1 Hz, 1H), 6.64 (d, J = 9.1 Hz, 1H), 4.53 (m, 0.5H), 4.28 (m, 1H), 4.00 (m, 1.5 H), 3.78 (m, 1H), 3.52 (m, 4H), 3.75 (m, 7H), 2.76 (d, J = 6.6 Hz, 2H), 2.72 (m, 2H), 2.32 (m, 1H), 2.03 (m, 1H), 1.59 (m, 1H), 1.55 (s, 3H), 1.48 (m, 1H), 1.12 (d, J = 6.7 Hz, 6H), 0.87 (m, 2H), 0.61 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{41}N_4O_6S$ calcd: 525.3, found: 525.2.

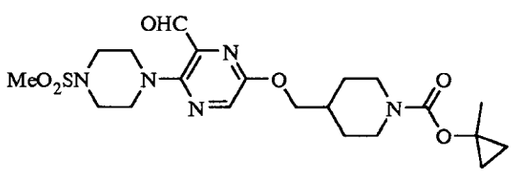
[00226]

Example K5: (+/-)-(Trans)-1-methylcyclopropyl 3-hydroxy-4-((6-(4-(isobutylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate



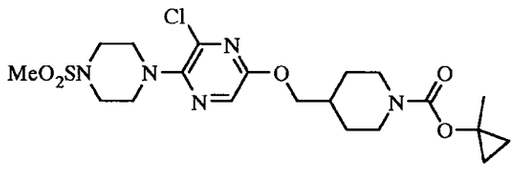
[00227] By following a similar procedure as the one used for preparing **K3** from **K3a** except substituting the trans- isomer of **K3a** (Helv. Chim. Acta **2004**, 87, 2629) for **K3a**, **K5** is prepared; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.93 (d, J = 3.0 Hz, 1H), 7.24 (dd, J = 3.0, 9.1 Hz, 1H), 6.69 (d, J = 9.2 Hz, 1H), 4.17 (m, 3H), 4.05 (m, 2H), 3.56 (m, 5 H), 3.37 (m, 4H), 2.77 (d, J = 6.6 Hz, 2H), 2.72 (m, 1H), 2.58 (m, 1H), 2.31 (m, 1H), 1.90 (m, 1H), 1.78 (m, 1H), 1.55 (s, 3H), 1.40 (m, 1H), 1.12 (d, J = 6.7 Hz, 6H), 0.87 (m, 2H), 0.61 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{39}N_4O_6S$ calcd: 511.3, found: 511.4.

Example L1: 1-methylcyclopropyl 4-((6-formyl-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



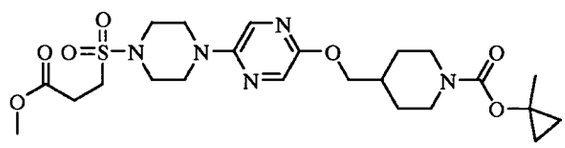
[00228] A solution of **E3** (109 mg, 0.24 mmol) in N,N-dimethylformamide (2.2 mL) is treated with $POCl_3$ (165 mg, 1.1 mmol) and heated to 70 °C for 2 hours. The reaction is then cooled to room temperature, quenched with water and diluted with ethyl acetate. The organics are exracted with water twice more, dried over $MgSO_4$, filtered evaporated and purified by silica gel using a linear gradient of 50-100% ethyl acetate in hexane to afford **L1**; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 9.93 (s, 1H), 8.04 (s, 1H), 4.19 (d, J = 6.4 Hz, 1H), 4.15 (m, 2H), 3.50 (m, 4H), 3.43 (m, 4H), 2.83 (s, 3H), 2.74 (m, 2H), 1.97 (m, 1H), 1.81 (m, 2H), 1.55 (s, 3H), 1.27 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{21}H_{32}N_5O_6S$ ($M+H^+$) 482.2, found 482.1.

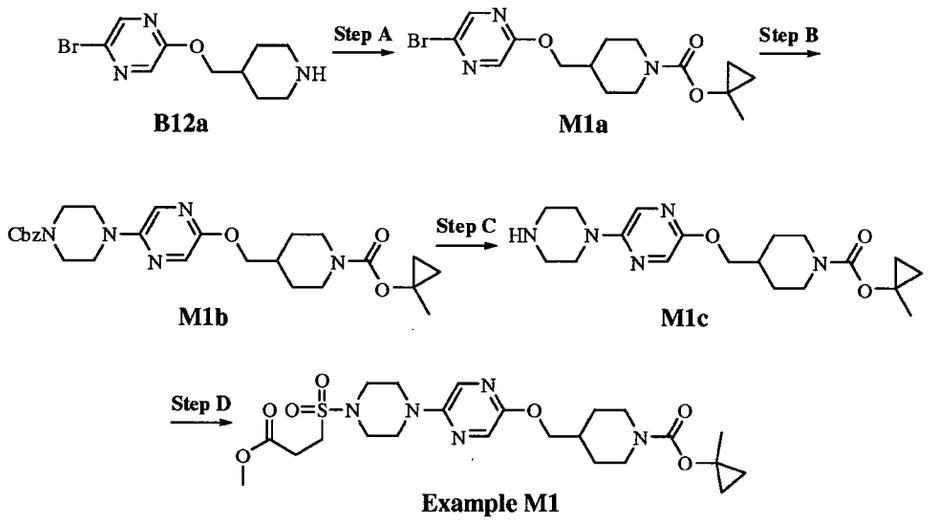
Example L2: 1-Methylcyclopropyl 4-((6-chloro-5-(4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00229] By following a similar procedure as the one used for preparing **L1** from **E3** except using NCS at 50 °C in dichloroethane overnight as the reaction conditions, **K5** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{31}ClN_5O_5S$ calcd: 488.2, found: 487.7.

Example M1: 1-Methylcyclopropyl 4-((5-(4-(3-methoxy-3-oxopropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





[00230] **Step A:** By following a similar procedure as the one used for preparing **E3** from **E3a** except substituting **B12a** for **E3a**, **M1a** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{15}H_{22}BrN_3O_3$ calcd: 371.2, found: 371.1.

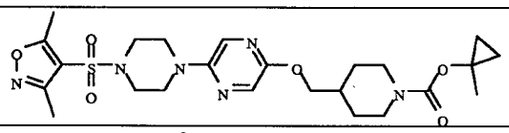
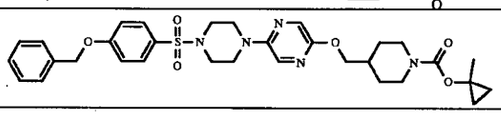
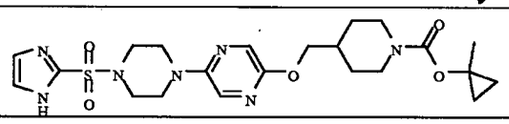
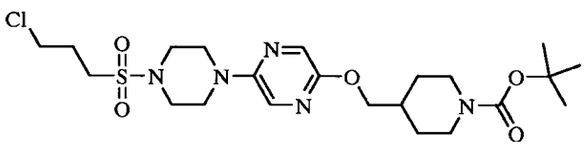
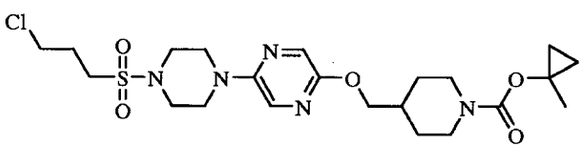
[00231] **Step B: :** By following a similar procedure as the one used for preparing **B1** from isopropyl 4-((6-chloropyridin-3-yloxy)methyl)piperidine-1-carboxylate except substituting **M1a** for isopropyl 4-((6-chloropyridin-3-yloxy)methyl)piperidine-1-carboxylate and benzyl piperazine-1-carboxylate for 1-(methylsulfonyl)piperazine, **M1b** is prepared; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 1.5 Hz, 1H), 7.59 (d, J = 1.4 Hz, 1H), 7.35 (m, 5H), 5.16 (s, 2H), 4.18 (m, 2H), 4.06 (d, J = 6.6 Hz, 2H), 3.65 (m, 4H), 3.38 (m, 4H), 2.74 (m, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.54 (s, 3H), 1.24 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{27}H_{36}N_5O_5$ calcd: 510.3, found: 510.0.

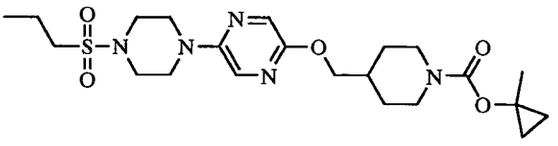
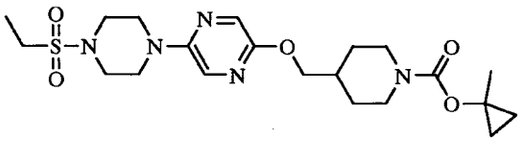
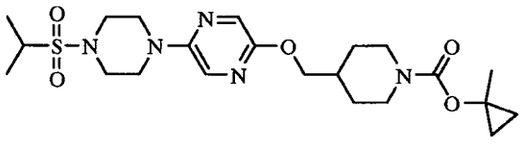
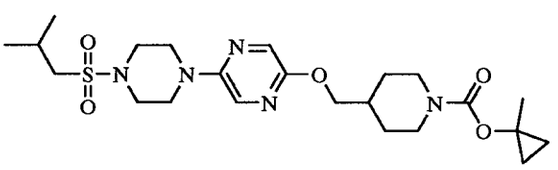
[00232] **Step C:** A mixture of **M1b** (494mg, 0.969 mmol) and 10% Pd/C (45 mg) in ethanol (5 mL) is purged with H_2 (g) for 30 minutes and then left to stir at room temperature under an atmosphere of H_2 overnight. The crude reaction is then filtered through a pad of Celite® and **M1c** is obtained with 95%+ purity. ESIMS *m/z* for $(M+H)^+$ $C_{19}H_{30}N_5O_3$ calcd: 376.2, found: 376.0.

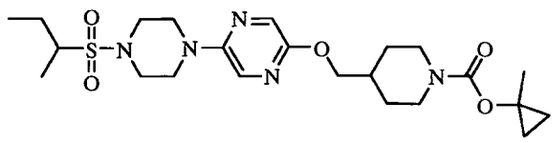
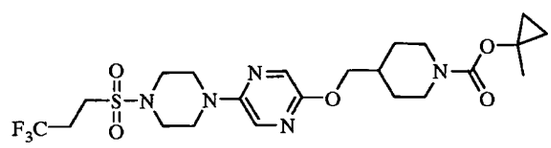
[00233] **Step D:** A solution of **M1c** (100 mg, 0.266 mmol) in dichloromethane (1 mL) is treated with triethylamine (74.2 mL, 0.533 mmol) followed by methyl 3-(chlorosulfonyl)propanoate (50 mg, 0.27 mmol) and stirred at room temperature for 4 hours. The crude reaction is then concentrated and purified directly via a mass-directed

HPLC to afford **M1**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.5 Hz, 1H), 7.61 (d, *J* = 1.5 Hz, 1H), 4.18 (m, 2H), 4.07 (d, *J* = 6.5 Hz, 2H), 3.73 (s, 3H), 3.49 (m, 4H), 3.42 (m, 4H), 3.28 (t, *J* = 7.3 H, 2H), 2.85 (t, *J* = 7.7 Hz, 2H), 2.74 (m, 2H), 1.93 (m, 1H), 1.81 (m, 2H), 1.54 (s, 3H), 1.24 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{36}N_5O_7S$ calcd: 526.2, found: 526.2.

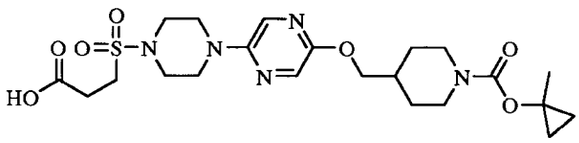
[00234] By following a similar procedure as the one used for preparing **M1** from **E12a** except substituting commercially available sulfonyl chlorides for methyl 3-(chlorosulfonyl)propanoate (in the case of **M5**, also substituting **B4bB** for **M1a**), the following examples are prepared;

Example	Structure	Analytical data
M2		ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{35}N_6O_6S$ calcd: 535.2, found: 535.2.
M3		ESIMS *m/z* for $(M)^+$ $C_{32}H_{39}N_5O_6S$ calcd: 621.3, found: 621.7.
M4		ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{32}N_7O_5S$ calcd: 506.2, found: 506.2.
M5		^{1}H NMR (400 MHz, CD_3CN) δ 7.87 (d, J = 1.4 hz, 1H), 7.62 (d, J - 1.5 Hz, 1H), 4.15 (m, 2H), 4.08 (d, J = 6.6 Hz, 2H), 3.70 (t, J = 6.1 Hz, 2H), 3.51 (m, 4H), 3.43 (m, 4H), 3.11 (t, J = 7.4 Hz, 2H), 2.73 (m, 2H), 2.32 (m, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.46 (s, 9H), 1.26 (m, 2H); ESIMS *m/z* for $(M-Boc+H)^+$ $C_{17}H_{29}ClN_5O_3S$ calcd: 418.2, found: 418.2.
M6		^{1}H-NMR (400MHz, $CDCl_3$) δ 7.87 (d, *J* = 1.4 Hz, 1H), 7.63 (d, *J* = 1.4 Hz, 1H), 4.21 (m, 2H), 4.08 (d, *J* = 6.5Hz, 2H), 3.70 (t, *J* = 6.1 Hz, 2H), 3.51 (m, 4H), 3.44 (m, 4H), 3.12 (m, 2H), 2.74 (dd, *J* = 12.3, 12.2 Hz, 2H), 2.32 (m, 2H), 1.95 (m, 1H),

		1.79 (m, 2H), 1.55 (s, 3H), 1.25 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{22}H_{35}ClN_5O_5S$ $[M]^+$ 516.2, found 516.0.
M7		^{1}H NMR (400 MHz, CD_3CN) δ 7.89 (d, J = 1.4 Hz, 1H), 7.82 (d, J = 1.2 Hz, 1H), 4.19 (m, 2H), 4.10 (d, J = 6.5 Hz, 2H), 3.51 (m, 8H), 2.93 (m, 2H), 2.74 (dd, J= 12.7, 12.0 Hz, 1H), 1.91 (m, 3H), 1.79 (m, 2H), 1.55 (s, 3H), 1.25 (m, 2H), 1.07 (t, J = 7.4 Hz, 3H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{36}N_5O_5S$ calcd: 482.3 , found: 482.2.
M8		^{1}H NMR (400 MHz, CD_3CN) δ 7.96 (s, 1H), 7.91 (d, J = 1.4 Hz, 1H), 4.17 (m, 2H), 4.11 (d, J = 6.5 Hz, 2H), 3.58 (m, 4H), 3.54 (m, 4H), 3.01 (m, 2H), 2.74 (dd, J = 12.2, 11.9 Hz, 2H), 1.95 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.40 (t, J = 7.4 Hz, 3H), 1.25 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{34}N_5O_5S$ calcd: 468.2 , found: 468.2.
M9		^{1}H NMR (400 MHz, CD_3CN) δ 7.91 (m, 2H), 4.18 (m, 2H), 4.11 (d, J = 6.5 Hz, 2H), 3.63 (m, 4H), 3.50 (m, 4H), 3.25 (sept., J = 6.8 Hz, 1H), 2.74 (dd, J = 12.2, 12.1 Hz, 2H), 1.94 (m, 1H), 1.78 (m, 2H), 1.55 (s, 3H), 1.37 (d, J = 6.9 Jz, 6H), 1.25 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{36}N_5O_5S$ calcd: 482.2 , found: 482.2.
M10		^{1}H NMR (400 MHz, CD_3CN) δ 7.89 (d, J = 1.4 Hz, 1H), 7.81 (d, J = 1.1 Hz, 1H), 4.18 (m, 2H), 4.10 (d, J = 6.5 Hz, 2H), 3.53 (m, 4H), 3.47 (m, 4H), 2.79 (d, J = 6.6 Hz, 2H), 2.74 (m, 2H), 2.32 (m, 1H), 1.95 (m, 1H), 1.78 (m, 2H), 1.55 (s, 3H), 1.24 (m, 2H), 1.12 (d, J =

		6.7 Hz, 6H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{38}N_5O_5S$ calcd: 496.3 , found: 496.3.
M11		^{1}H NMR (400 MHz, CD_3CN) δ 7.87 (d, J = 1.5 Hz, 1H), 7.62 (d, J = 1.5 Hz, 1H), 4.19 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.50 (m, 4H), 3.46 (m, 4H), 2.98 (m, 1H), 2.75 (dd, J = 12.2, 12.1 Hz, 2H), 2.03 (m, 1H), 1.80 (m, 1H), 1.79 (m, 2H), 1.56 (m, 1H), 1.55 (s, 3H), 1.35 (d, J = 6.9 Hz, 3H), 1.26 (m, 2H), 1.03 (t, J = 7.5 hz, 3H), 0.87 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{38}N_5O_5S$ calcd: 496.3 , found: 496.2.
M12		^{1}H-NMR (400MHz, $CDCl_3$) δ 7.87 (d, *J* = 1.4Hz, 1H), 7.62 (d, *J* = 1.4Hz, 1H), 4.20 (m, 2H), 4.08 (d, *J* = 6.5Hz, 2H), 3.52 (m, 4H), 3.45 (m, 2H), 3.13 (m, 2H), 2.74 (dd, *J* = 12.2, 12.2 Hz, 2H), 2.66 (m, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.56 (s, 3H), 1.25 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. $C_{22}H_{33}F_3N_5O_5S$ $[M+H]^+$ 536.2, found 536.3.

Example M13: 3-(4-(5-((1-((1-Methylcyclopropoxy)carbonyl)piperidin-4-yl)methoxy)pyrazin-2-yl)piperazin-1-ylsulfonyl)propanoic acid.

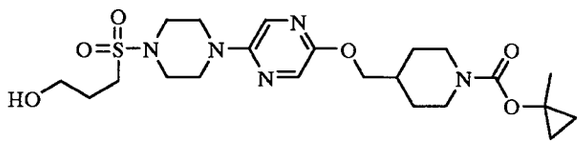


[00235] A solution of **M1** (18.8 mg, 0.035 mmol) in TETRAHYDROFURAN (1 mL) and water (0.25 mL) is treated with LiOH (3 mg) and stirred overnight. The crude

reaction is then concentrated and purified directly via a mass-directed HPLC to afford **M13**. ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{34}N_5O_7S$ calcd: 512.2, found: 512.3.

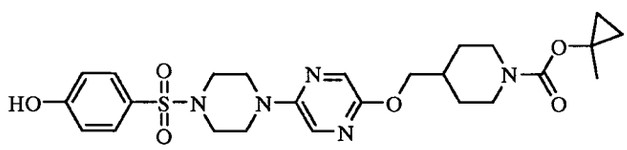
[00236]

Example M14: 1-Methylcyclopropyl 4-((5-(4-(3-hydroxypropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00237] A solution of **M1** (18.8 mg, 0.035 mmol) in 2 M $LiBH_4$ in tetrahydrofuran (1 mL) is heated to 50 °C and stirred overnight. The crude reaction is then concentrated and purified directly via a mass-directed HPLC to afford **M14**. ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{36}N_5O_6S$ calcd: 498.2, found: 498.3.

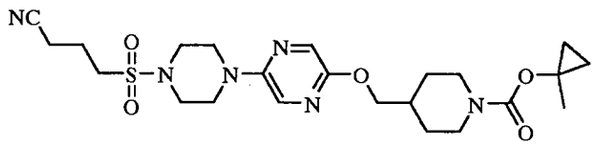
Example M15: 1-Methylcyclopropyl 4-((5-(4-(4-hydroxyphenylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00238] A solution of **M3** (44.5 mg, 0.071 mmol) in ethanol (2 mL) is treated with 5% Pd/C (10 mg) and hydrogenated under atmospheric pressure overnight. The catalyst is removed by filtration through Celite® and the reaction is concentrated and purified directly via a mass-directed HPLC to afford **M15**. ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{33}N_5O_6S$ calcd: 531.2, found: 531.7.

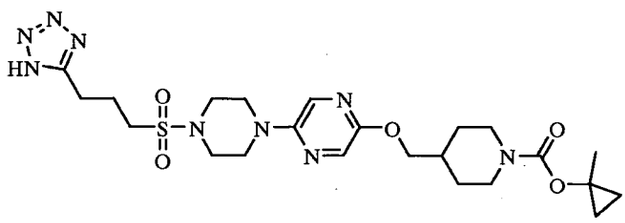
115

Example M16: 1-Methylcyclopropyl 4-((5-(4-(3-cyanopropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00239] A solution of **M6** (19 mg, 0.037 mmol) in N,N-dimethylformamide (0.5 mL) is treated with KCN (3.6 mg, 0.055 mmol) and cesium carbonate (24 mg, 0.077 mmol) and heated to 80 °C for 1.5 hours. The reaction is then diluted with water and extracted with ethyl acetate three times and diethyl ether twice. The combined organics are dried over $MgSO_4$, filtered evaporated and purified by silica gel using a linear gradient of 50-100% ethyl acetate in hexane to afford **M16**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 1.6 Hz, 1H), 7.62 (d, J = 1.6 Hz, 1H), 4.28-3.95 (m, 2H), 4.08 (d, J = 6.4 Hz, 2H), 3.53-3.50 (m, 4H), 3.44-3.42 (m, 4H), 3.07 (t, J = 6.8 Hz, 2H), 2.74 (br t, J = 12.0 Hz, 2H), 2.64 (t, J = 7.2 Hz, 2H), 2.24 (quintet, J = 7.2 Hz, 2H), 2.01-1.89 (m, 1H), 1.81-1.77 (m, 2H), 1.54 (s, 3H), 1.30-1.17 (m, 2H), 0.88-0.84 (m, 2H), 0.64-0.60 (m, 2H); ESIMS m/z for $(M+H)^+$ $C_{23}H_{35}N_6O_5S$ calcd: 507.2, found: 507.2.

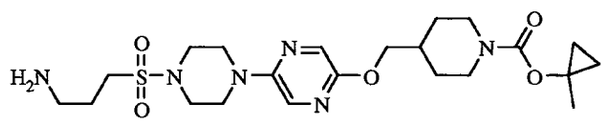
Example M17: 1-Methylcyclopropyl 4-((5-(4-(3-(1H-tetrazol-5-yl)propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



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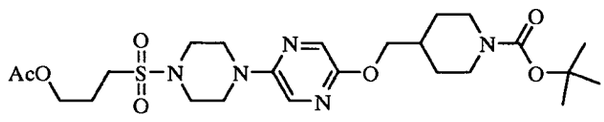
[00240] A solution of **M16** (12 mg, 0.024 mmol) in isopropanol (0.1 mL) and water (0.3 mL) is treated with $ZnBr_2$ (27 mg, 0.12 mmol) and NaN_3 (7.7 mg, 0.12 mmol) and heated to 150 °C overnight. The reaction is filtered through a syringe filter and purified directly via a mass-directed HPLC to afford **M17**; ^{1}H NMR (400 MHz, CD_3CN) δ 7.83 (d, *J* = 1.6 Hz, 1H), 7.71 (d, *J* = 1.6 Hz, 1H), 4.16-3.89 (m, 2H), 4.06 (d, *J* = 6.4 Hz, 2H), 3.49-3.46 (m, 4H), 3.35-3.32 (m, 4H), 3.12-3.04 (m, 4H), 2.81-2.70 (m, 2H), 2.28-2.20 (m, 2H), 1.78-1.71 (m, 3H), 1.48 (s, 3H), 1.22-1.12 (m, 2H), 0.81-0.78 (m, 2H), 0.60-0.57 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{36}N_9O_5S$ calcd: 550.3, found: 550.3.

Example M18: 1-Methylcyclopropyl 4-((5-(4-(3-aminopropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



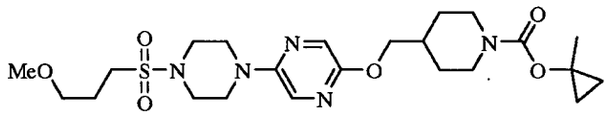
[00241] A solution of **M6** (113 mg, 0.22 mmol) in N,N-dimethylformamide (1 mL) is treated with NaN_3 (42.7 mg, 0.67 mmol) and heated to 90 °C overnight. The reaction is cooled to room temperature, partitioned between water and ethyl acetate. The organics are exracted with water twice more, dried over $MgSO_4$, filtered evaporated and purified by silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford the intermediate azide which is dissolved in ethanol (1 mL) and treated with 10% Pd/C (20 mg) and hydrogenated at room temperature overnight. The catalyst is removed by filtration through Celite® and the reaction is concentrated and purified directly via a mass-directed HPLC to afford **M18.** ^{1}H NMR (400 MHz, CD_3CN) δ 7.86 (d, J = 1.4 Hz, 1H), 7.61 (d, J = 1.5 Hz, 1H), 4.19 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.50 (m, 4H), 3.42 (m, 4H), 3.05 (m, 2H), 2.88 (t, J = 6.7 Hz, 2H), 2.74 (dd, J = 13.0, 12.0 Hz, 2H), 1.98 (m, 3H), 1.79 (m, 2H), 1.54 (s, 3H), 1.24 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{37}N_6O_5S$ calcd: 497.3 , found: 497.6.

Example M19: *Tert*-butyl 4-((5-(4-(3-acetoxypropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00242] A solution of **M5** (154 mg, 0.30 mmol) in N,N-dimethylformamide (2 mL) is treated with sodium acetate (73 mg, 0.89 mmol) and sodium iodide (45 mg, 0.30 mmol) and heated to 120 °C overnight . The reaction is cooled to room temperature, partitioned between water and ethyl acetate. The organics are exracted with water twice more, dried over $MgSO_4$, filtered evaporated and purified by silica gel using a linear gradient of 0-100% ethyl acetate in dichloromethane to afford **M19;** ^{1}H NMR (400 MHz, CD_3CN) δ 7.87 (d, J = 1.4 Hz, 1H), 7.83 (d, J = 1.5 Hz, 1H), 4.20 (t, J = 6.1 Hz, 2H), 1.14 (m, 2H), 4.08 (d, J = 6.6 Hz, 1H), 3.51 (m, 4H), 3.44 (m, 4H), 3.02 (m, 2H), 2.74 (m, 2H), 2.19 (m, 2H), 2.07 (s, 3H), 1.95 (m, 1H), 1.80 (m, 2H), 1.46 (s, 9H), 1.26 (m, 2H); ESIMS *m/z* for $(M\text{-}Boc+H)^+$ $C_{19}H_{32}N_5O_5S$ calcd: 442.2 , found: 442.3.

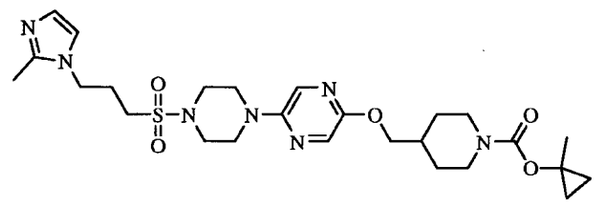
Example M20: 1-Methylcyclopropyl 4-((5-(4-(3-methoxypropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00243] A solution of **M6** (26 mg, 0.049 mmol) in methanol (1 mL) is treated with a 0.5 M solution of sodium methoxide in methanol (0.2 mL, 0.1 mmol) and heated to 65 °C overnight and at 95 °C for 10 hours. The reaction is cooled to room temperature, the

solvent is removed *in vacuo* and the crude residue is purified by silica gel using a linear gradient of 0-80% ethyl acetate in hexane to afford **M20.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 1.2 Hz, 1H), 7.61 (d, J = 1.6 Hz, 1H), 4.15 (m, 2H), 4.07 (d, J = 6.4 Hz, 2H), 3.49 (m, 6H), 3.42 (m, 4H), 3.33 (s, 3H), 3.04 (m, 2H), 2.74 (t, J = 12.4 Hz, 2H), 2.09 (m, 2H), 1.94 (m, 1H), 1.79 (d, J = 12.4 Hz, 2H), 1.54 (s, 3H), 1.24 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{37}N_5O_6S$ calcd: 511.3, found: 512.2.

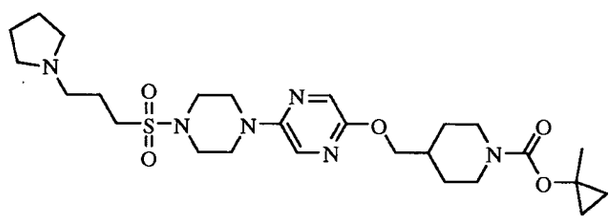
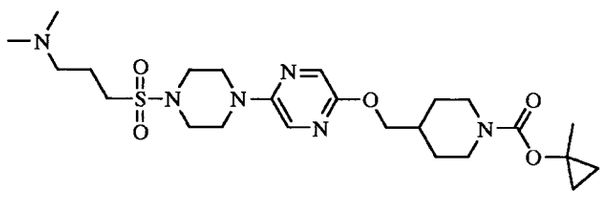
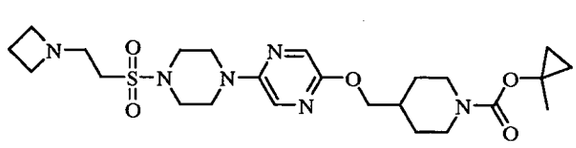
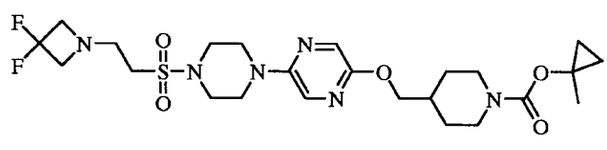
Example M21: 1-Methylcyclopropyl 4-((5-(4-(3-(2-methyl-1H-imidazol-1-yl)propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00244] A solution of **M6** (53 mg, 0.10 mmol) in tetrahydorfuran (1 mL) is treated with 2-methylimidazole (8.5 mg, 0.10 mmol) and heated to 65 °C overnight. The reaction is cooled to room temperature, the solvent is removed *in vacuo* and the crude residue is purified directly *via* a mass-directed HPLC to afford **M21**. ^{1}H NMR (400 MHz, CD_3CN) δ 7.86 (d, J = 1.4 Hz, 1H), 7.62 (d, J = 1.4 Hz, 1H), 7.29 (d, J = 2.0 Hz, 1H), 7.18 (d, J = 1.8 Hz, 1H), 4.34 (t, J = 7.0 Hz, 2H), 4.18 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.51 (m, 4H), 3.41 (m, 4H), 2.93 (m, 2H), 2.83 (s, 3H), 2.74 (m, 2H), 2.42 (m, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.54 (s, 3H), 1.25 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{40}N_7O_5S$ calcd: 562.3 , found: 562.5.

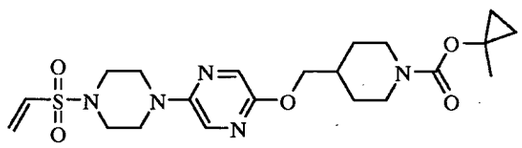
[00245] By following the procedure for **M21** using the appropriate amine nucleophiles, the following examples are obtained:

Example	Structure	Analytical data

M22		^{1}H NMR (400 MHz, CD_3CN) δ 7.85 (d, J = 1.4 Hz, 1H), 7.61 (d, J = 1.5 Hz, 1H), 4.18 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.51 (m, 4H), 3.43 (m, 4H), 3.19 (m, 6H), 2.74 (dd, J = 12.4, 12.3 Hz, 2H), 2.36 (m, 2H), 2.08 (m, 5H), 1.94 (m, 2H), 1.79 (m, 2H), 1.54 (s, 3H), 1.25 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{43}N_6O_5S$ calcd: 551.3 , found: 551.5.
M23		^{1}H NMR (400 MHz, CD_3CN) δ 7.85 (d, J = 1.5 Hz, 1H), 7.61 (d, J = 1.5 Hz, 1H), 4.18 (m, 2H), 4.07 (d, J = 6.6 Hz, 2H), 3.51 (m, 4H), 3.44 (m, 4H), 3.18 (m, 2H), 2.98 (m, 2H), 2.74 (dd, J = 12.4, 12.3, Hz, 2H), 2.63 (s, 6H), 2.30 (m, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.54 (s, 3H), 1.25 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{41}N_6O_5S$ calcd: 525.3 , found: 525.3.
M-24		^{1}H NMR (400 MHz, CD_3CN) δ 7.86 (d, J = 1.2 Hz, 1H), 7.82 (d, J = 1.6 Hz, 1H), 4.10 (d, J = 6.4 Hz, 2H), 4.07 (m, 2H), 3.55 (m, 2H), 3.41 (m, 2H), 3.15 (t, J = 7.2 Hz, 4H), 3.01 (m, 2H), 2.83 (m, 2H), 2.74 (m, 2H), 1.95 (m, 3H), 1.78 (m, 2H), 1.50 (s, 3H), 1.22 (m, 2H), 0.79 (m, 2H), 0.58 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{38}N_6O_5S$ calcd: 522.3, found: 523.2.
M-25		^{1}H NMR (400 MHz, CD_3CN) δ 7.83 (d, J = 1.2 Hz, 1H), 7.71 (d, J = 1.6 Hz, 1H), 4.06 (d, J = 6.8 Hz, 2H), 4.00 (m, 2H), 3.59 (t, J = 12.4 Hz, 4H), 3.48 (m, 4H), 3.32 (m, 4H), 3.06 (m, 2H), 2.95 (m, 2H), 2.74 (m, 2H), 2.10 (m, 1H), 1.76 (m, 2H), 1.49 (s, 3H), 1.17 (m, 2H), 0.79 (m, 2H), 0.59 (m, 2H);

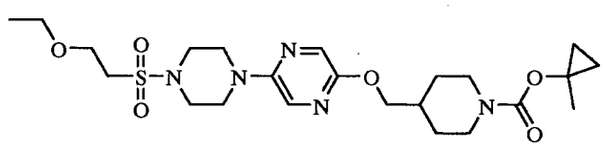
		ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{36}F_2N_6O_5S$ calcd: 558.2, found: 559.2.

Example M26: 1-Methylcyclopropyl 4-((5-(4-(vinylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



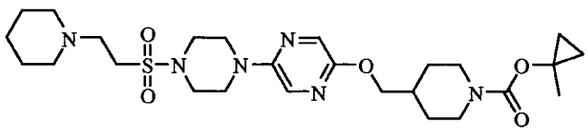
[00246] A solution of **M1c** (308 mg, 0.82 mmol) in tetrahydorfuran (4 mL) is cooled in an ice/water bath and treated with triethylamine (299 mg, 3.0 mmol) followed by 2-chloroethanesulfonyl chloride (401 mg, 2.5 mmol) added over 10 minutes. The reaction is stirred for an hour and then evaporated and partitioned between water and ethyl acetate. The organics are exracted with water twice more, dried over $MgSO_4$, filtered evaporated and purified by silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M26**; ^1H NMR (400 MHz, CD_3CN) δ 7.91 (d, J = 2.9Hz, 1H), 7.15 (dd, J = 9.1, 3.1 Hz, 1H), 6.65 (d, J = 9.1 Hz, 1H), 4.19 (m, 2H), 3.81 (d, J = 6.3 Hz, 2H), 3.54 (m, 4H), 3.34 (m, 4H), 3.08 (ddd, J = 13.1, 2.8, 2.8 Hz, 2H), 2.80 (s, 3H), 2.04 (m, 1H), 1.92 (m, 2H), 1.44 (m, 2H), 1.28 (m, 6H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{32}N_5O_5S$ calcd: 466.2, found: 466.2.

Example M27: 1-Methylcyclopropyl 4-((5-(4-(2-ethoxyethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00247] By following a similar procedure as the one used for preparing **M20** from **M6** except substituting **M26** for **M6**, **M27** is prepared; ^{1}H NMR (400 MHz, CD_3CN) δ 7.86 (d, J = 1.5 Hz, 1H), 7.61 (d, J = 1.5 Hz, 1H), 4.18 (m, 2H), 4.07 (d, J = 6.6 Hz, 2H), 3.80 (t, J = 6.0 Hz, 2H), 3.51 (m, 6H), 3.43 (m, 4H), 3.24 (t, J = 5.9 Hz, 2H), 2.74 (dd, J = 12.3, 12.0 Hz, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.54 (s, 3H), 1.23 (m, 2H), 1.17 (t, J = 7.0 Hz, 3H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{38}N_5O_6S$ calcd: 512.3 , found: 512.6.

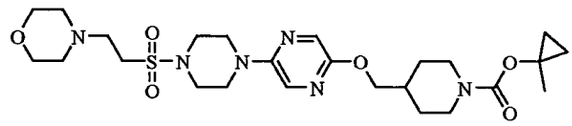
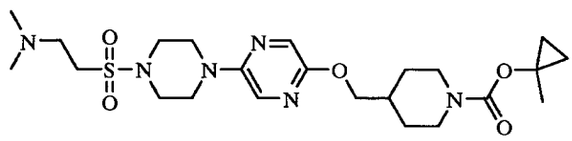
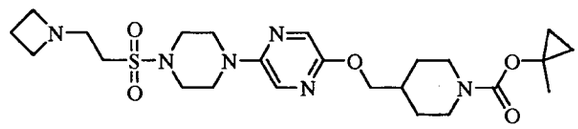
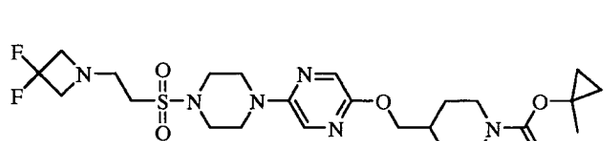
Example M28: 1-Methylcyclopropyl 4-((5-(4-(2-(piperidin-1-yl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



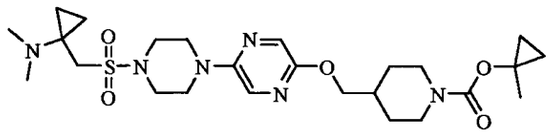
[00248] A solution of **M26** (27 mg, 0.058 mmol) in ethanol (0.5 mL) is treated with piperidine (13.3 mg, 0.12 mmol) and stirred at room temperture overnight. The reaction is diluted with N,N-dimethylformamide and purified directly *via* a mass-directed HPLC to afford **M27**; ^{1}H NMR (400 MHz, CD_3CN) δ 7.87 (d, J = 1.4 Hz, 1H), 7.64 (d, J = 1.4 Hz, 1H), 4.19 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.70 (m, 2H), 3.49 (m, 8H), 3.42 (m, 4H), 2.75 (m, 4H), 1.93 (m, 6H), 1.80 (m, 2H), 1.54 (s, 3H), 1.45 (m, 1H), 1.24 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{43}N_6O_5S$ calcd: 551.3, found: 551.3.

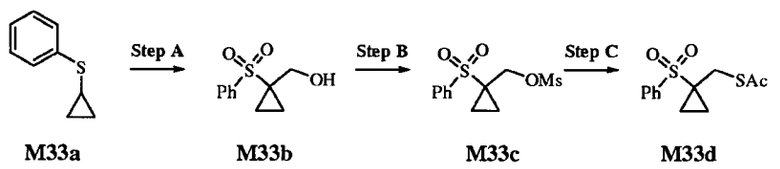
[00249] By following a similar procedure as the one used for preparing **M28** from **M26** except substituting a commercially available amine for piperidine, the following examples are prepared;

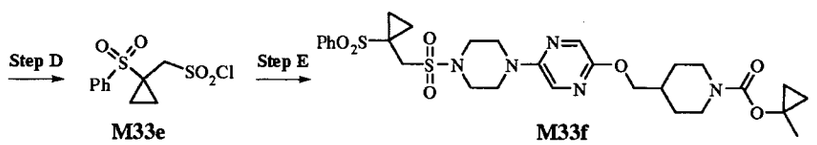
Example	Structure	Analytical data

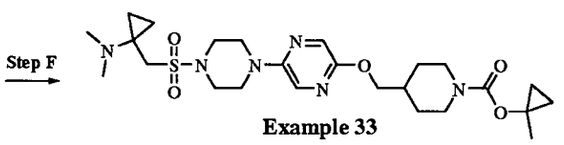
M29		^{1}H NMR (400 MHz, CD_3CN) δ 7.86 (s, 1H), 7.62 (s, 1H), 4.19 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.97 (m, 5H), 3.49 (m, 5H), 3.42 (m, 5H), 2.74 (m, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.54 (s, 3H), 1.24 (m, 2H), 0.86 (m, 2H), 0.61 (m, 2); ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{41}N_6O_6S$ calcd: 553.3, found: 553.2.
M30		^{1}H NMR (400 MHz, CD_3CN) δ 7.88 (s, 1H), 7.64 (s, 1H), 4.18 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.51 (m, 8H), 3.44 (m, 4H), 2.94 (s, 6H), 2.76 (m, 2H), 1.96 (m, 1H), 1.80 (m, 2H), 1.54 (s, 3H), 1.24 (m, 2H), 0.87 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{39}N_6O_5S$ calcd: 511.3, found: 511.2.
M31		^{1}H NMR (400 MHz, CD_3CN) δ 7.86 (d, J = 1.2 Hz, 1H), 7.82 (d, J = 1.6 Hz, 1H), 4.10 (d, J = 6.4 Hz, 2H), 4.07 (m, 2H), 3.55 (m, 2H), 3.41 (m, 2H), 3.15 (t, J = 7.2 Hz, 4H), 3.01 (m, 2H), 2.83 (m, 2H), 2.74 (m, 2H), 1.95 (m, 3H), 1.78 (m, 2H), 1.50 (s, 3H), 1.22 (m, 2H), 0.79 (m, 2H), 0.58 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{38}N_6O_5S$ calcd: 522.3, found: 523.2.
M32		^{1}H NMR (400 MHz, CD_3CN) δ 7.83 (d, J = 1.2 Hz, 1H), 7.71 (d, J = 1.6 Hz, 1H), 4.06 (d, J = 6.8 Hz, 2H), 4.00 (m, 2H), 3.59 (t, J = 12.4 Hz, 4H), 3.48 (m, 4H), 3.32 (m, 4H), 3.06 (m, 2H), 2.95 (m, 2H), 2.74 (m, 2H), 2.10 (m, 1H), 1.76 (m, 2H), 1.49 (s, 3H), 1.17 (m, 2H), 0.79 (m, 2H), 0.59 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{36}F_2N_6O_5S$ calcd: 558.2, found: 559.2.

Example M33: 1-Methylcyclopropyl 4-((5-(4-((1-(dimethylamino)cyclopropyl)methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.









[00250] **Step A**: A solution of **M33a** (5.0 g, 33 mmol) in acetic acid (50 mL) is treated with 30% aqueous hydrogen peroxide (7.92 g of solution, 70 mmol) and stirred at 100 °C for 1 hour. The solvent was then removed and the reaction was coevaporated with toluene 3 times.

[00251] A sample of **M33a** (4 g, 22 mmol) in tetrahydrofuran (40 mL) is cooled in an ice/water bath and treated with BuLi in hexane (13.2 mL of a 2 M solution, 26 mmol) and stirred for 20 minutes. The resulting yellow solution is treated with paraformaldehyde (1.65 g, 55 mmol) and allowed to stir for 1 hour. The reaction is then quenched with saturated aqueous ammonium chloride and filtered through a pad of Celite® using ethyl acetate. The organics are isolated, dried over $MgSO_4$, filtered,

evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M33b**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (m, 2H), 7.68 (m, 1H), 7.59 (m, 2H), 3.64 (d, J = 6.4 Hz, 2H), 2.72 (dd, J = 6.4, 6.4 Hz, 1H), 1.64 (m, 2H), 1.07 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{10}H_{13}O_3S$ calcd: 213.1, found: 213.0.

[00252] **Step B**: A solution of **M33b** (4.2 g, 20 mmol) in dichloromethane (40 mL) is treated with triethylamine (3.0 g of solution, 30 mmol), cooled in an ice/water bath and treated methanesulfonyl chloride (2.95 g, 26 mmol). The solution is stirred overnight an allowed to come to room temperature. The reaction is then quenched with aqueous 1 M HCl and extracted with dichloromethane twice. The organics are dried over $MgSO_4$, filtered, evaporated and triturated with diethyl ether to afford **M33c**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (m, 2H), 7.68 (m, 1H), 7.59 (m, 2H), 4.41 (s, 2H), 2.82 (s, 3H), 1.80 (m, 2H), 1.21 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{11}H_{15}O_5S_2$ calcd: 291.0, found: 291.0.

[00253] **Step C**: A solution of **M33c** (3 g, 10 mmol) in N, N-dimethylformide (30 mL) is treated with potassium thioacetate (1.3 g, 11 mmol) and water (20 mL) and stirred at 60 °C overnight. The reaction is diluted with ethyl acetate and extracted with water twice. The organics are isolated, dried over $MgSO_4$, filtered, evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M33d**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (m, 2H), 7.69 (m, 1H), 7.59 (m, 2H), 3.26 (s, 2H), 2.26 (m, 3H), 1.68 (m, 2H), 1.02 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{12}H_{15}O_3S_2$ calcd: 271.1, found: 271.0.

[00254] **Step D**: A cold (ice/water bath) solution of acetonitrile (2.1 mL) and 2 M HCl (419 μL, 0.84 mmol) is treated with NCS (838 mg, 6.27 mmol), allowed to stir for 5 minutes and treated dropwise with a solution of **M33d** (358 mg, 1.6 mmol) in acetonitrile (419 μL). After 30 minutes of stirring, the reaction is diluted with diethyl ether and extracted with brine, water and saturated sodium thiosulfate. The organics are isolated, dried over $MgSO_4$, filtered and to afford **M33e**; ESIMS *m/z* for $(M+H)^+$ $C_{10}H_{12}ClO_4S_2$ calcd: 295.0, found: 294.9.

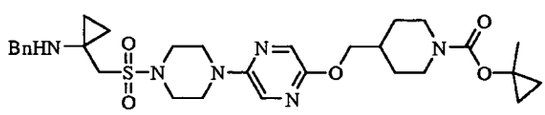
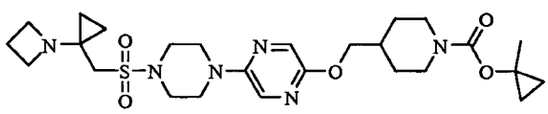
[00255] **Step E**: A cold (ice/water bath) solution of **M1c** (524 mg, 1.4 mmol) and triethylamine (282 mg, 2.8 mmol) in dichloromethane (5 mL) is treated with a solution of **M33e** (solution of the crude from the last step) in dichlormethane (3 mL). After 2 hours

of stirring, the reaction is evaporated and purified silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M33f**; ESIMS *m/z* for $(M+H)^+$ $C_{29}H_{40}N_5O_7S_2$ calcd: 634.2, found: 634.2.

[00256] **Step F**: A solution of **M33f** (157 mg, 0.25 mmol) in 2 M dimethylamine in tetrahydrofuran (2 mL, 4 mmol) is treated with potassium *tert*-butoxide (28 mg, 0.25 mmol) and stirred for 1 hour. The reaction is evaporated, diluted with methanol and purified directly *via* a mass-directed HPLC to afford **M33**; ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.86 (d, J = 1.4 Hz, 1H), 7.61 (d, J = 1.4 Hz, 1H), 4.20 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.50 (m, 4H), 3.39 (m, 4H), 3.07 (s, 2H), 2.74 (dd, J = 12.4, 12.3 Hz, 2H), 2.37 (s, 6H), 1.94 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.25 (m, 2H), 0.93 (m, 2H), 0.86 (m, 4H); ESIMS calcd. for $C_{25}H_{41}N_6O_5S$ $[M+H]^+$ 537.3, found 537.4.

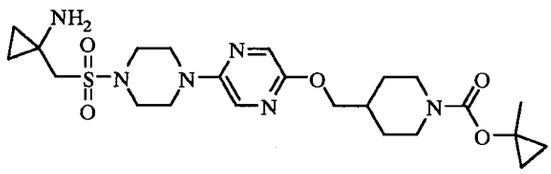
[00257]

[00258] By following the procedure for **M33** using the appropriate amine nucleophiles in step F, the following examples are obtained:

Example	Structure	Analytical data
M34		^{1}H-NMR (400MHz, $CDCl_3$) δ 7.86 (d, J = 1.5 Hz, 1H), 7.61 (d, J = 1.5 Hz, 1H), 7.31 (m, 5H), 4.14 (m, 2H), 4.09 (d, J = 6.5 Hz, 2H), 3.83 (s, 2H), 3.49 (m, 4H), 3.38 (m, 4H), 3.06 (s, 2H), 2.75 (m, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.26 (m, 2H), 0.92 (m, 2H), 0.87 (m, 2H), 0.71 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{30}H_{43}N_6O_5S$ $[M+H]^+$ 599.3, found 599.5.
M35		^{1}H-NMR (400MHz, $CDCl_3$) δ 7.86 (d, J = 1.4 Hz, 1H), 7.61 (d, J = 1.4 Hz, 1H), 3.82-4.21 (m, 6H), 4.07 (d, J = 6.5 Hz, 2H), 3.49 (m, 7H), 3.41 (m, 5H), 2.74 (dd, J = 12.5, 12.3 Hz, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.24 (m, 6H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{26}H_{41}N_6O_5S$ $[M+H]^+$

		549.3, found 549.4.

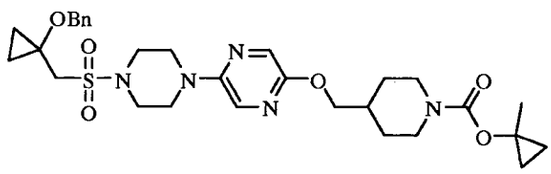
Example M36: 1-Methylcyclopropyl 4-((5-(4-((1-aminocyclopropyl)methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00259] A solution of **M34** (29 mg, 0.048 mmol) in ethanol (1 mL) and acetic acid (0.1 mL) is treated with 10% Pd/C (Degussa type) and hydrogenated at room pressure for 2 hours. The atmosphere is exchanged for nitrogen and the catalyst is removed by filtration through Celite®. The crude material is diluted with methanol and purified directly *via* a mass-directed HPLC to afford **M36;** ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.86 (d, J = 1.4 Hz, 1H), 7.61 (d, J = 1.4 Hz, 1H), 4.20 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.50 (m, 4H), 3.39 (m, 4H), 3.07 (s, 2H), 2.74 (dd, J = 12.4, 12.3 Hz, 2H), 2.37 (s, 6H), 1.94 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.25 (m, 2H), 0.93 (m, 2H), 0.86 (m, 4H); ESIMS calcd. for $C_{23}H_{37}N_6O_5S$ $[M+H]^+$ 509.3, found 509.5.

[00260]

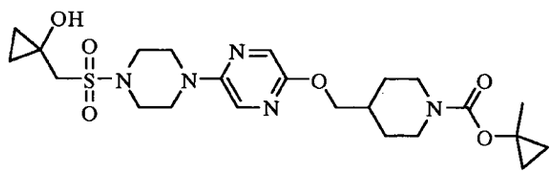
Example M37: 1-methylcyclopropyl 4-((5-(4-((1-(benzyloxy)cyclopropyl)methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00261] A solution of **M33f** (147 mg, 0.23 mmol) in benzyl alcohol (1 mL) is treated with sodium hydride (12 mg, 0.5 mmol) and stirred for 24 hours. The reaction is purified directly *via* a mass-directed HPLC to afford **M37**; ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.84 (d, J = 1.4 Hz, 1H), 7.56 (d, J = 1.4 Hz, 1H), 7.25 (m, 5H), 4.55 (s, 2H), 4.20 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.46 (m, 8H), 3.31 (s, 2H), 2.75 (dd, J = 12.3, 12.3 Hz, 2H), 1.94 (m, 1H), 1.80 (m, 2H), 1.54 (s, 3H), 1.25 (m, 2H), 1.08 (m, 2H), 0.87 (m, 4H), 0.62 (m, 2H); ESIMS calcd. for $C_{30}H_{42}N_5O_6S$ $[M+H]^+$ 600.3, found 600.5.

[00262]

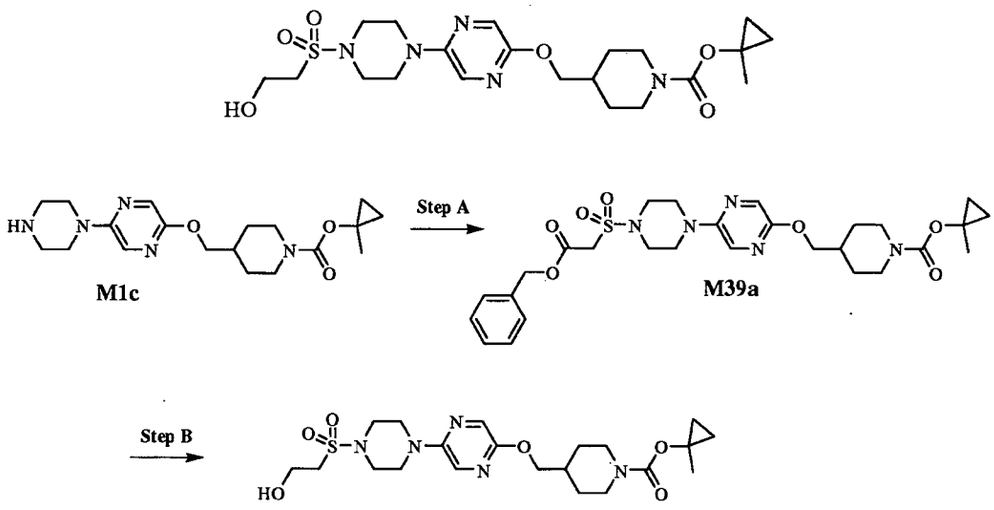
Example M38: 1-Methylcyclopropyl 4-((5-(4-((1-hydroxycyclopropyl)methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00263] A solution of **M33f** (11.6 mg, 0.018 mmol) in tetrahydrofuran (0.5 mL) is treated with potassium *tert*-butoxide (2 mg, 0.02 mmol) and stirred for 5 minutes. The reaction is then treated with water (50 μL) and trimethylphosphine (9 μL of a 1 M solution in tetrahydrofuran, 0.009 mmol) and stirred at 45 °C overnight. The reaction is diluted with ethyl acetate and washed with water. The organics are dried over $MgSO_4$, filtered evaporated and purified *via* a mass-directed HPLC to afford **M38**; ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.62 (s, 1H), 4.18 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.51 (m, 8H), 3.21 (s, 2H), 2.75 (dd, J = 12.4, 12.4 Hz, 2H), 2.34 (bs, 1H), 1.94 (m, 1H), 1.79 (m, 2H), 1.54 (s, 3H), 1.28 (m, 2H), 1.10 (m, 2H), 0.86 (m, 4H), 0.62 (m, 2H); ESIMS calcd. for $C_{23}H_{36}N_5O_6S$ $[M+H]^+$ 510.2, found 510.4.

[00264]

Example M39: 1-Methylcyclopropyl 4-((5-(4-(2-hydroxyethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate



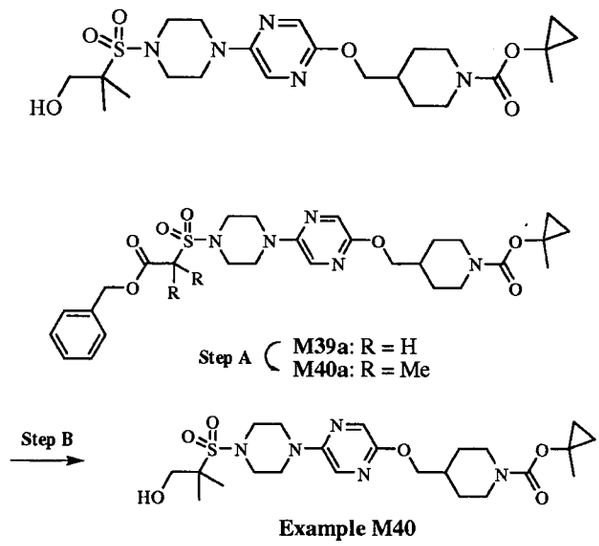
Example M39

Step A: By following a similar procedure as the one used for preparing **M1** from **M1c** except substituting benzyl 2-(chlorosulfonyl)acetate for methyl 3-(chlorosulfonyl)propanoate, **M39a** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{28}H_{38}N_5O_7S$ calcd: 588.3, found: 588.2.

Step B: A solution of **M39a** (20 mg, 0.034 mmol) in methanol (3 mL) is treated with sodium borohydride (13 mg, 0.34 mmol) and heated at 80 °C for 2 hours. The mixture is cooled, diluted with water and extracted with ethyl acetate. The organic layer is washed with brine, dried ($MgSO_4$), filtered, concentrated and purified using mass-triggered reverse phase HPLC to afford **M39**; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 1.6 Hz, 1H), 7.64 (d, J = 1.6 Hz, 1H), 4.11 (s, 4H), 3.54 (m, 4H), 3.47 (m, 4H), 3.21 (m, 2H), 2.77 (m, 2H), 1.96 (m, 1H), 1.82 (m, 2H), 1.57 (s, 3H), 1.28 (m, 2H), 0.89 (m, 2H), 0.65 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{34}N_5O_6S$ calcd: 484.2, found: 484.2.

Example M40: 1-Methylcyclopropyl 4-((5-(4-(1-hydroxy-2-methylpropan-2-ylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.

729



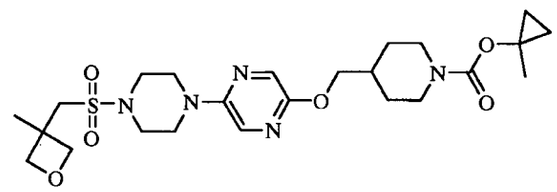
Example M40

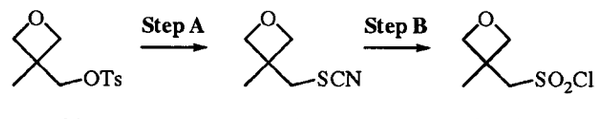
Step A: A solution of **M39a** (40 mg, 0.068 mmol) in dimethylformamide (2 mL) is treated with potassium carbonate (50 mg, 0.36 mmol) and methyl iodide (46 mg, 0.32 mmol) and heated to 60 °C for 2 hours. The reaction is then partitioned between ethyl acetate and water. The organics are washed with water and brine, dried over $MgSO_4$, filtered evaporated and used crude for the next step; ESIMS *m/z* for $(M+H)^+$ $C_{30}H_{42}N_5O_7S$ calcd: 616.3, found: 616.3.

By following a similar procedure as the one used for preparing **M39** from **M39a** except substituting **M40a** for **M39a**, **M40** is prepared; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 1.6 Hz, 1H), 7.62 (d, J = 1.6 Hz, 1H), 4.10 (d, J = 6.4 Hz, 2H), 3.75 (s, 2H), 3.59 (m, 4H), 3.48 (m, 4H), 2.76 (m, 2H), 1.97 (m, 1H), 1.81 (m, 2H), 1.57 (s, 3H), 1.40 (m, 6H), 1.27 (m, 2H), 0.89 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{38}N_5O_6S$ calcd: 512.3, found: 512.2.

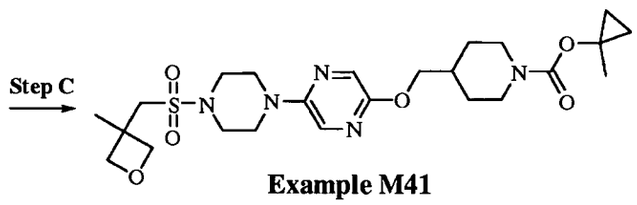
Example M41: 1-Methylcyclopropyl 4-((5-(4-((3-methyloxetan-3-yl)methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.

130





M41a **M41b** **M41c**



Example M41

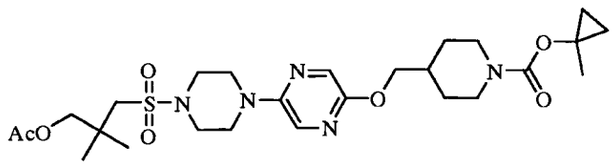
[00265] **Step A**: A solution of **M41a** (1.01 g, 3.9 mmol) in ethanol (25 mL) is treated with potassium thiocyanate (767 mg, 7.9 mmol) and stirred at reflux overnight. The solvent is then removed to afford **M41b** which is used crude. ESIMS *m/z* for $(M+H)^+$ $C_6H_{10}NOS$ calcd: 144.1, found: 144.0.

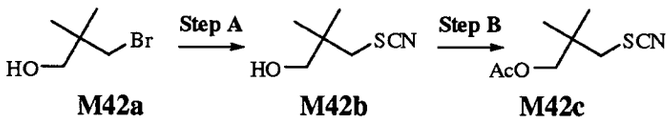
[00266] **Step B:** A suspension of **M41b** (crude from step A) in water (5 mL) is cooled in an ice/water bath and treated with a slow stream of chlorine gas for 30 minutes. The reaction is then extracted with diethyl ether and the organics are washed with saturted aqueous sodium bisulfate solution followed by saturated aqueous sodiumhydrogencarbonate solution. The organics are then dried over Na_2SO_4, filtered and evaporated to afford **M41b** which was used crude in the next reaction; ESIMS *m/z* for $(M+H)^+$ $C_5H_{10}ClO_3S$ calcd: 185.0, found: 185.0.

[00267] **Step C**: By following a similar procedure as the one used for preparing **M1** from **M1c** except substituting **M41c** for methyl 3-(chlorosulfonyl)propanoate, **M41** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.87 (d, J = 1.4 Hz, 1H), 7.62 (d, J = 1.5 Hz, 1H), 4.64 (d, J = 6.3 Hz, 2H), 4.46 (d, J = 6.4 Hz, 2H), 4.22 (m, 2H), 4.08 (d, J = 6.6 Hz, 2H), 3.53 (m, 4H), 3.40 (m, 4H), 3.25 (s, 2H), 2.74 (dd, J = 12.4, 12.4 Hz, 2H), 1.94 (m,

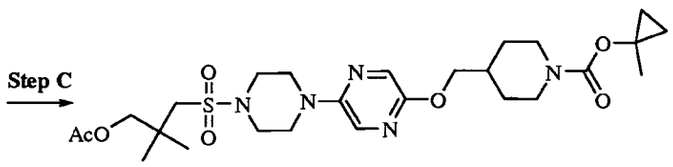
1H), 1.79 (m, 2H), 1.65 (s, 3H), 1.55 (s, 3H), 1.25 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{24}H_{38}N_5O_6S$ $[M+H]^+$ 524.3, found 524.2.

Example M42: 1-Methylcyclopropyl 4-((5-(4-(3-acetoxy-2,2-dimethylpropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





M42a **M42b** **M42c**



Example M42

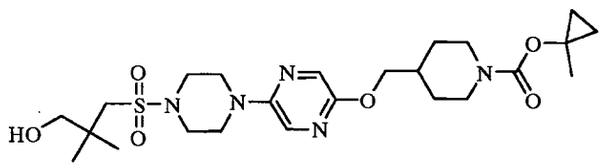
[00268] **Step A**: A solution of **M42a** (2 g, 12 mmol) in N,N-dimethylformamide (7.2 mL) is treated with potassium thiocyanate (1.75 g, 18 mmol) and stirred at 140 °C for 4 hours. The reaction is cooled to room temperature and partitioned between diethyl ether and water. The aqueous phase is extracted with diethyl ether once more and discarded. The combined organics are dried over $MgSO_4$, filtered, evaporated and distilled on a Kugelrohr apparatus to afford **M42b**; ESIMS *m/z* for $(M+H)^+$ $C_6H_{12}NOS$ calcd: 146.1, found: 146.1.

[00269] **Step B:** A solution of **M42b** (1.54 g, 10.6 mmol) in pyridine (10 mL) is cooled in an ice/water bath and treated with aetic anhydride (10 mL). The reaction is allowed to stir overnight as the ice bath melts. The solvent is removed and the residue is

partitioned between ethyl acetate and water. The organics are washed with 1 M HCl twice and then saturated aqueous sodiumhydrogencarbonate solution. The organics are then dried over $MgSO_4$, filtered and evaporated to afford **M42c** which was used crude in the next reaction; ESIMS *m/z* for $(M+H)^+$ $C_8H_{14}NO_2S$ calcd: 188.1, found: 188.1.

[00270] **Step C**: By following a similar procedure as the one used for preparing **M41** from **M41b** except substituting **M42c** for **M41b**, **M42** is obtained; ^1H NMR (400 MHz, CD_3CN) δ 7.86 (d, J = 1.4 Hz, 1H), 7.61 (d, J = 1.4 Hz, 1H), 4.19 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 4.00 (s, 2H), 3.50 (m, 5H), 3.37 (m, 4H), 2.86 (s, 2H), 2.73 (dd, J = 12.4, 12.3 Hz, 2H), 2.08 (s, 3H), 1.94 (m, 1H), 1.79 (m, 2H), 1.54 (s, 3H), 1.27 (m, 2H), 1.22 (s, 6H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{42}N_5O_7S$ calcd: 568.3 , found: 568.4.

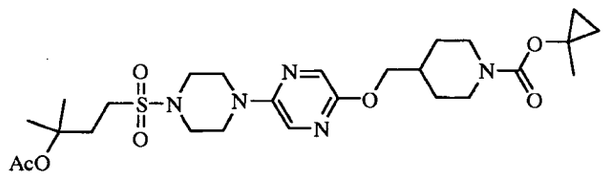
Example M43: 1-Methylcyclopropyl 4-((5-(4-(3-hydroxy-2,2-dimethylpropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.

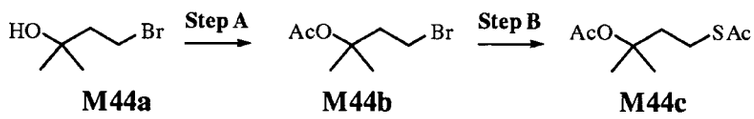


[00271] **Step A**: A solution of **M42** (48 mg, 0.085 mmol) in tetrahydrofuran (1.5 mL) is treated with lithium hydroxide (7 mg, 0.17 mmol) and stirred for 1 day. The solvent is removed and the residue is purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M43**; ^1H NMR (400 MHz, CD_3CN) δ 7.89 (d, J = 1.4 Hz, 1H), 7.67 (s, 1H), 4.36 (s, 2H), 4.17 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.51 (m, 4H), 3.37 (m, 4H), 2.87 (s, 2H), 2.76 (dd, J = 12.2, 11.6 Hz, 2H), 1.94 (m, 2H), 1.80 (m, 2H), 1.53 (s, 3H), 1.26 (m, 2H), 1.24 (s, 6H), 1.14 (s, 1H), 0.87 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{40}N_5O_6S$ calcd: 526.3 , found: 526.2.

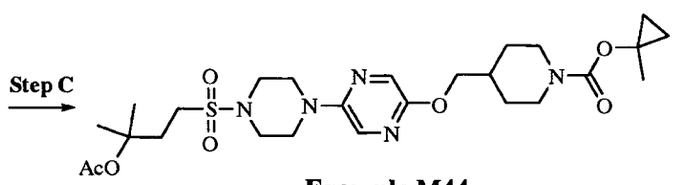
733

Example M44: 1-Methylcyclopropyl 4-((5-(4-(3-acetoxy-3-methylbutylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





M44a **M44b** **M44c**



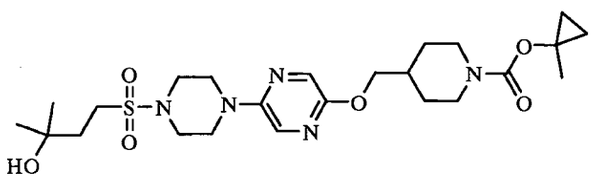
Example M44

[00272] **Step A**: A solution of **M44a** (1.48 g, 8.9 mmol) in dichloromethane (49 mL) is cooled in an ice/water bath and treated with pyridine (913 mg, 12mmol) and acetyl chloride (868 mg, 11 mmol) and the reaction is allowed to stir overnight as the ice bath melts. The reaction is then quenched with water. The organic phase is isolated, dried over $MgSO_4$, filtered, evaporated and the residue is purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M44b**; A satisfactory ESIMS could not be obtained.

[00273] **Step B:** A solution of **M44b** (750 mg, 3.6 mmol) in N,N-dimethylfromamide (10 mL) is cooled in an ice/water bath and treated with potassium thioacetate (410 mg, 3.6 mmol). The reaction is stirred overnight and partitioned between ethyl acetate and water. The organics are extracted with water once more, dried over $MgSO_4$, filtered and evaporated to afford **M44c** which is used in the next step crude; ESIMS *m/z* for $(M+Na)^+$ $C_9H_{16}NaO_3S$ calcd: 227.1, found: 227.0.

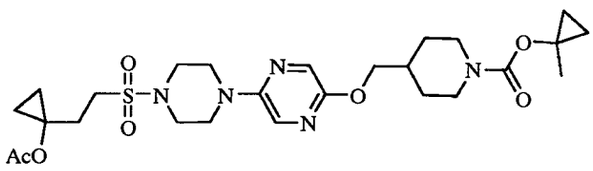
[00274] **Step C**: By following a similar procedure as the one used for preparing **M32** from **M32d** except substituting **M44c** for **M32d**, **M44** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.86 (d, J = 1.4 Hz, 1H), 7.61 (d, J = 1.5 Hz, 1H), 4.20 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.50 (m, 4H), 3.44 (m, 4H), 3.02 (m, 2H), 2.74 (dd, J = 13.2, 12.6 Hz, 2H), 2.22 (m, 2H), 1.98 (s, 3H), 1.96 (m, 1H), 1.80 (m, 2H), 1.55 (s, 3H), 1.48 (s, 6H), 1.25 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{24}H_{38}N_5O_5S$ [M-OAc]$^+$ 508.3, found 508.4.

Example M45: 1-Methylcyclopropyl 4-((5-(4-(3-hydroxy-3-methylbutylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



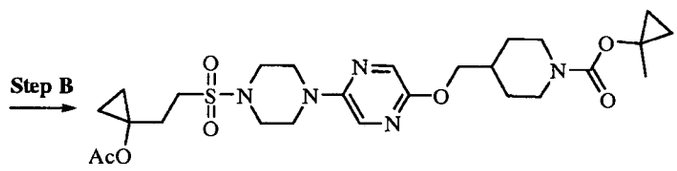
A solution of **M44** (199 mg, 0.35 mmol) in methanol (3.9 mL) is treated with NaOMe (1.1 mL of a 6.4M solution, 7 mmol) and stirred for 2.5 hours. The reaction is quenched with saturated aqueous ammonium chloride and the solvent is removed. The residue is dissolved in dichloromethane and washed with water, dried over $MgSO_4$, filtered, evaporated and the residue is purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M45**; ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.86 (d, J = 1.5 Hz, 1H), 7.62 (d, J = 1.5Hz, 1H), 4.20 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.50 (m, 4H), 3.44 (m, 4H), 3.09 (m, 2H), 2.74 (dd, J = 12.9, 12.7 Hz, 2H), 1.92-2.01 (m, 3H), 1.79 (m, 2H), 1.55 (s, 3H), 1.27 (m, 8H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{24}H_{40}N_5O_6S$ [M+H]$^+$ 526.3, found 526.2.

Example M46: 1-Methylcyclopropyl 4-((5-(4-(2-(1-acetoxycyclopropyl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





M46a M46b



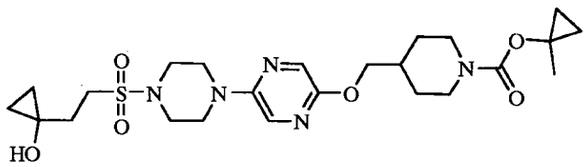
Example M46

[00275] **Step A**: A solution of **M46a** (1.99 g, 12 mmol) in diethyl ether (40 mL) is treated with titanium(IV)isopropoxide (369 mg, 1.2 mmol) followed by dropwise addition of ethylmagnesium bromide (8.8 mL of a 3 M solution in diethyl ether, 26 mmol). The reaction is quenched into ice cold 10% sulfuric acid and the aqueous phase is extracted with ether once more. The combined organics are dried over $MgSO_4$, filtered, evaporated and the residue is purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M46b**; ^{1}H-NMR (400MHz, $CDCl_3$) δ 3.60 (dd, *J* = 7.3, 7.3 Hz, 2H), 2.41 (s, 1H), 2.10 (dd, *J* = 7.3, 7.3 Hz, 2H), 0.78 (m, 2H), 0.52 (m, 2H); A satisfactory ESIMS spectrum could not be obtained.

[00276] **Step B**: By following a similar procedure as the one used for preparing **M33** from **M33c** except substituting **M46b** for **M33c**, **M46** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.4 Hz, 1H), 7.61 (d, *J* = 1.4 Hz, 1H), 4.20 (m, 2H), 4.07 (d, *J* = 6.5 Hz, 2H), 3.49 (m, 4H), 3.41 (m, 4H), 3.11 (ddd, *J* = 8.2, 5.2, 5.2 Hz, 2H), 2.74 (dd, *J* = 12.2, 12.0 Hz, 2H), 2.25 (ddd, J = 8.2, 4.7, 4.7 Hz, 2H), 2.00 (s, 3H), 1.94 (m, 1H), 1.79 (m, 2H), 1.54 (s, 3H), 1.25 (m, 2H), 0.93 (m, 2H), 0.86 (m, 2H), 0.76 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{26}H_{40}N_5O_7S$ $[M+H]^+$ 566.3, found 566.4.

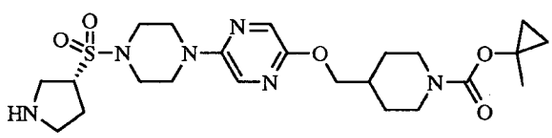
[00277]

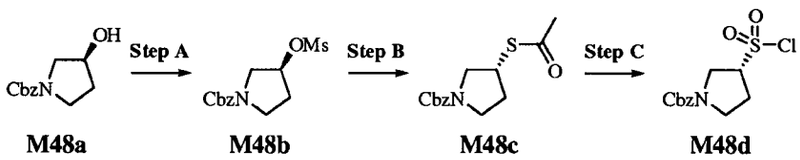
Example M47: 1-Methylcyclopropyl 4-((5-(4-(2-(1-hydroxycyclopropyl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



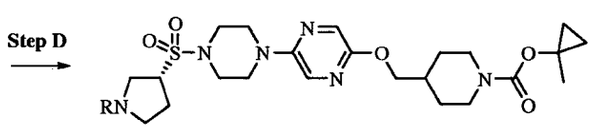
By following a similar procedure as the one used for preparing **M43** from **M42** except substituting **M46** for **M42**, **M47** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.87 (d, J = 1.5 Hz, 1H), 7.62 (d, J = 1.4 Hz, 1H), 4.19 (m, 2H), 4.08 (d, J = 6.5 Hz, 2H), 3.51 (m, 4H), 3.43 (m, 4H), 3.21 (m, 2H), 2.74 (dd, J = 12.3, 12.3 Hz, 2H), 2.27 (bs, 1H), 2.08 (m, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.25 (m, 2H), 0.86 (m, 4H), 0.62 (m, 2H), 0.56 (m, 2H); ESIMS calcd. for $C_{24}H_{38}N_5O_6S$ $[M+H]^+$ 524.3, found 524.5.

Example M48: (R)-1-methylcyclopropyl 4-((5-(4-(pyrrolidin-3-ylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate





M48a **M48b** **M48c** **M48d**



Step E **M48e**: R=Cbz
Example M48: R=H

737

737

Step A: A solution of **M48a** (10 g, 45.2 mmol) in dichloromethane (200 mL) is cooled in an ice/water bath and treated with diisopropylethylamine (9.4 mL, 54.3 mmol) followed by dropwise addition of methanesulfonyl chloride (3.8 mL, 50 mmol). The resulting solution is stirred at 0 °C for 1 hour, concentrated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M48b**; ESIMS *m/z* for $(M+H)^+$ $C_{13}H_{18}NO_5S$ calcd: 300.1, found: 300.0.

Step B: A solution of **M48b** (14.1 g, 45 mmol) and thiolacetic acid (6.4 mL, 90 mmol) in dimethylformamide (200 mL) is treated with Cs_2CO_3 (30 g, 90 mmol) and heated at 60 °C for 14 hours. The mixture is diluted with water and extracted with ethyl acetate (3x). The organic layers are combined, washed with water (2x) and brine, dried over $MgSO_4$, filtered, concentrated, and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M48c**; ESIMS *m/z* for $(M+H)^+$ $C_{14}H_{18}NO_3S$ calcd: 280.1, found: 280.0.

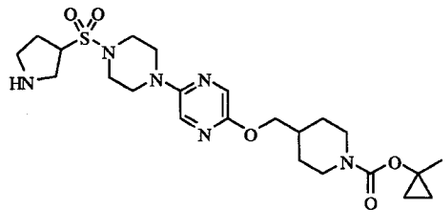
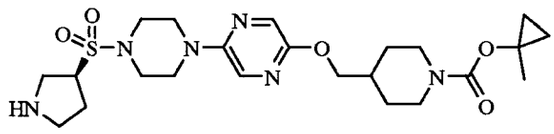
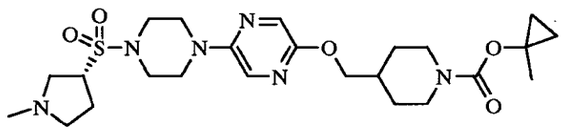
Step C: A solution of N-chlorosuccinimide (16.7 g, 125 mmol) in 2N HCl (24 mL) and acetonitrile (120 mL) is cooled in an ice/water bath and treated dropwise with a solution of **M48c** (9.2 g, 31 mmol) in acetonitrile (20 mL) over 1 hour. The solution is concentrated and partitioned between ethyl acetate and a saturated aqueous sodiumhydrogencarbonate solution. The organic layer iss washed with aqueous sodium thiosulfate and brine, dried ($MgSO_4$), filtered and concentrated to provide **M48d** as a golden oil; ESIMS *m/z* for $(M+H)^+$ $C_{12}H_{15}ClNO_4S$ calcd: 304.0, found: 304.0.

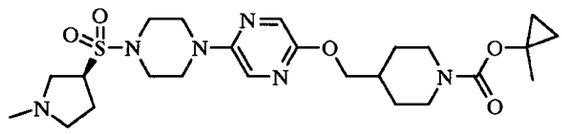
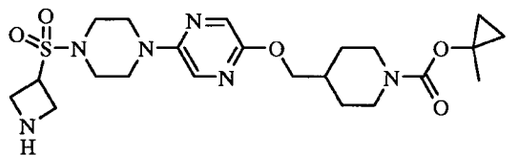
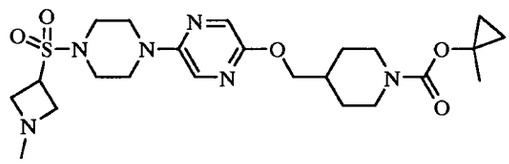
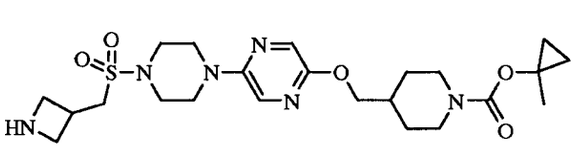
Step D: A solution of **M1c** (74 mg, 0.2 mmol) and **M48d** (67 mg, 0.22 mmol) in dichloromethane (5 mL) is treated with diisopropylethylamine (69 μL, 0.4 mmol) and stirred at room temperature for 3 hours. The mixture is concentrated and purified on silica gel using 0-100% ethyl acetate in hexane to afford **M48e**; ESIMS *m/z* for $(M+H)^+$ $C_{31}H_{43}N_6O_7S$ calcd: 643.3, found: 643.2.

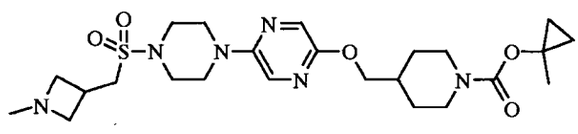
Step E: A solution of **M48e** (104 mg, .16 mmol) in methanol (10 mL) is treated with Pd/C (10%, wet) and stirred under 1 atm H_2 for 14 hours. The mixture is filtered through Celite®, concentrated, and purified on silica gel using 0-10% MeOH in dichloromethane to afford **M48**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 1.2 Hz, 1H), 7.54 (d, J = 1.2 Hz, 1H), 4.01 (d, J = 4.8 Hz, 2H), 3.52 (m, 1H), 3.40 (m, 9H), 3.14 (m, 1H), 3.07 (dd, J = 5.2, 8.4 Hz, 1H), 2.80 (m, 1H), 2.67 (m, 2H), 2.08 (m, 2H), 1.98 (s,

2H), 1.87 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.79 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{37}N_6O_5S$ calcd: 509.3, found: 509.2.

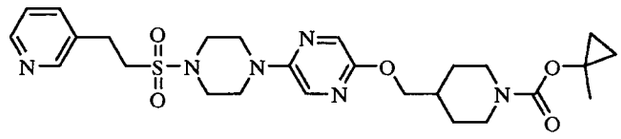
[00278] By following the procedure for making **M48** from **M48a** using the appropriate commercially available starting alcohols in place of **M48a** and in some cases performing reductive methylations, the following examples are prepared;

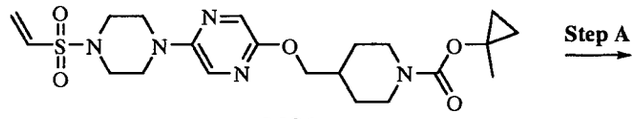
Example	Structure	Analytical data
M49		^{1}H NMR (400 MHz, CD_3CN) δ 7.82 (d, J = 1.6 Hz, 1H), 7.70 (d, J = 1.6 Hz, 1H), 4.06 (d, J = 6.8 Hz, 2H), 4.00 (m, 2H), 3.63 (m, 1H), 3.46 (m, 4H), 3.36 (m, 4H), 3.12 (m, 2H), 2.95 (m, 1H), 2.77 (m, 3H), 2.10 (m, 5H), 1.76 (m, 2H), 1.73 (s, 3H), 1.18 (m, 2H), 0.79 (m, 2H), 0.59 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{37}N_6O_5S$ calcd: 509.3, found: 509.2.
M50		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 0.8 Hz, 1H), 7.54 (d, J = 0.8 Hz, 1H), 4.01 (d, J = 4.8 Hz, 2H), 3.53 (m, 1H), 3.40 (m, 9H), 3.14 (m, 1H), 3.08 (dd, J = 5.2, 8.4 Hz, 1H), 2.81 (m, 1H), 2.68 (m, 2H), 2.08 (m, 2H), 2.00 (s, 2H), 1.87 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.79 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{37}N_6O_5S$ calcd: 509.3, found: 509.2.
M51		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 1.2 Hz, 1H), 7.54 (d, J = 1.2 Hz, 1H), 4.01 (d, J = 4.8 Hz, 2H), 3.64 (m, 1H), 3.40 (m, 8H), 2.87 (m, 1H), 2.73 (m, 1H), 2.67 (m, 2H), 2.61 (m, 1H), 2.31 (s, 3H), 2.00 (m, 2H), 1.98 (s, 2H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.79 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for

		$(M+H)^+$ $C_{24}H_{39}N_6O_5S$ calcd: 523.3, found: 523.2.
M52		^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 1.2 Hz, 1H), 7.54 (d, J = 1.2 Hz, 1H), 4.01 (d, J = 4.8 Hz, 2H), 3.64 (m, 1H), 3.40 (m, 8H), 2.87 (m, 1H), 2.73 (m, 1H), 2.67 (m, 2H), 2.61 (m, 1H), 2.31 (s, 3H), 2.00 (m, 2H), 1.98 (s, 2H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.79 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{39}N_6O_5S$ calcd: 523.3, found: 523.2.
M53		^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 1.0 Hz, 1H), 7.53 (d, J = 1.0 Hz, 1H), 4.09 (m, 1H), 4.05 (m, 2H), 4.01 (d, J = 4.4 Hz, 2H), 3.40 (m, 4H), 3.38 (m, 4H), 2.67 (m, 2H), 1.94 (br s, 1H), 1.87 (m, 1H), 1.71 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.79 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{35}N_6O_5S$ calcd: 495.2, found: 495.2.
M54		^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 0.8 Hz, 1H), 7.53 (d, J = 0.8 Hz, 1H), 4.00 (d, J = 4.4 Hz, 2H), 3.85 (m, 1H), 3.57 (m, 2H), 3.41 (m, 4H), 3.34 (m, 4H), 2.67 (m, 2H), 2.29 (s, 3H), 1.87 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.79 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{37}N_6O_5S$ calcd: 509.3, found: 509.2.
M55		^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 1.4 Hz, 1H), 7.53 (d, J = 1.4 Hz, 1H), 4.01 (d, J = 6.8 Hz, 2H), 3.75 (m, 2H), 3.43 (m, 6H), 3.33 (m, 4H), 3.16 (m, 2H), 2.67 (m, 2H), 1.87 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 3H), 0.79 (m, 2H), 0.54 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{37}N_6O_5S$ calcd: 509.3, found: 509.2

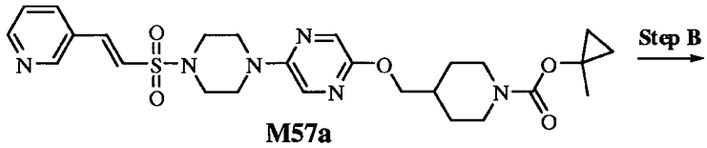
M56		^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 1.6 Hz, 1H), 7.53 (d, J = 1.6 Hz, 1H), 4.01 (d, J = 6.8 Hz, 2H), 3.42 (m, 6H), 3.33 (m, 4H), 3.14 (d, J = 7.2 Hz, 2H), 2.98 (m, 2H), 2.69 (m, 2H), 2.25 (s, 3H), 1.87 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 3H), 0.80 (m, 2H), 0.54 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{39}N_6O_5S$ calcd: 523.3, found: 523.2

Example M57: 1-Methylcyclopropyl 4-((5-(4-(2-(pyridin-3-yl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate

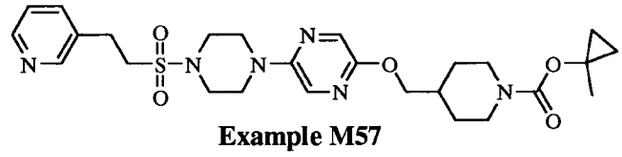




M26



M57a



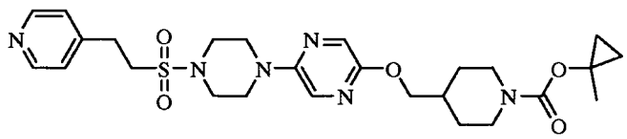
Example M57

[00279] **Step A:** A sealed vessel containing **M26** (50 mg, 0.11 mmol), 3-bromopyridine (10 μL, 0.11 mmol), Pd_2dba_3 (3.0 mg, 0.0032 mmol), tri-t-butylphosphonium tetrafluoroborate (2.0 mg, 0.0064 mmol), dicyclohexylmethylamine (45 mL, 0.21 mmol), and dioxane (1 mL) is heated at 120 °C overnight. The reaction is

cooled to room temperature and is diluted with water and extracted with ethyl acetate. The organic phase is dried over $MgSO_4$, filtered, evaporated, and purified on silica gel using a linear gradient of 0 to 100% ethyl acetate in dichloromethane to afford **M57a**; ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{34}N_6O_5S$ calcd: 543.2 , found: 543.2.

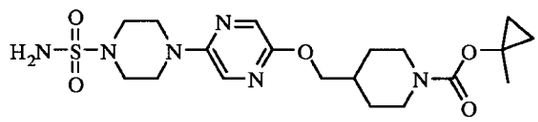
[00280] **Step B:** A solution of **M57a** from the previous step in ethanol (1mL) is sparged with H_2 (g) for 30 minutes and then left under an atmosphere of H_2 (g) overnight. The reaction is filtered over Celite®, concentrated, and purified by mass directed HPLC using a linear gradient of 10 to 90% acetonitrile in water to afford **M57**; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.79 (s, 1H), 8.65 (m, 1H), 8.09 (m, 1H), 7.86 (d, J = 1.4 Hz, 1H), 7.68 (m, 1H), 7.61 (d, J = 1.4 Hz, 1H), 4.20 (m, 2H), 4.08 (d, J = 6.5 Hz, 2H), 3.50 (m, 4H), 3.42 (m, 2H), 3.33 (m, 2H), 3.24 (m, 2H), 2.74 (m, 2H), 1.79 (m, 2H), 1.55 (s, 3H), 1.25 (m, 3H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{37}N_6O_5S$ calcd.: 545.3, found: 545.3.

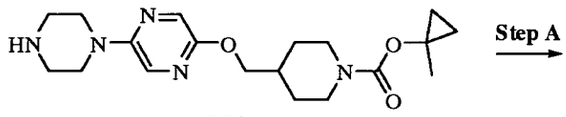
Example M58: 1-Methylcyclopropyl 4-((5-(4-(2-(pyridin-4-yl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate



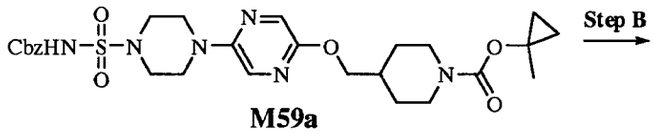
[00281] By following a similar procedure as for the preparation of **M57** from **M26** except substituting 4-bromopyridine for 3-bromopyridine, **M58** is prepared; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.80 (s, 2H), 7.87 (s, 1H), 7.74 (s, 2H), 7.63 (s, 1H), 4.20 (m, 2H), 4.07 (d, J = 6.5 Hz, 2H), 3.50 (m, 4H), 3.43 (m, 4H), 3.40 (m, 2H), 3.26 (m, 2H), 2.74 (m, 2H), 1.94 (m, 1H), 1.78 (m, 2H), 1.54 (s, 3H), 1.24 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{37}N_6O_5S$ calcd.: 545.3, found: 545.4.

Example M59: 1-Methylcyclopropyl 4-((5-(4-sulfamoylpiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate

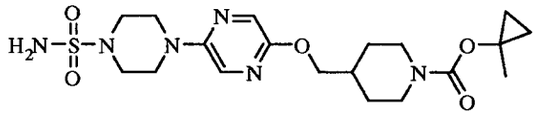




M1c



M59a

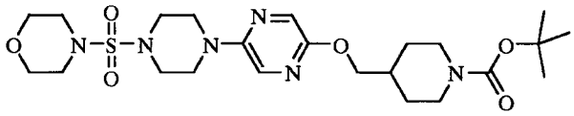


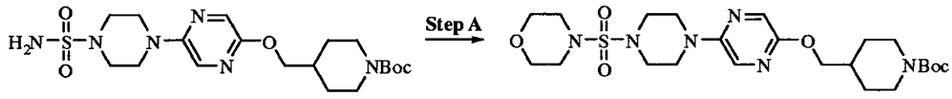
Example M59

[00282] **Step A:** A solution of chlorosulfonyl isocyanate (230 µL, 2.65 mmol) in *n*-hexanes (2.4 mL) is added dropwise to a solution **M1c** (1.0g, 2.7 mmol) in *n*-hexanes (5 mL) and stirred at room temperature for 45 minutes. A solution of benzyl alcohol (274µL, 2.65 mmol) and triethylamine (554 µL, 3.97 mmol) in tetrahydrofuran (10 mL) is then introduced dropwise. After 2 hr., the reaction is treated with water and extracted with dichloromethane. The organic phase is dried ($MgSO_4$), filtered, evaporated and chromatographed on silica gel using a linear gradient of 0 to 100% ethyl acetate in dichloromethane to afford **M59a**. ESIMS *m/z* for $(M+H)^+$ $C_{27}H_{37}N_6O_7S$ calcd.: 589.2, found: 589.3.

[00283] **Step B:** A solution of **M59a** (300 mg, 0.509mmol) in ethanol (5 mL) is treated with 5% Pd/C (30 mg) and subjected to a H_2 (g) flush for 30 minutes. The reaction is left under an atmosphere of H_2 (g) overnight and is then filtered over Celite® and concentrated to afford **M59**; ESIMS *m/z* for $(M+H)^+$ $C_{19}H_{31}N_6O_5S$ calcd.: 455.2, found: 455.3.

Example M60: *tert*-Butyl 4-((5-(4-(morpholinosulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate

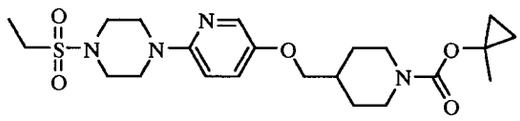


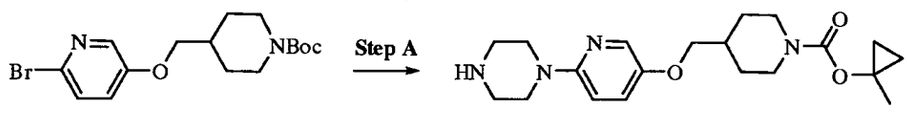


M60a **Example 60**

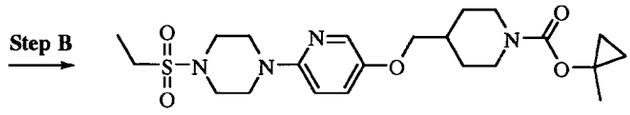
[00284] A sample of **M60a** is prepared in an analogous manner to **M30**. A microwave reaction vial is charged **M60a** (64 mg, 0.14 mmol), 2-bromoethyl ether (18 μL, 0.14 mmol), potassium carbonate (40 mg, 0.28 mmol) and N,N-dimethylformamide (2 mL), sealed and heated to 150 °C for 5 minutes *via* microwave. The reaction is cooled to room temperature and poured over water and extracted with ethyl acetate. The organic phase is dried ($MgSO_4$), filtered, evaporated, and purified on silica gel using a linear gradient of 0 to 100% ethyl acetate in hexane to afford **M60**; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.95 (s, 1H), 7.91 (s, 1H), 4.16 (m, 2H), 4.11 (d, J = 6.5 Hz, 2H), 3.74 (m, 4H), 3.53 (m, 6H), 3.44 (m, 1H), 3.27 (m, 5H), 2.73 (m, 2H), 1.96 (m, 1H), 1.78 (m, 2H), 1.46 (s, 9H), 1.26 (m, 2H). ESIMS *m/z* for $(M+H-CO_2{}^tBu)^+$ $C_{18}H_{31}N_6O_4S$ calcd.: 427.2, found: 427.2.

Example M61: 1-Methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate





B2b M61a

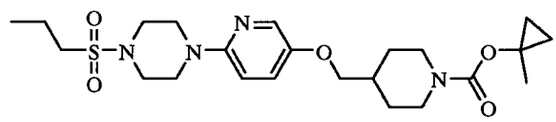


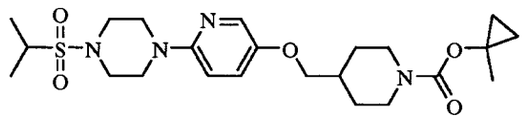
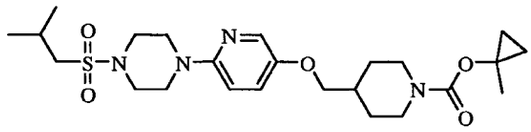
M61

[00285] **Step A:** By following a similar procedure as for the one used for the preparation of **M1c** from **B12a** except substituting **B2b** for **B12a**, **M61a** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{31}N_4O_3$ calcd.: 375.2, found: 375.2.

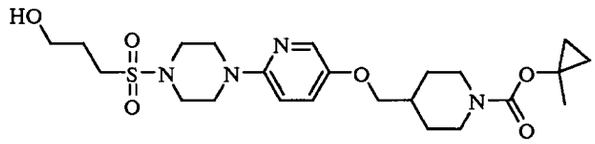
Step A: By following a similar procedure as the one used for preparing **M1** from **M1c** except substituting **M61a** for **M1c** and ethanesulfonyl chloride for methyl 3-(chlorosulfonyl)propanoate, **M61** is prepared; ^{1}H NMR (400 MHz, CD_3CN) δ 7.80 (m, 1H), 7.26 (m, 1H), 6.65 (m, 1H), 4.05 (m, 2H), 3.70 (d, J = 6.3 Hz, 2H), 3.52 (m, 3H), 3.37 (m, 4H), 3.21 (m, 1H), 2.92 (m, 2H), 2.67 (dd, J = 12.4, 12.4 Hz, 2H), 1.86 (m, 1H), 1.72 (m, 2H), 1.47 (s, 3H), 1.31 (t, J = 7.3 Hz, 3H), 1.17 (m, 2H), 0.79 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{35}N_4O_5S$ calcd: 467.2 , found: 467.2.

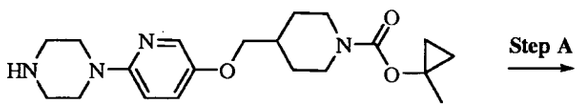
[00286] By following a similar procedure as for the one used for the preparation of **M61** from **M61a** except substituting commercially available sulfonyl chlorides for **M61a**, the following examples are obtained:

Example	Structure	Analytical data
M62		^{1}H NMR (400 MHz, CD_3CN) δ 7.88 (m, 1H), 7.24 (m, 1H), 6.71 (m, 1H), 4.13 (m, 2H), 3.78 (d, J = 6.3 Hz, 2H), 3.59 (m, 3H), 3.43 (m, 4H), 3.28 (m, 1H), 2.91 (m, 2H), 2.74 (dd, J = 12.2, 12.1 Hz, 2H), 1.89 (m, 3H), 1.80 (m, 2H), 1.55 (s, 3H), 1.24 (m, 2H), 1.07 (t, J = 7.4 Hz, 3H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for

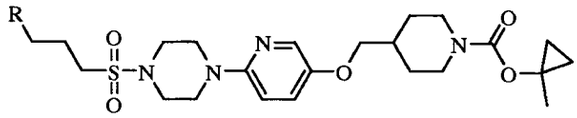
		$(M+H)^+$ $C_{23}H_{37}N_4O_5S$ calcd: 481.2 , found: 481.2.
M63		^1H NMR (400 MHz, CD_3CN) δ 7.89 (d, J = 2.8 Hz, 1H), 7.24 (m, 1H), 6.67 (d, J = 8.9 Hz, 1H), 4.12 (m, 2H), 3.77 (d, J = 6.3 Hz, 2H), 3.50 (m, 8H), 3.22 (sept., J = 6.8 Hz, 1H), 2.74 (dd, J = 12.4, 12.3 Hz, 2H), 1.93 (m, 1H), 1.80 (m, 2H), 1.55 (s, 3H), 1.36 (d, J = 6.9 Hz, 6H), 1.23 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{37}N_4O_5S$ calcd: 481.2 , found: 481.2.
M64		^1H NMR (400 MHz, CD_3CN) δ 7.88 (m, 1H), 7.24 (m, 1H), 6.71 (m, 1H), 4.13 (m, 2H), 3.78 (d, J = 6.3 Hz, 2H), 3.59 (m, 3H), 3.40 (m, 4H), 3.29 (m, 1H), 2.77 (d, J = 6.6 Hz, 2H), 2.74 (dd, J = 12.6, 12.6 Hz, 2H), 2.31 (m, 1H), 1.94 (m, 1H), 1.80 (m, 2H), 1.55 (s, 3H), 1.24 (m, 2H), 1.12 (d, J = 6.7 Hz, 6H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{39}N_4O_5S$ calcd: 495.3 , found: 495.3.

Example M65: 1-Methylcyclopropyl 4-((6-(4-(3-hydroxypropylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate





M61a



Step B **M65a**: R =Cl

Step C **M65b**: R =OAc

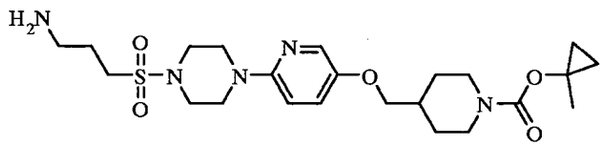
Example 65: R =OH

[00287] **Step A:** By following a similar procedure as for the one used for the preparation of **M6** from **M1c** except substituting **M61a** for **M1c**, **M65a** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{36}ClN_4O_5S$ calcd.: 515.2, found: 515.2.

Step B: By following a similar procedure as the one used for preparing **M19** from **M5** except substituting **M65a** for **M5**, **M65b** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{39}N_4O_7S$ calcd: 539.3 , found: 539.2.

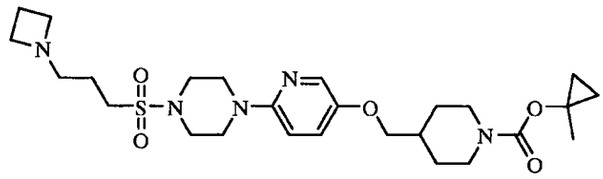
Step C: By following a similar procedure as the one used for preparing **M43** from **M42** except substituting **M65b** for **M42**, **Example 65** is prepared; ^1H NMR (400 MHz, CD_3CN) δ 7.88 (d, J = 3.0 Hz, 1H), 7.19 (dd, J = 9.2, 2.8 Hz, 1H), 6.68 (d, J = 9.1 Hz, 1H), 4.11 (m, 2H), 3.77 (m, 4H), 3.55 (m, 4H), 3.41 (m, 4H), 3.08 (m, 2H), 2.74 (dd, J = 12.3, 12.3 Hz, 2H), 2.08 (m, 2H), 1.92 (m, 2H), 1.80 (m, 2H), 1.54 (s, 3H), 1.24 (m, 2H), 0.85 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{37}N_4O_6S$ calcd: 497.2 , found: 497.3.

Example M66: 1-Methylcyclopropyl 4-((6-(4-(3-aminopropylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate



[00288] By following a similar procedure as for the one used for the preparation of **M18** from **M16** except substituting **M65a** for **M16**, **M66** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{38}N_5O_5S$ calcd: 496.3 , found: 496.3.

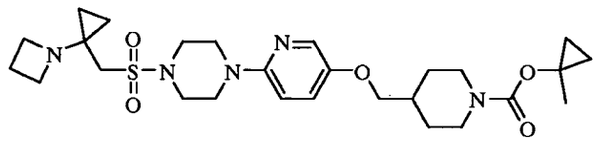
Example M67: 1-Methylcyclopropyl 4-((6-(4-(3-(azetidin-1-yl)propylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate.



[00289] By following a similar procedure as for the one used for the preparation of **M21** from **M6** except substituting **M65a** for **M21** and azetidine for 2-methylimidazole, **M67** is prepared; ^1H NMR (400 MHz, Acetone-d_6) δ 7.91 (d, J = 3.2 Hz, 1H), 7.27 (dd, J = 3.2, 9.2 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 4.06 (m, 2H), 3.85 (d, J = 6.4 Hz, 2H), 3.52 (m, 4H), 3.34 (m, 4H), 3.09 (t, J = 6.8 Hz, 4H), 3.05 (m, 2H), 2.80 (m, 2H), 2.44 (d, J = 6.8 Hz, 2H), 1.96 (m, 3H), 1.78 (m, 4H), 1.50 (s, 3H), 1.23 (m, 2H), 0.79 (m, 2H), 0.58 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{41}N_5O_5S$ calcd: 535.3, found: 536.3.

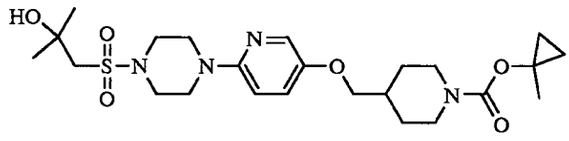
[00290]

Example M68: 1-Methylcyclopropyl 4-((6-(4-((1-(azetidin-1-yl)cyclopropyl)methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate.



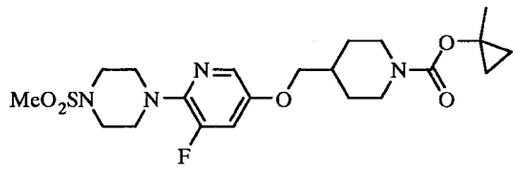
[00291] By following a similar procedure as for the one used for the preparation of **M35** from **M1c** except substituting **M61a** for **M1c**, **M68** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.92 (d, *J* = 2.9 Hz, 1H), 7.14 (dd, *J* = 9.1, 3.0 Hz, 1H), 6.64 (d, *J* = 9.1 Hz, 1H), 4.13 (m, 2H), 3.77 (d, *J* = 6.3 Hz, 2H), 3.54 (m, 4H), 3.49 (m, 4H), 3.06 (m, 4H), 3.01 (s, 2H), 2.74 (m, 2H), 1.91 (m, 2H), 1.85 (m, 2H), 1.80 (m, 2H), 1.55 (s, 3H), 1.25 (m, 2H), 0.86 (m, 4H), 0.70 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{27}H_{42}N_5O_5S$ $[M+H]^+$ 548.3, found 548.4.

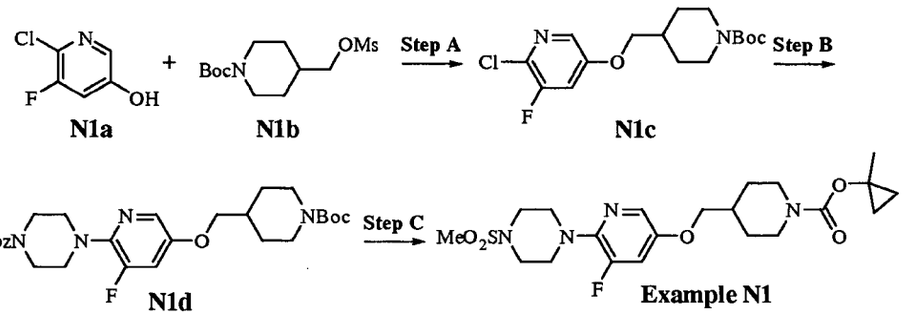
Example M69: 1-Methylcyclopropyl 4-((6-(4-(2-hydroxy-2-methylpropylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate



[00292] A solution of **E10** (50 mg, 0.11 mmol) in tetrahydrofuran (3 mL) is cooled to –78 °C and treated excess butyllithium in hexane (2M, 250 μL). After stirring for 15 minutes, excess dry acetone is added and the reaction is stirred for an additional 30 minutes. The reaction is quenched with saturated aqueous ammonium chloride solution, warmed to room temperature and partitioned between ethyl acetate and water. The organics are isolated, dried over $MgSO_4$, filtered, evaporated and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **M69**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 2.8 Hz, 1H), 7.15 (dd, J = 3.0, 9.1 Hz, 1H), 6.64 (d, J = 9.1 Hz, 1H), 4.13 (m, 2H), 3.77 (d, J = 6.3 Hz, 2H), 3.52 (m, 5H), 3.36 (m, 4H), 3.04 (s, 2H), 2.73 (m, 2H), 1.93 (m, 1H), 1.80 (m, 2H), 1.54 (s, 3H), 1.44 (s, 6H), 1.25 (m, 2H), 0.87 (m, 2H), 0.61 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{39}N_4O_6S$ calcd: 511.3, found: 511.5.

Example N1: 1-Methylcyclopropyl 4-((5-fluoro-6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate





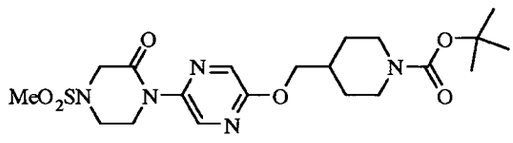
[00293] **Step A:** A solution of **N1a** (100 mg, 0.678 mmol) and **N1b** (219 mg, 0.746 mmol) in N-methylpyrrolidinone (2 mL) is treated with Cs_2CO_3 (331 mg, 1.01 mmol) and heated to 80 °C for 2 hours. The reaction is cooled to room temperature, diluted with ethyl acetate and extracted with water twice. The organics are dried over $MgSO_4$, filtered, evaporated and purified on silica using a linear gradient of 0 to 50% ethyl acetate in hexanes to afford **N1c**. ESIMS *m/z* for $(M+H)^+$ $C_{16}H_{23}ClFN_2O_3$ calcd: 345.1, found: 289.0 (M-*t*Bu+H^+).

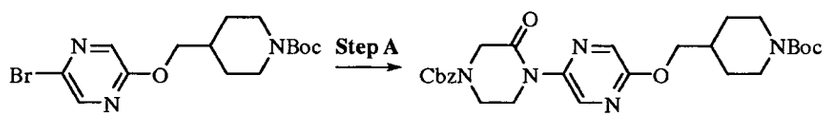
[00294] **Step B:** By following a similar procedure as the one used for preparing **B1** from isopropyl 4-((6-chloropyridin-3-yloxy)methyl)piperidine-1-carboxylate except substituting **N1c** for isopropyl 4-((6-chloropyridin-3-yloxy)methyl)piperidine-1-carboxylate and benzyl piperazine-1-carboxylate for 1-(methylsulfonyl)piperazine, **N1d** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{28}H_{38}FN_4O_5$ calcd: 529.3, found: 529.2.

[00295] **Step C:** A solution of **N1d** (132 mg, 0.25 mmol) in a mixture of methanol and dioxane (2 mL, 1:1) is treated with 10 mg of 5% Pd/C and hydrogenated overnight at balloon pressure. The atmosphere in the reaction is then exchanged back to N_2 and the reaction is filtered through Celite® and the the solvent is removed. The resulting oil is coevaporated with toluene twice, dissolved in dichloromethane (2 mL) containing triethylamine (51 mg, 0.50 mmol) and treated with methanesulfonyl chloride (43 mg, 0.38 mmol) as a solution in dichloromethane (1 mL) and stirred for 1 hour. The solvent

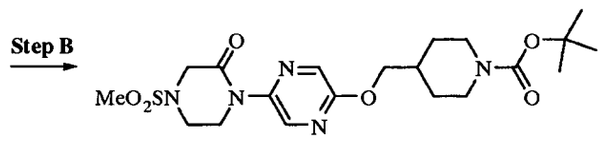
is removed and the reaction is treated with neat trifluoroacetic acid (3 mL). After 20 minutes of stirring, the solvent is removed and the reaction is coevaporated with toluene twice and treated with dichlormethane (2 mL), **E3b** (71 mg, 0.30 mmol) and excess triethylamine. After 2 h of stirring, the reaction is diluted with ethyl acetate, extracted with 1 M NaOH twice, saturated sodiumhydrogencarbonate once, dried over $MgSO_4$, filtered, evaporated and purified on silica gel using a linear gradient of 0 to 100% ethyl acetate in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 2.5 Hz, 1H), 7.07 (dd, J = 2.5, 13.0 Hz, 1H), 4.14 (m, 2H), 3.80 (d, J = 6.3 Hz, 2H), 3.53 (m, 4H), 3.40 (m, 4H), 2.82 (s, 3H), 2.74 (m, 2H), 1.95 (m, 1H), 1.80 (m, 2H), 1.55 (s, 3H), 1.26 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{32}FN_4O_5S$ calcd: 471.2, found: 471.2.

Example O1: tert-Butyl 4-((5-(4-(methylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





B4b **O1a**



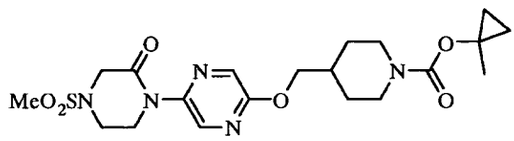
Example O1

[00296] **Step A:** A sealable flask is charged with **B4b** (4.00 g, 11 mmol) and benzyl 3-oxopiperazine-1-carboxylate (3.02 g, 13 mmol), Pd_2dba_3 (295 mg, 0.32 mmol), Xantphos (560 mg, 0.97 mmol) and Cs_2CO_3 (10.5 g, 32 mmol). The flask is evacuated

and back filled with nitrogen, sealed, treated with dioxane (60 mL) and dipped into a pre-heated 120 °C bathours. After 2 hours, the reaction is cooled to room temperature, diluted with ethyl acetate and extracted with water twice. The organics are dried over $MgSO_4$, filtered, evaporated and purified on silica using a step gradient of 25, 50 and 75% ethyl acetate in hexanes to afford **O1a**; ESIMS *m/z* for $(M\text{-}Boc+H)^+$ $C_{22}H_{28}N_5O_4$ calcd: 426.2, found: 426.1.

[00297] **Step B:** A solution of **O1a** (80 mg, 0.15 mmol) in MeOH (2 mL) is treated with 10 mg of 5% Pd/C and hydrogenated at balloon pressure overnight. The catalyst is removed by filtration through Celite® and the solvent is removed. The residue is coevaporated with toluene twice, dissolved in dichloromethane (2 mL) and treated with excess triethylamine followed by methanesulfonyl chloride (21 mg, 0.18 mmol) dissolved in dichloromethane (1 mL). After 1 hour of stirring, the reaction is diluted with ethyl acetate and extracted with water twice. The organics are dried over $MgSO_4$, filtered, evaporated and purified on silica using a linear gradient of 30 to 100% ethyl acetate in hexanes to afford **O1**; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 1.4 Hz, 1H), 8.02 (d, J = 1.4 Hz, 1H), 4.19 (d, J = 6.5 Hz, 2H), 4.15 (m, 2H), 4.13 (s, 2H), 4.08 (m, 2H), 3.68 (m, 2H), 2.92 (s, 3H), 2.74 (m, 2H), 1.98 (m, 1H), 1.79 (m, 2H), 1.46 (s, 9H), 1.27 (m, 2H); ESIMS *m/z* for $(M+Na)^+$ $C_{20}H_{31}N_5NaO_6S$ calcd: 492.2, found: 492.2.

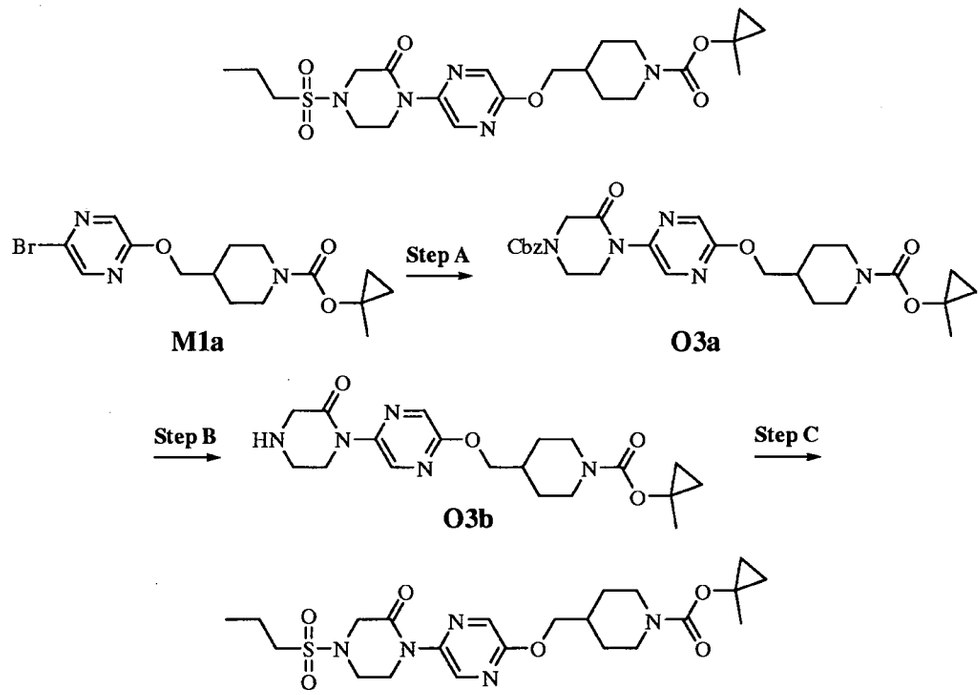
Example O2: 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00298] A sample of **O1** (50 mg, 0.11 mmol) is treated with trifluoroacetic acid (1 mL) and aged for 20 minutes. The solvent is removed and the residue is treated with dichloromethane (2 mL), excess triethylamine and **E3b** (30.3 mg, 0.13 mmol). After stirring for 3 hours, the reaction is diluted with ethyl acetate, extracted with 1 M NaOH twice, saturated sodiumhydrogencarbonate once, dried over $MgSO_4$, filtered, evaporated

and purified on silica gel using a linear gradient of 0 to 100% ethyl acetate in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 1.4 Hz, 1H), 8.02 (d, J = 1.4 Hz, 1H), 4.18 (d, J = 6.5 Hz, 2H), 4.12 (s, 2H), 4.12 (m, 2H), 4.07 (m, 2H), 3.67 (m, 2H), 2.93 (s, 3H), 2.72 (m, 2H), 1.98 (m, 1H), 1.79 (m, 2H), 1.54 (s, 3H), 1.25 (m, 2H), 0.87 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{30}N_5O_6S$ calcd: 468.2, found: 468.1.

Example O3: 1-Methylcyclopropyl 4-((5-(2-oxo-4-(propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



Example O3

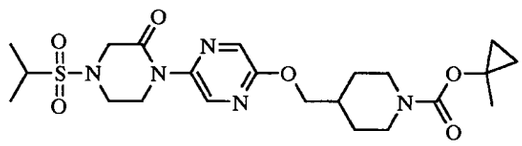
[00299] **Step A:** By following a similar procedure as the one used for preparing **O1a** from **B4b** except substituting **M1a** for **B4b**, **O3a** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{27}H_{34}N_5O_6$ calcd: 524.2, found: 524.2.

[00300] **Step B:** A solution of **O3a** (3.01 g, 0.15 mmol) in MeOH (30 mL) is treated with 101 mg of 20% $Pd(OH)_2/C$ and hydrogenated at balloon pressure for 5

hours. The catalyst is removed by filtration through Celite® and the solvent is removed to afford **O3b**; ESIMS *m/z* for $(M+H)^+$ $C_{19}H_{28}N_5O_4$ calcd: 390.2, found: 390.1.

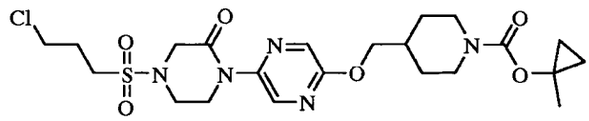
[00301] **Step C:** A solution of **O3b** (203 mg, 0.52 mmol) in dichloromethane (1.5 mL) is treated with triethylamine (55 mg, 0.54 mmol) and *n*-propanesulfonyl chloride (77 mg, 0.54 mmol) and stirred for 4 hours. Then, another identical portion of triethylamine and *n*-propylsulfonyl chloride is added and the reaction is stirred overnight. The reaction mixture is then loaded directly onto a silica gel column and eluted with a linear gradient of 0 to 100% ethyl acetate in hexane to afford **O3**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 1.4 Hz, 1H), 8.02 (d, J = 1.4 Hz, 1H), 4.18 (d, J = 6.5 Hz, 1H), 4.17 (m, 2H), 4.15 (s, 2H), 4.05 (m, 2H), 3.70 (m, 2H), 3.01 (m, 2H), 2.75 (dd, J = 12.3, 12.2 Hz, 2H), 1.98 (m, 1H), 1.89 (m, 2H), 1.79 (m, 2H), 1.55 (s, 3H), 1.26 (m, 2H), 1.09 (t, J = 7.4 Hz, 3H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{34}N_5O_6S$ calcd: 496.2, found: 496.2.

Example O4: 1-Methylcyclopropyl 4-((5-(4-(isopropylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate



[00302] By following a similar procedure as the one used for preparing **O3** from **O3b** except substituting 3-chloropropanesulfonyl chloride for *n*-propanesulfonyl chloride, **O4** is prepared; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 1.4 Hz, 1H), 8.02 (d, J = 1.4 Hz, 1H), 4.21 (s, 2H), 4.19 (m, 2H), 4.19 (d, J = 6.5 Hz, 2H), 4.04 (m, 2H), 3.75 (m, 2H), 3.28 (sept., J = 6.8 Hz, 1H), 2.75 (dd, J = 12.3, 12.3 Hz, 2H), 1.98 (m, 1H), 1.78 (m, 2H), 1.55 (s, 3H), 1.40 (d, J = 6.8 Hz, 6H), 1.26 (m, 2H), 0.87 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{34}N_5O_6S$ calcd: 496.2, found: 496.2.

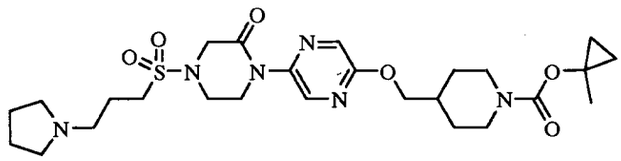
Example O5: 1-Methylcyclopropyl 4-((5-(4-(3-chloropropylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate



[00303] By following a similar procedure as the one used for preparing **O3** from **O3b** except substituting *iso*-propylsulfonyl chloride for *n*-propylsulfonyl chloride, **O5** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.65 (d, *J* = 1.4 Hz, 1H), 8.02 (d, *J* = 1.4Hz, 1H), 4.21 (m, 2H), 4.18 (d, *J* = 6.6 Hz, 2 H), 4.17 (s, 2H), 4.07 (m, 2H), 3.71 (m, 4H), 3.21 (m, 2H), 2.75 (dd, *J* = 12.4, 12.3 Hz, 2H), 2.33 (m, 2H), 1.97 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.26 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{22}H_{33}ClN_5O_6S$ $[M+H]^+$ 530.2, found 530.3.

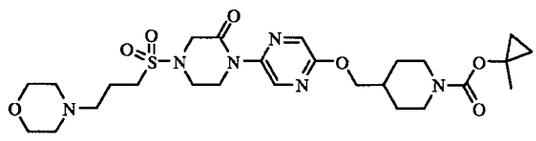
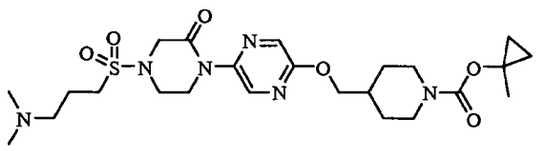
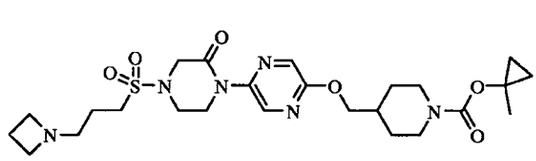
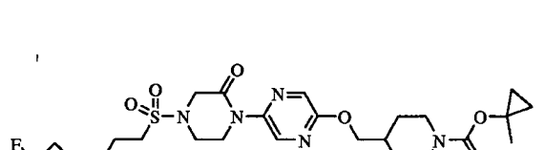
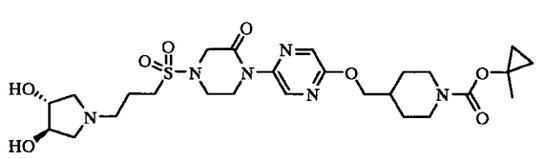
[00304]

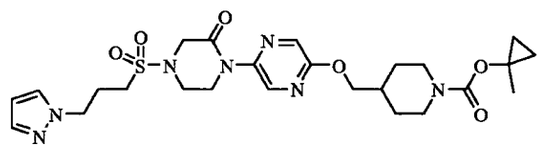
Example O6: 1-Methylcyclopropyl 4-((5-(2-oxo-4-(3-(pyrrolidin-1-yl)propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate



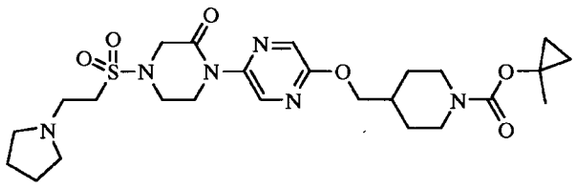
A solution of **O5** (15 mg, 0.03 mmol) in N,N-dimethylformamide (700 μL) is treated with pyrrolidine (23 μL, 0.28 mmol) and subjected to microwave irradiation (200 °C, 5 min). The solution is purified using mass directed reverse phase HPLC to afford **O6**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 1.2 Hz, 1H), 8.04 (d, J = 1.2 Hz, 1H), 4.20 (d, J = 6.8 Hz, 2H), 4.18 (s, 2H), 4.07 (m, 2H), 3.72 (m, 2H), 3.18 (m, 2H), 2.77 (m, 2H), 2.66 (m, 2H), 2.59 (br s, 3H), 2.07 (m, 3H),1.83 (m, 5H), 1.57 (s, 3H), 1.28 (m, 2H), 0.89 (m, 2H), 0.65 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{41}N_6O_6S$ calcd: 565.3, found: 565.2.

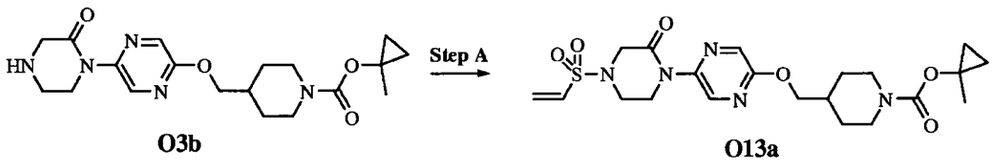
[00305] By following a similar procedure as for the one used for the preparation of **O6** from **O5** except substituting the appropriate amines for pyrrolidine, the following examples are obtained:

O7		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 d, J = 1.6 Hz, 1H), 8.04 (d, J = 1.6 Hz, 1H), 4.20 (d, J = 6.4 Hz, 2H), 4.18 (s, 2H), 4.07 (m, 2H), 3.72 (m, 4H), 3.32 (m, 8H), 3.15 (m, 2H), 2.77 (m, 2H), 2.46 (m, 4H), 2.02 (m, 4H), 1.80 (m, 2H), 1.56 (s, 3H), 1.29 (m, 2H), 0.87 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{41}N_6O_7S$ calcd: 581.3, found: 581.2.
O8		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 d, J = 1.4 Hz, 1H), 7.86 (d, J = 1.4 Hz, 1H), 4.03 (d, J = 6.4 Hz, 2H), 4.00 (s, 2H), 3.89 (m, 2H), 3.54 (m, 2H), 2.97 (m, 2H), 2.59 (m, 2H), 2.33 (m, 2H), 2.12 (s, 6H), 1.87 (m, 4H), 1.64 (m, 2H), 1.39 (s, 3H), 1.10 (m, 2H), 0.71 (m, 2H), 0.46 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{39}N_6O_6S$ calcd: 539.3, found: 539.2.
O9		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 1.6 Hz, 1H), 7.81 (d, J = 1.6 Hz, 1H), 3.98 (d, J = 6.8 Hz, 2H), 3.94 (s, 2H), 3.84 (m, 2H), 3.48 (m, 2H), 2.98 (m, 3H), 2.89 (m, 2H), 2.54 (m, 2H), 2.31 (m, 2H), 1.86 (m, 2H), 1.78 (m, 1H), 1.65 (m, 4H), 1.34 (s, 3H), 1.05 (m, 2H), 0.66 (m, 2H), 0.41 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{39}N_6O_6S$ calcd: 551.3, found: 551.3.
O10		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 1.2 Hz, 1H), 7.88 (d, J = 1.2 Hz, 1H), 4.04 (d, J = 6.4 Hz, 2H), 4.01 (s, 2H), 3.91 (m, 3H), 3.56 (m, 2H), 3.43 (t, J = 12.0 Hz, 4H), 2.97 (m, 2H), 2.56 (m, 4H), 1.84 (m, 1H), 1.78 (m, 2H), 1.66 (m, 2H), 1.41 (s, 3H), 1.13 (m, 2H), 0.73 (m, 2H), 0.48 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{37}F_2N_6O_6S$ calcd: 587.3, found: 587.2.
O11		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 1.4 Hz, 1H), 7.95 (d, J = 1.4 Hz, 1H), 4.12 (d, J = 6.4 Hz, 2H), 4.10 (s, 2H), 4.06 (m, 2H), 3.98 (m, 3H), 3.64 (m, 2H), 3.07 (m, 2H), 2.94 (m, 2H), 2.68 (m, 2H), 2.58 (m, 2H), 2.43 (dd, J = 3.6,

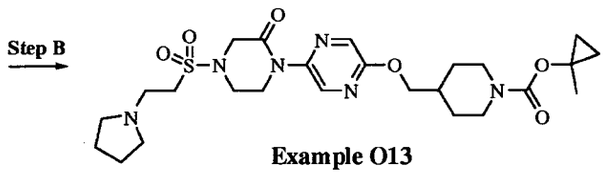
		10.4 Hz, 2H), 1.95 (m, 4H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.80 (m, 2H), 0.56 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{41}N_6O_8S$ calcd: 597.3, found: 597.3.
O12		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 1.2 Hz, 1H), 8.04 (d, J = 1.2 Hz, 1H), 7.54 (d, J = 1.6 Hz, 1H), 7.46 (d, J = 1.6 Hz, 1H), 6.29 (m, 1H), 4.35 (m, 2H), 4.20 (d, J = 6.4 Hz, 2H), 4.12 (s, 2H), 4.05 (m, 3H), 3.68 (m, 2H), 2.99 (m, 2H), 2.77 (m, 2H), 2.45 (m, 2H), 2.00 (m, 1H), 1.82 (m, 2H), 1.57 (s, 3H), 1.28 (m, 2H), 0.89 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{36}N_7O_6S$ calcd: 562.2, found: 562.3.

Example O13: 1-Methylcyclopropyl 4-((5-(2-oxo-4-(2-(pyrrolidin-1-yl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate





O3b **O13a**



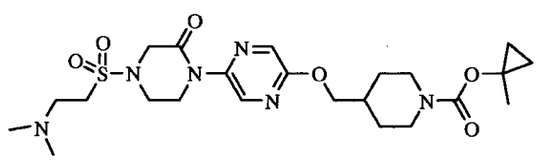
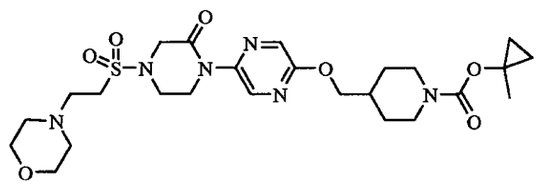
Example O13

Step A: A solution of **O3b** (600 mg, 1.51 mmol) in dichloromethane (10 mL) is

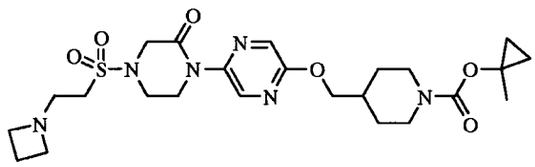
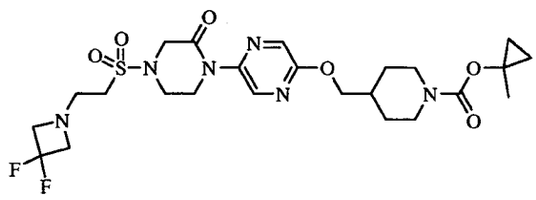
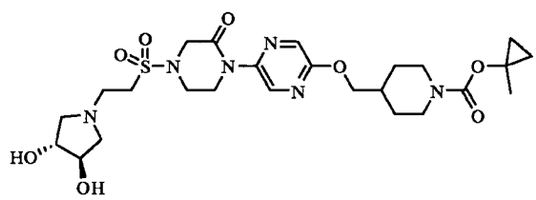
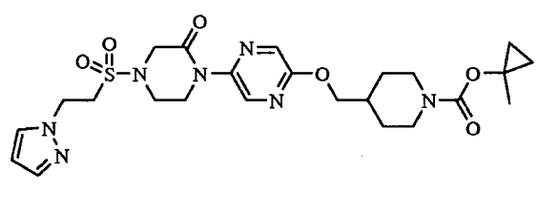
treated with N,N-diisopropylethylamine (521 μL, 3.02 mmol) and 2-chloroethanesulfonyl chloride (173 μL, 1.66 mmol) and stirred for 2 hours. The reaction mixture is then loaded directly onto a silica gel column and eluted with a linear gradient of 0 to 100% ethyl acetate in hexane to afford **O13a**. ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{30}N_5O_6S$ calcd: 480.2, found: 480.2.

Step B: A solution of **O13a** (15 mg, 0.03 mmol) in N,N-dimethylformamide (1 mL) is treated with pyrrolidine (26 μL, 0.31 mmol) and stirred for 16 hours at room temperture. The solution is purified using mass-triggered reverse phase HPLC to afford **O13.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 1.4 Hz, 1H), 8.04 (d, J = 1.4 Hz, 1H), 4.20 (m, 4H), 4.06 (m, 3H), 3.72 (m, 2H), 3.34 (m, 2H), 3.04 (m, 2H), 2.75 (m, 6H), 2.00 (m, 1H), 1.83 (m, 6H), 1.57 (s, 3H), 1.28 (m, 2H), 0.89 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{39}N_6O_6S$ calcd: 551.3, found: 551.2.

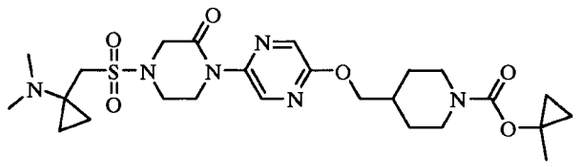
By following a similar procedure as for the one used for the preparation of **O13** from **O13a** except substituting the appropriate amines for pyrrolidine, the following examples are obtained:

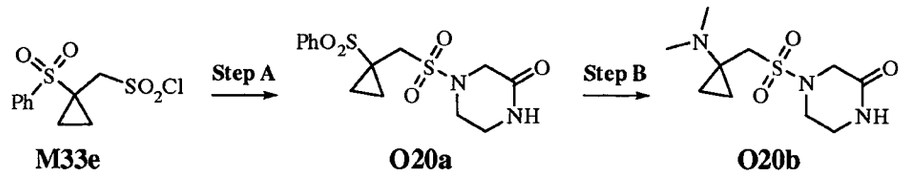
Ex.	Structure	Analytical data
O14		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 1.4 Hz, 1H), 8.04 (d, J = 1.4 Hz, 1H), 4.20 (m, 4H), 4.06 (m, 3H), 3.73 (m, 2H), 3.26 (m, 2H), 2.84 (m, 2H), 2.77 (m, 2H), 2.33 (s, 6H), 2.00 (m, 1H), 1.82 (m, 2H), 1.57 (s, 3H), 1.28 (m, 2H), 0.89 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{37}N_6O_6S$ calcd: 525.3, found: 525.2.
O15		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 1.2 Hz, 1H), 8.04 (d, J = 1.2 Hz, 1H), 4.21 (m, 4H), 4.08 (m, 2H), 3.72 (m, 6H), 3.25 (m, 2H), 2.88 (m, 2H), 2.77 (m, 2H), 2.53 (m, 4H), 2.00 (m, 1H), 1.81 (m, 2H), 1.57 (s, 3H), 1.28 (m, 2H), 0.89 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{39}N_6O_7S$ calcd: 567.3, found: 567.2.

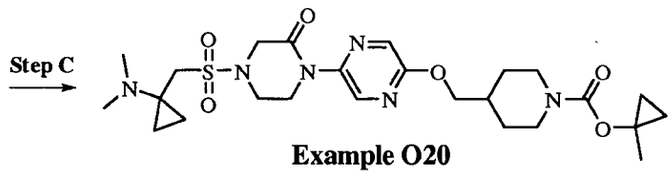
158

O16		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 1.2 Hz, 1H), 7.95 (d, J = 1.2 Hz, 1H), 4.15 (s, 2H), 4.12 (d, J = 6.4 Hz, 2H), 3.97 (m, 2H), 3.65 (m, 3H), 3.15 (m, 3H), 2.98 (m, 2H), 2.77 (m, 2H), 2.68 (m, 2H), 1.98 (m, 2H), 1.94 (m, 1H), 1.73 (m, 2H), 1.48 (s, 3H), 1.19 (m, 2H), 0.80 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{37}N_6O_6S$ calcd: 537.3, found: 567.3.
O17		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 1.6 Hz, 1H), 8.04 (d, J = 1.6 Hz, 1H), 4.20 (m, 5H), 4.07 (m, 3H), 3.74 (m, 2H), 3.66 (t, J = 11.6 Hz, 4H), 3.09 (m, 4H), 2.77 (m, 2H), 2.00 (m, 1H), 1.81 (m, 2H), 1.57 (s, 3H), 1.29 (m, 2H), 0.89 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{35}F_2N_6O_6S$ calcd: 573.2, found: 573.2.
O18		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 1.4 Hz, 1H), 7.95 (d, J = 1.4 Hz, 1H), 4.15 (s, 2H), 4.12 (d, J = 6.4 Hz, 2H), 4.03 (m, 2H), 3.98 (m, 2H), 3.66 (m, 2H), 3.26 (m, 2H), 2.95 (m, 4H), 2.68 (m, 2H), 2.48 (dd, J = 3.2, 10 Hz, 2H), 1.91 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.20 (m, 2H), 0.80 (m, 2H), 0.56 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{39}N_6O_8S$ calcd: 583.3, found: 583.3.
O19		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 1.2 Hz, 1H), 7.94 (d, J = 1.2 Hz, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.41 (d, J = 2.0 Hz, 1H), 6.19 (m, 1H), 4.52 (m, 2H), 4.11 (d, J = 6.4 Hz, 2H), 3.87 (s, 2H), 3.85 (m, 2H), 3.65 (m, 2H), 3.40 (m, 2H) 2.68 (m, 2H), 1.91 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.80 (m, 2H), 0.56 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{34}N_7O_6S$ calcd: 548.2, found: 548.2.

Example O20: 1-methylcyclopropyl 4-((5-(4-((1-(dimethylamino)cyclopropyl)methylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.







Example O20

Step A: A solution of piperazin-2-one (36.5 mg, 3.7 mmol) in dichloromethane (10 mL) is treated with triethylamine (74 mg, 0.73 mmol) followed by **M33e** (108 mg, 3.7 mmol) and stirred overnight. The solvent is removed and the residue is dissolved in dimethylformamide, filtered and purified by mass triggered reverse phase HPLC to afford **O20a**; ESIMS *m/z* for $(M+H)^+$ $C_{14}H_{19}N_2O_5S_2$ calcd: 359.1, found: 359.0.

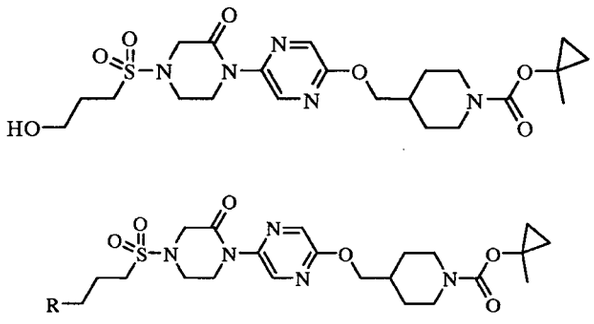
Step B: A solution of **O20a** (71.7 mg, 0.20 mmol) in 2 M dimethylamine in tetrahydrofuran solution (6 mL, 12 mmol) is treated with potassium *tert*-butoxide (34 mg, 0.30 mmol) and stirred for 1 hour at room temperture The solvent is removed and the residue is dissolved in dimethylformamide, filtered and purified by mass triggered reverse phase HPLC to afford **O20a**; ESIMS *m/z* for $(M+H)^+$ $C_{10}H_{20}N_3O_3S$ calcd: 262.1, found: 262.1.

Step C: By following a similar procedure as the one used for preparing **O3a** from **M1a** except substituting **O20b** for benzyl 3-oxopiperazine-1-carboxylate, **O20** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.65 (d, J = 1.4 Hz, 1H), 8.02 (d, J = 1.4Hz, 1H), 4.25 (m, 2H), 4.19 (d, J = 6.5 Hz, 2H), 4.17 (s, 2H), 4.04 (m, 2H), 3.70 (m, 2H), 3.16 (s, 2H), 2.75 (dd, J = 15.2, 13.8 Hz, 2H), 2.29 (s, 6H), 1.98 (m, 1H), 1.80 (m, 2H), 1.55 (s,

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3H), 1.27 (m, 2H), 0.88 (m, 6H), 0.62 (m, 2H); ESIMS calcd. for $C_{25}H_{39}N_6O_6S$ $[M+H]^+$ 551.3, found 551.4.

Example O21: 1-Methylcyclopropyl 4-((5-(4-(3-hydroxypropylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



Step A **O5**: R=Cl

Step B **O21a**: R=OCHO

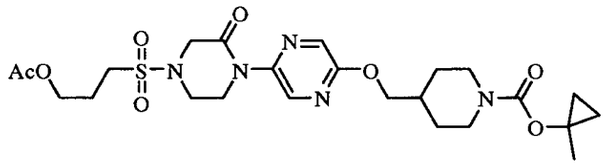
Example O21: R=OH

Step A: A solution of **O5** (2.76 g, 5.2 mmol), NaI (790 mg, 5.3 mmol) and sodium formate (1.06 g, 15.6 mmol) in dimethylformamide (30 mL) is heated at 120 °C for 2 hours. The mixture is diluted with water, extracted with ethyl acetate (2x) and the organics are washed with water & brine, dried ($MgSO_4$), filtered and concentrated to provide crude **O21a**, which is used in the next step without further purification; ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{34}N_5O_8S$ calcd: 540.2, found: 540.2.

Step B: A solution of **O21a** (crude from the last step) in a 1:1 mixture of methanol and water (40 mL) is treated with sodiumhydrogencarbonate (2.2 g, 26.0 mmol) and stirred at room temperature for 1 hour. The mixture is extracted with ethyl acetate and the organics are washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue is purified on silica gel using 0-10% methanol in dichloromethane to afford **O21**; ^1H NMR (400 MHz, $CDCl_3$) □ 8.66 (d, J = 1.4 Hz, 1H), 8.04 (d, J = 1.4 Hz, 1H), 4.20 (m, 4H), 4.08 (m, 2H), 3.82 (m, 2H), 3.74 (m, 2H), 3.22 (m, 2H), 2.77 (m, 2H), 2.12 (m, 2H), 2.00 (m, 1H), 1.83 (m, 2H), 1.74 (t, J = 4.8 Hz, 1H), 1.60 (s, 2H), 1.57 (s, 3H),

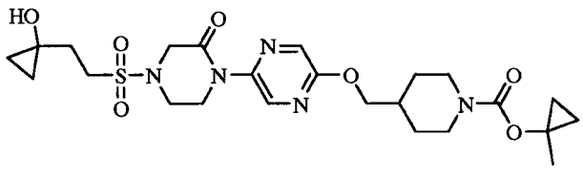
1.28 (m, 2H), 0.89 (m, 2H), 0.65 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{34}N_5O_7S$ calcd: 512.2, found: 512.2.

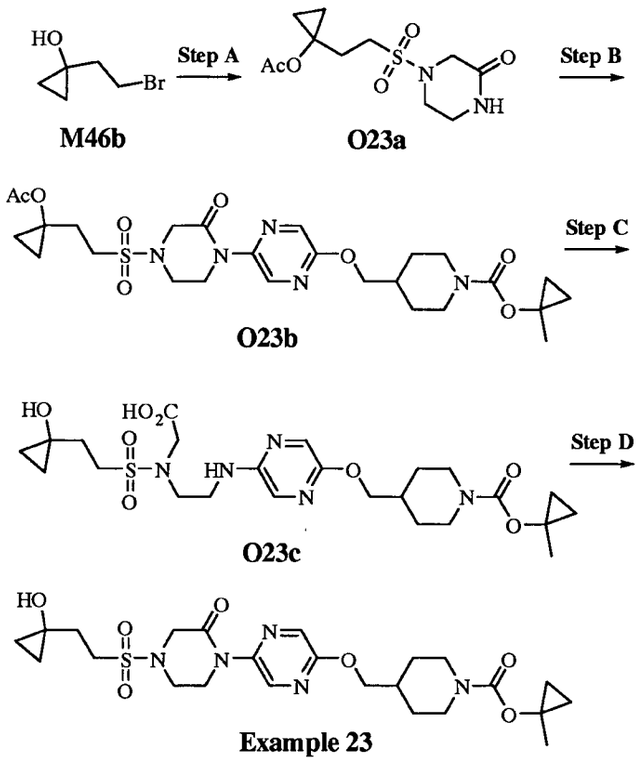
Example O22: 1-Methylcyclopropyl 4-((5-(4-(3-acetoxypropylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00306] By following a similar procedure as the one used for preparing **M19** from **M5** except substituting **O5** for **M5**, **O22** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.65 (d, *J* = 1.4 Hz, 1H), 8.02 (d, *J* = 1.4 Hz, 1H), 4.19 (m, 8H), 4.06 (m, 2H), 3.72 (m, 2H), 3.12 (m, 2H), 2.75 (dd, *J* = 12.4, 12.4 Hz, 2H), 2.15-2.22 (m, 2H), 2.08 (s, 3H), 1.98 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.27 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{24}H_{36}N_5O_8S$ $[M+H]^+$ 554.2, found 554.2.

Example O23: 1-Methylcyclopropyl 4-((5-(4-(2-(1-hydroxycyclopropyl)ethylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





[00307] **Step A**: By following a similar procedure as the one used for preparing **M46** from **M46b** except substituting piperazin-2-one for **M1c** and purifying by HPLC, **O23a** is prepared; ESIMS calcd. for $C_{11}H_{19}N_2O_5S$ $[M+H]^+$ 291.1, found 291.1.

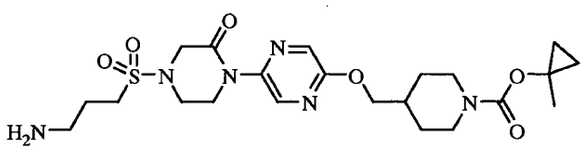
Step B: By following a similar procedure as the one used for preparing **O3a** from **M1a** except substituting **O23b** for benzyl 3-oxopiperazine-1-carboxylate, **O23b** is prepared; ESIMS calcd. for $C_{26}H_{38}N_5O_8S$ $[M+H]^+$ 580.2, found 580.3.

Step C: A solution of **O23b** (37.4 mg, 0.65 mmol) in methanol (1 mL) and water (0.1 mL) is treated with LiOH (5.7 mg, 0.1 mmol) and stirred overnight. The reaction is then purified directly by mass triggered reverse phase HPLC to afford **O23c**. ESIMS calcd. for $C_{24}H_{38}N_5O_8S$ $[M+H]^+$ 556.2, found 556.2.

Step D: A solution of **O23c** (20 mg, 0.036 mmol) in dichloromethane (1 mL) is treated with HATU (13.7 mg, 0.036 mmol) and N,N-diisopropylethylamine (4.6 mg, 0.036 mmol) and stirred overnight. The solvent is removed and the residue is dissolved in methanol and purified directly by mass triggered reverse phase HPLC. ^{1}H-NMR

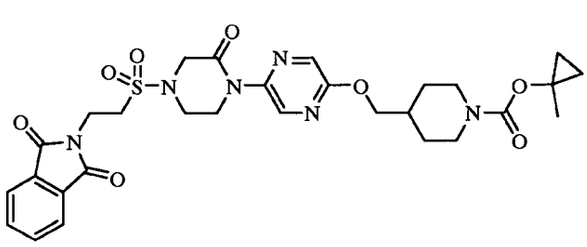
(400MHz, $CDCl_3$) δ 8.64 (d, *J* = 1.4 Hz, 1H), 8.02 (d, *J* = 1.4 Hz, 1H), 4.25 (m, 2H), 4.20 (s, 2H), 4.18 (s, 2H), 4.06 (m, 2H), 3.73 (m, 2H), 3.33 (ddd, *J* = 7.7, 5.3, 5.3 Hz, 2H), 2.74 (dd, *J* = 12.3, 12.1 Hz, 2H), 2.27 (s, 1H), 2.07 (ddd, *J* = 7.7, 5.2, 5.2 Hz, 2H), 1.98 (m, 1H), 1.80 (m, 2H), 1.55 (s, 3H), 1.26 (m, 2H), 0.86 (m, 4H), 0.62 (m, 2H), 0.57 (m, 2H); ESIMS calcd. for $C_{24}H_{36}N_5O_7S$ $[M+H]^+$ 538.2, found 538.8.

Example O24: 1-Methylcyclopropyl 4-((5-(4-(3-aminopropylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



By following a similar procedure as the one used for preparing **M18** from **M6** except substituting **O5** for **M6**, **O23b** is prepared; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 1.4 Hz, 1H), 7.82 (d, J = 1.4 Hz, 1H), 3.99 (d, J = 6.8 Hz, 2H), 3.97 (s, 2H), 3.86 (m, 2H), 3.51 (m, 2H), 2.96 (m, 2H), 2.68 (t, J = 6.8 Hz, 2H), 2.55 (m, 2H), 1.78 (m, 3H), 1.60 (m, 2H), 1.35 (s, 3H), 1.18 (br s, 2H), 1.06 (m, 2H), 0.67 (m, 2H), 0.42 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{35}N_6O_6S$ calcd: 511.2, found: 511.2.

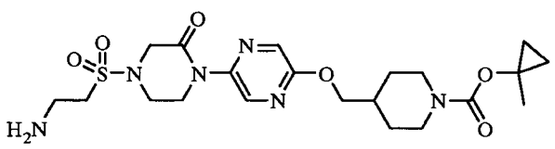
Example O25: 1-Methylcyclopropyl 4-((5-(4-(2-(1,3-dioxoisoindolin-2-yl)ethylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



By following a similar procedure as the one used for preparing **O3** from **O3b**

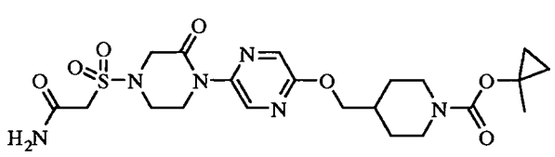
except substituting 2-(1,3-dioxoisoindolin-2-yl)ethanesulfonyl chloride for *n*-propanesulfonyl chloride, **O25** is prepared; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 1.4 Hz, 1H), 7.94 (d, J = 1.4 Hz, 1H), 7.80 (m, 2H), 7.67 (m, 2H), 4.10 (s, 7H), 3.99 (m, 2H), 3.67 (m, 2H), 3.40 (t, J = 6.8 Hz, 2H), 2.68 (m, 2H), 1.94 (m, 1H), 1.73 (m, 2H), 1.50 (s, 3H), 1.20 (m, 2H), 0.80 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{29}H_{35}N_6O_8S$ calcd: 627.2, found: 627.2.

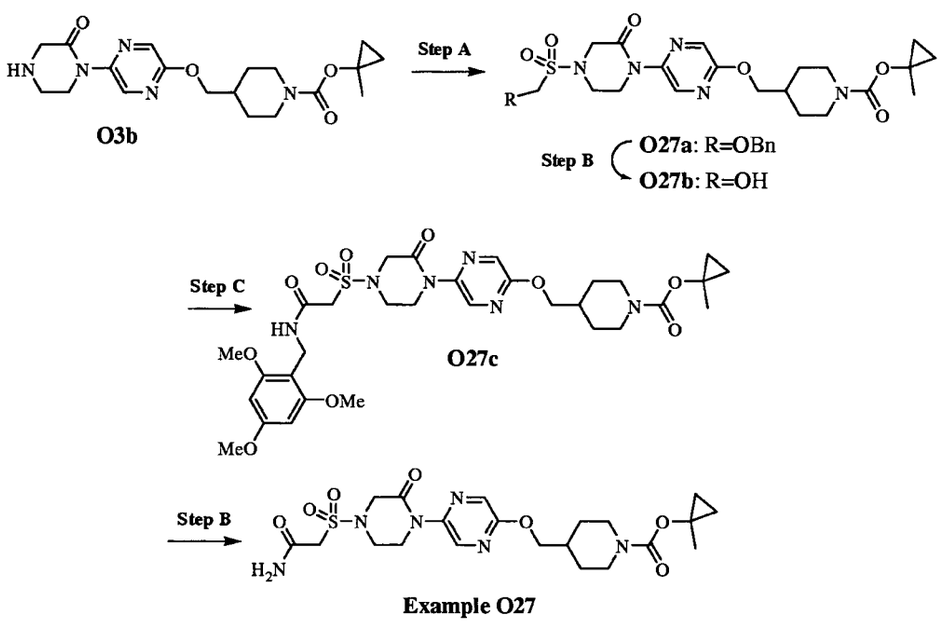
Example O26: 1-Methylcyclopropyl 4-((5-(4-(2-aminoethylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



A solution of **O25** (15 mg, 0.02 mmol) in ethanol (2 mL) is treated with hydrazine (8 μL, 0.24 mmol) and stirred for 1 hour. The solution iss concentrated and purified using mass-triggered reverse phase HPLC to afford **O26**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 1.4 Hz, 1H), 7.88 (d, J = 1.4 Hz, 1H), 4.05 (m, 4H), 3.92 (m, 2H), 3.58 (m, 2H), 3.10 (m, 2H), 3.03 (m, 2H), 2.61 (m, 2H), 1.85 (m, 1H), 1.66 (m, 2H), 1.41 (s, 3H), 1.13 (m, 2H), 0.73 (m, 2H), 0.49 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{33}N_6O_6S$ calcd: 497.2, found: 497.2.

Example O27: 1-Methylcyclopropyl 4-((5-(4-(2-amino-2-oxoethylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





Example O27

Step A: By following a similar procedure as the one used for preparing **O3** from **O3b** except substituting benzyl 2-(chlorosulfonyl)acetate for *n*-propanesulfonyl chloride, **O27a** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{28}H_{36}N_5O_8S$ calcd: 602.2, found: 602.1.

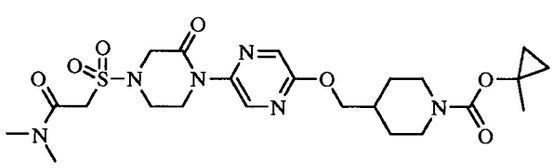
Step B: By following a similar procedure as the one used for preparing **M48** from **M48e**, **O27b** is prepared; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 1.2 Hz, 1H), 7.80 (d, J = 1.2 Hz, 1H), 4.11 (s, 2H), 3.96 (m, 3H), 3.84 (m, 5H), 3.59 (m, 2H), 2.53 (m, 2H), 1.76 (m, 1H), 1.57 (m, 2H), 1.32 (s, 3H), 1.05 (m, 2H), 0.64 (m, 2H), 0.40 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{30}N_5O_8S$ calcd: 512.2, found: 512.1.

Step C: A solution of **O27b** (60 mg, 0.12 mmol), HATU (89 mg, 0.23 mmol) and 2,4,6-trimethoxybenzylamine-HCl (33 mg, 0.14 mmol) in dichloromethane (10 mL) is treated with diisopropylethylamine (61 μL, 0.35 mmol) and the mixture is stirred at room temperature for 14 hours. The mixture is diluted with water and extracted with dichloromethane. The organics are dried, filtered, and concentrated to provide **O27c**, which was used without further purification. ESIMS *m/z* for $(M+H)^+$ $C_{31}H_{43}N_6O_{10}S$ calcd: 691.3, found: 691.2.

Step B: A solution of **O27c** (0.12 mmol) in dichloromethane (2 mL) is

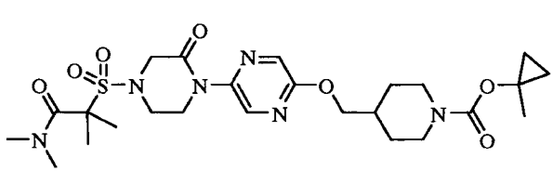
treated with TFA (1 mL) and aged for 1 hour at room temperature. The residue is concentrated and purified using mass-triggered reverse phase HPLC to afford **O27**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 1.6 Hz, 1H), 7.95 (d, J = 1.6 Hz, 1H), 4.19 (s, 2H), 4.12 (d, J = 6.4 Hz, 2H), 3.99 (m, 2H), 3.90 (s, 2H), 3.72 (m, 2H), 2.68 (m, 3H), 1.89 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.13 (m, 2H), 0.80 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{31}N_6O_7S$ calcd: 511.2, found: 511.2.

Example O28: 1-Methylcyclopropyl 4-((5-(4-(2-(dimethylamino)-2-oxoethylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.

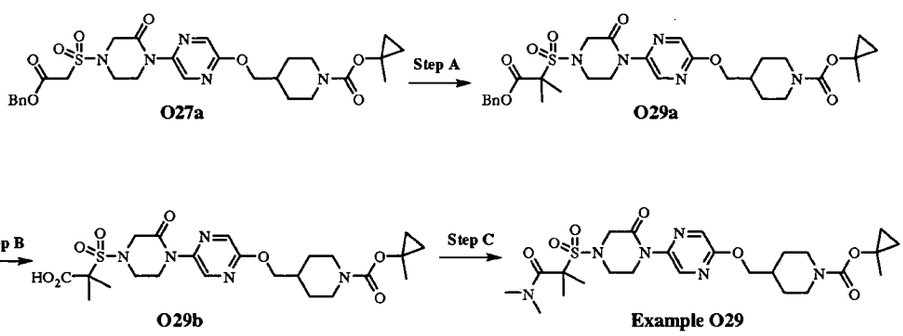


By following a similar procedure as the one used for preparing **O27c** from **O27b** except substituting dimethylamine-HCl for 2,4,6-trimethoxybenzylamine-HCl, **O28** is prepared; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 1.6 Hz, 1H), 8.03 (d, J = 1.6 Hz, 1H), 4.28 (s, 2H), 4.19 (m, 4H), 4.06 (m, 2H), 3.82 (s, 2H), 3.23 (s, 3H), 3.04 (s, 3H), 2.77 (m, 2H), 2.00 (m, 1H), 1.81 (m, 2H), 1.57 (s, 3H), 1.28 (m, 2H), 0.88 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{35}N_6O_7S$ calcd: 539.2, found: 539.2.

Example O29: 1-Methylcyclopropyl 4-((5-(4-(1-(dimethylamino)-2-methyl-1-oxopropan-2-ylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



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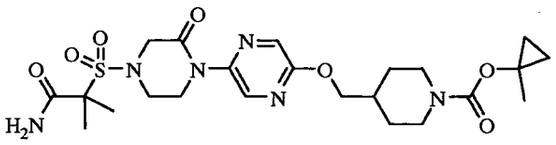


Step A: A solution of **O27a** (200 mg, 0.33 mmol) in dimethylformamide (5 mL) is treated with potassium carbonate (138 mg, 1.0 mmol) and iodomethane (63 μL, 1.0 mmol) and heated at 70 °C for 1 hour. The mixture is diluted with water and extracted with ethyl acetate. The organic layer is washed with water and brine, dried ($MgSO_4$), filtered and concentrated to provide **O29a**; ESIMS *m/z* for $(M+H)^+$ $C_{30}H_{40}N_5O_8S$ calcd: 630.3, found: 630.3.

Step B: A solution of **O29a** (crude from **Step A**) and ammonium formate (~1 mmol) in methanol (5 mL) is treated with Pd/C (wet, 10%) and heated at 80 °C for 1 hour. The mixture is cooled, filtered, and the filtrate is washed with water and ethyl acetate. The layers are separated and the organic layer is washed with 1N HCl and brine, then dried over $MgSO_4$, filtered and concentrated. The residue is purified using mass-triggered reverse phase HPLC to afford **O29b**; ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 1.6 Hz, 1H), 8.05 (d, J = 1.6 Hz, 1H), 4.43 (s, 2H), 4.21 (d, J = 6.4 Hz, 2H), 4.05 (m, 2H), 3.87 (br s, 2H), 2.78 (m, 2H), 2.03 (m, 1H), 1.82 (s, 6H), 1.57 (s, 3H), 1.28 (m, 2H), 0.89 (m, 2H), 0.65 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{34}N_5O_8S$ calcd: 540.2, found: 540.1.

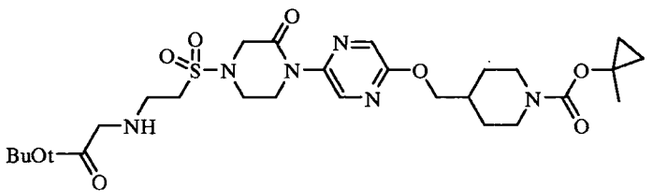
Step C: By following a similar procedure as the one used for preparing **O27c** from **O27b** except substituting dimethylamine-HCl for 2,4,6-trimethoxybenzylamine-HCl and **O29b** for **O27c**, **O29** is prepared; ^1H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 1.4 Hz, 1H), 7.87 (d, J = 1.4 Hz, 1H), 4.14 (s, 2H), 4.04 (d, J = 6.4 Hz, 2H), 3.88 (m, 2H), 3.66 (s, 2H), 2.60 (m, 2H), 1.84 (m, 1H), 1.65 (m, 2H), 1.54 (s, 6H), 1.41 (s, 6H), 1.11 (m, 2H), 0.73 (m, 2H), 0.48 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{39}N_6O_7S$ calcd: 567.3, found: 567.2.

Example O30: 1-Methylcyclopropyl 4-((5-(4-(1-amino-2-methyl-1-oxopropan-2-ylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



By following a similar procedure as the one used for preparing **O27** from **O27b** except substituting **O29b** for **O27b**, **O30** is prepared; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 1.4 Hz, 1H), 8.03 (d, J = 1.4 Hz, 1H), 4.23 (s, 2H), 4.20 (d, J = 6.4 Hz, 2H), 4.02 (m, 2H), 3.78 (s, 2H), 2.77 (m, 2H), 2.00 (m, 1H), 1.81 (s, 6H), 1.57 (s, 3H), 1.27 (m, 2H), 0.89 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{35}N_6O_7S$ calcd: 539.2, found: 539.2.

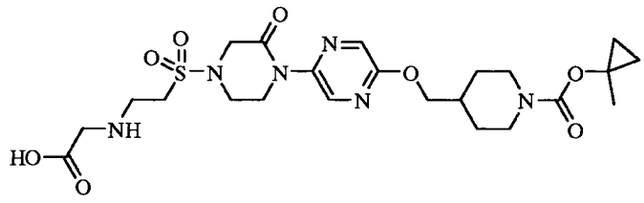
Example O31: 1-Methylcyclopropyl 4-((5-(4-(2-(2-tert-butoxy-2-oxoethylamino)ethylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



A solution of **O13a** (50 mg, 0.10 mmol), t-butylglycine-HCl (105 mg, 0.62 mmol) and diisopropylethylamine (108 μL, 0.62 mmol) in methanol (2 mL) and dimethylformamide (2 mL) and stirred at room temperture for 14 hours. The mixture is diluted with water and extracted with ethyl acetate. The organics are washed with water then brine, dried over $MgSO_4$, and filtered. The residue is concentrated and purified using mass-triggered reverse phase HPLC to afford **O31**; ^{1}H NMR (400 MHz, $CDCl_3$) δ

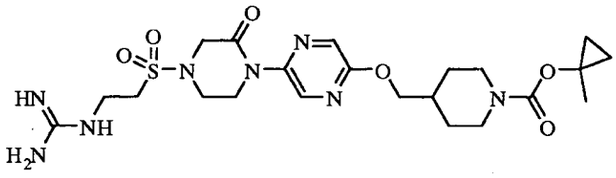
8.66 (d, J = 1.2 Hz, 1H), 8.04 (d, J = 1.2 Hz, 1H), 4.20 (s, 4H), 4.07 (m, 2H), 3.76 (m, 2H), 3.48 (s, 2H), 3.40 (m, 2H), 3.28 (m, 2H), 2.77 (m, 2H), 2.00 (m, 1H), 1.82 (m, 2H), 1.57 (s, 3H), 1.49 (s, 9H), 1.28 (m, 2H), 0.89 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{27}H_{43}N_6O_8S$ calcd: 611.3, found: 611.2.

Example O32: 2-(2-(4-(5-((1-((1-Methylcyclopropoxy)carbonyl)piperidin-4-yl)methoxy)pyrazin-2-yl)-3-oxopiperazin-1-ylsulfonyl)ethylamino)acetic acid.



A solution of **O31** (31 mg, 0.05 mmol) in dichloromethane (1 mL) is treated with HCl (1 mL of 4N in dioxane) and aged for 2 hours at room temperature. The mixture is concentrated and purified using mass-triggered reverse phase HPLC to afford the **O32**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 1.4 Hz, 1H), 7.90 (d, J = 1.4 Hz, 1H), 4.01 (m, 4H), 3.88 (m, 2H), 3.46 (m, 8H), 2.69 (m, 2H), 1.88 (m, 1H), 1.69 (m, 2H), 1.47 (s, 3H), 1.18 (m, 2H), 0.80 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{35}N_6O_8S$ calcd: 555.2, found: 555.1.

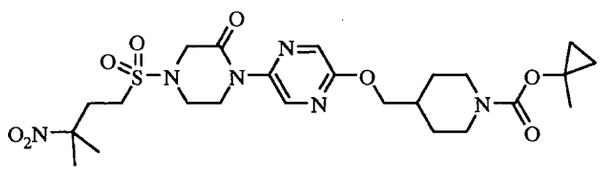
Example O33: 1-Methylcyclopropyl 4-((5-(4-(2-guanidinoethylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



A solution of **O26** (22 mg, 0.044 mmol) and 3,5-dimethoxypyrazole-1-carboxamidine nitrate (13 mg, 0.066 mmol) in dimethylformamide (3 mL) is treated with

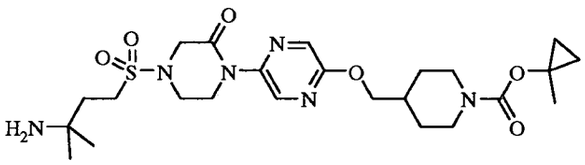
diisopropylethylamine (23 μL, 0.13 mmol) and stirred at room temperature for 14 hours. The mixture is diluted with aqueous sodiumhydrogencarbonate and extracted with ethyl acetate. The organic layer is washed with brine, dried over $MgSO_4$, filtered, concentrated and purified using mass-triggered reverse phase HPLC to afford **O33**; ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 1.4 Hz, 1H), 7.93 (d, J = 1.4 Hz, 1H), 4.11 (m, 4H), 4.06 (m, 2H), 3.92 (m, 2H), 3.62 (m, 3H), 2.68 (m, 2H), 1.80 (m, 1H), 1.72 (m, 2H), 1.18 (m, 3H), 0.80 (m, 2H), 0.56 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{35}N_8O_6S$ calcd: 539.2, found: 539.2.

Example O34: 1-Methylcyclopropyl 4-((5-(4-(3-methyl-3-nitrobutylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



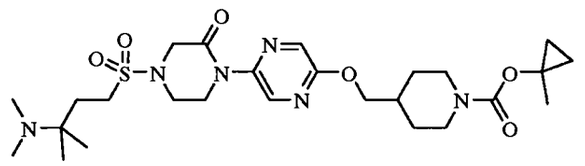
A solution of **O13a** (62 mg, 0.13 mmol) and 2-nitropropane (116 μL, 1.29 mmol) in methanol (0.5 mL) and tetrahydrofuran (1 mL) is treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (154 μL, 1.03 mmol) and stirred at room temperature for 14 hours. The mixture is diluted with water, extracted with ethyl acetate, and washed with brine. The organic layer is dried ($MgSO_4$), filtered, concentrated and purified on silica gel using 0-100% ethyl acetate in dichloromethane to afford **O34**; ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 1.4 Hz, 1H), 7.95 (d, J = 1.4 Hz, 1H), 4.11 (m, 4H), 4.00 (m, 2H), 3.65 (m, 2H), 2.99 (m, 2H), 2.68 (m, 2H), 2.35 (m, 2H), 1.92 (m, 1H), 1.72 (m, 2H), 1.59 (s, 6H), 1.48 (s, 3H), 1.18 (m, 2H), 0.80 (m, 2H), 0.56 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{37}N_6O_8S$ calcd: 569.2, found: 569.2.

Example O35: 1-Methylcyclopropyl 4-((5-(4-(3-amino-3-methylbutylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



A solution of **O34** (105 mg, 0.18 mmol) in a mixture of methanol (5 mL) and tetrahydrofuran (4 mL) is treated with $NiCl_2$ (72 mg, 0.55 mmol) followed by sodium borohydride (21 mg, 0.55 mmol) and the resulting mixture is stirred at room temperature for 3 hours. The mixture is diluted with ethyl acetate and filtered, then washed with saturated aqueous sodium hydrogencarbonate and brine. The organic layer is dried ($MgSO_4$), filtered, concentrated and purified using mass-triggered reverse phase HPLC to afford **O35**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 1.2 Hz, 1H), 8.04 (d, J = 1.2 Hz, 1H), 4.20 (d, J = 6.4 Hz, 2H), 4.18 (s, 2H), 4.05 (m, 2H), 3.74 (m, 2H), 3.27 (m, 2H), 2.75 (m, 2H), 2.00 (m, 3H), 1.80 (m, 2H), 1.56 (s, 3H), 1.35 (m, 2H), 1.29 (s, 6H), 0.88 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{39}N_6O_6S$ calcd: 539.3, found: 539.2.

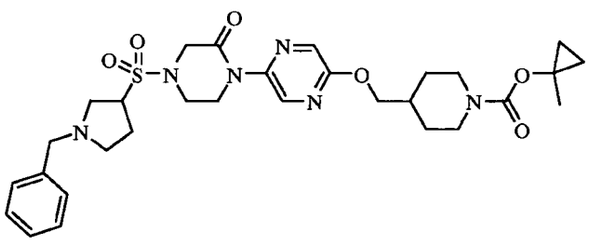
Example O36: 1-Methylcyclopropyl 4-((5-(4-(3-(dimethylamino)-3-methylbutylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



A solution of **O35** (56 mg, 0.10 mmol) in dimethylformamide (2 mL) is treated with K_2CO_3 (43 mg, 0.31 mmol) and iodomethane (13 μL, 0.21 mmol) and stirred at room temperature for 3 hours. The mixture is diluted with water, extracted with ethyl acetate, and washed with water and brine. The organic extracts are dried ($MgSO_4$), filtered, concentrated and purified using mass-triggered reverse phase HPLC to afford **O36**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 1.2 Hz, 1H), 8.04 (d, J = 1.2 Hz, 1H), 4.20 (d, J = 6.4 Hz, 2H), 4.18 (s, 2H), 4.07 (m, 2H), 3.72 (m, 2H), 3.21 (m, 2H), 2.77 (m,

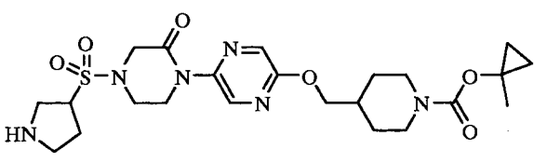
2H), 2.35 (br s, 4H), 2.02 (m, 3H), 1.82 (m, 2H), 1.57 (s, 3H), 1.29 (m, 2H), 1.15 (br s, 6H), 0.88 (m, 2H), 0.64 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{43}N_6O_6S$ calcd: 567.3, found: 567.2.

Example O37: 1-Methylcyclopropyl 4-((5-(4-(1-benzylpyrrolidin-3-ylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



A solution of **O13a** (96 mg, 0.20 mmol) and N-trimethylsilyl-N-cyanomethylbenzylamine (104 μL, 0.42 mmol) in acetonitrile (5 mL) is treated with AgF (54 mg, 0.42 mmol) and heated at 75 °C for 4 hours. The mixture is filtered, washed with ethyl acetate, concentrated and purified on silica gel using 0-100% ethyl acetate in hexane to afford **O37**; ESIMS *m/z* for $(M+H)^+$ $C_{30}H_{41}N_6O_6S$ calcd: 613.3, found: 613.2.

Example O38: 1-Methylcyclopropyl 4-((5-(2-oxo-4-(pyrrolidin-3-ylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.

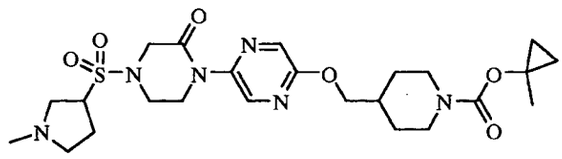


A solution of **O37** (45 mg) in EtOH (5 mL) is hydrogenated in an H-cube® (Pd/C, 50 bar H_2, 70 °C, 1 mL/min) device. The residue is concentrated to provide **O38** ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 1.4 Hz, 1H), 7.95 (d, J = 1.4 Hz, 1H), 4.11 (m, 4H), 3.98 (m, 2H), 3.68 (m, 2H), 3.50 (m, 1H), 3.40 (dd, J = 4.0, 13.2 Hz, 1H), 3.13 (m, 2H), 2.83 (m, 1H), 2.68 (m, 2H), 2.10 (m, 2H), 1.89 (m, 1H), 1.73 (m, 5H), 1.48 (s,

173

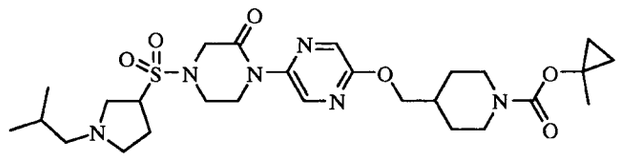
3H), 1.18 (m, 2H), 0.80 (m, 2H), 0.56 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{35}N_6O_6S$ calcd: 523.2, found: 523.2.

Example O39: 1-Methylcyclopropyl 4-((5-(4-(1-methylpyrrolidin-3-ylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



A solution of **O38** (24 mg, 0.05 mmol) and paraformaldehyde (~0.25 mmol) in 1,2-dichloroethane (5 mL) was treated with acetic acid (50 μL) and heated at 80 °C for 1 hour. $NaBH(OAc)_3$ (20 mg, 0.09 mmol) is added and the mixture is stirred at 80 °C for an additional 2 hours. The mixture is cooled, diluted with saturted aqueous sodiumhydrogencarbonate, and extracted with dichloromethane (2x). The organic layers are dried over $MgSO_4$, filtered, concentrated, and purified using mass-triggered reverse phase HPLC to afford **O39**; ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 1.4 Hz, 1H), 7.95 (d, J = 1.4 Hz, 1H), 4.17 (d, J = 7.2 Hz, 2H), 4.12 (d, J = 6.4 Hz, 2H), 3.71 (m, 3H), 2.86 (m, 1H), 2.66 (m, 3H), 2.33 (s, 3H), 2.18 (m, 2H), 1.91 (m, 1H), 1.73 (m, 2H), 1.48 (s, 3H), 1.20 (m, 2H), 0.80 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{37}N_6O_6S$ calcd: 537.3, found: 537.2.

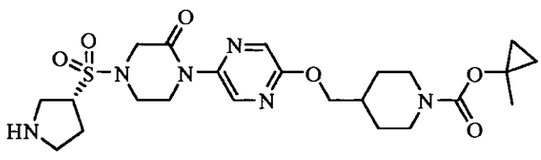
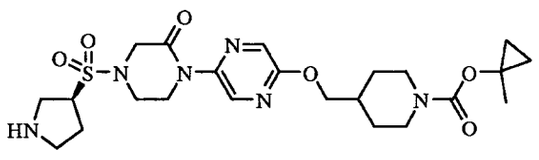
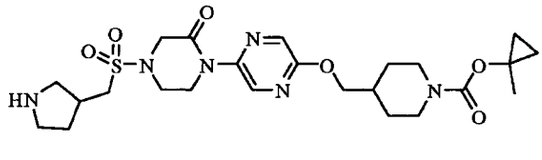
Example O40: 1-Methylcyclopropyl 4-((5-(4-(1-isobutylpyrrolidin-3-ylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.

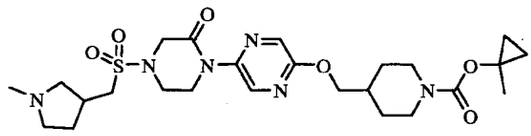
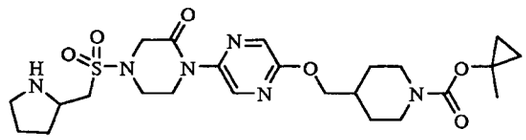
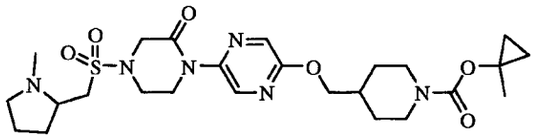
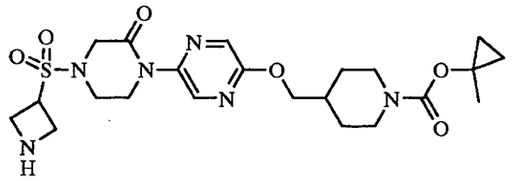
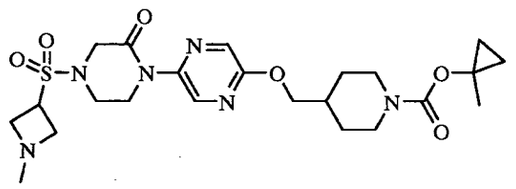


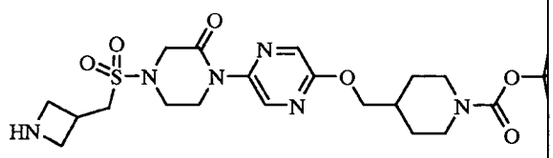
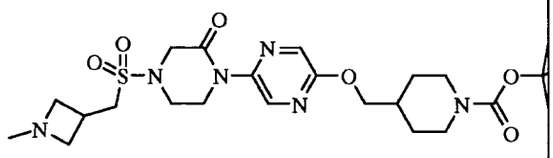
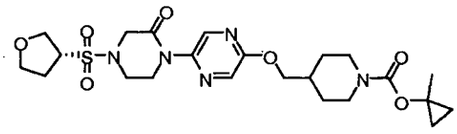
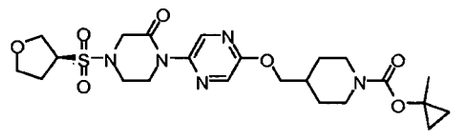
By following a similar procedure as the one used for preparing **O39** from **O38** except substituting isobutyraldehyde for paraformaldehyde, **O40** is prepared; ^1H

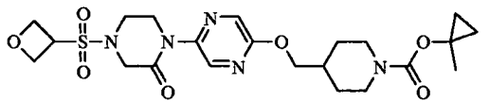
NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 1.2 Hz, 1H), 7.94 (d, J = 1.2 Hz, 1H), 4.18 (d, J = 6.0 Hz, 2H), 4.12 (d, J = 4.4 Hz, 2H), 3.96 (m, 2H), 3.69 (m, 2H), 2.80 (m, 2H), 2.68 (m, 2H), 2.58 (m, 2H), 2.17 (m, 3H), 1.91 (m, 1H), 1.73 (m, 2H), 1.65 (m, 1H), 1.48 (s, 3H), 1.20 (m, 2H), 0.84 (m, 6H), 0.79 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{27}H_{43}N_6O_6S$ calcd: 579.3, found: 579.2

By following a similar procedure as the one used for preparing **M48** from **M48a** except substituting the appropriate alcohol for **M48a** and **O3b** for **M1c**, followed in some cases by reductive aminations as in the preparation of **O39** and **O40**, the following compounds are prepared;

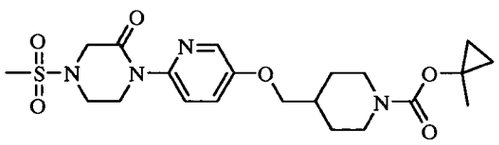
Ex.	Structure	Analytical data
O41		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 1.4 Hz, 1H), 7.95 (d, J = 1.4 Hz, 1H), 4.11 (m, 4H), 3.97 (m, 2H), 3.68 (m, 2H), 3.60 (m, 1H), 3.39 (dd, J = 4.0, 12.8 Hz, 1H), 3.10 (m, 2H), 2.82 (m, 1H), 2.68 (m, 2H), 2.08 (m, 2H), 1.91 (s, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.20 (m, 2H), 0.80 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{35}N_6O_6S$ calcd: 523.2, found: 523.2.
O42		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 1.4 Hz, 1H), 7.95 (d, J = 1.4 Hz, 1H), 4.11 (m, 4H), 3.97 (m, 2H), 3.68 (m, 2H), 3.60 (m, 1H), 3.39 (dd, J = 4.0, 12.8 Hz, 1H), 3.10 (m, 2H), 2.82 (m, 1H), 2.68 (m, 2H), 2.08 (m, 2H), 1.91 (s, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.20 (m, 2H), 0.80 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{35}N_6O_6S$ calcd: 523.2, found: 523.2.
O43		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 1.4 Hz, 1H), 7.82 (d, J = 1.4 Hz, 1H), 3.98 (d, J = 6.4 Hz, 2H), 3.95 (s, 2H), 3.85 (m, 2H), 3.50 (m, 2H), 3.13 (m, 2H), 2.89 (m, 4H), 2.61 (m, 5H), 1.97 (m, 5H), 1.78 (m, 2H), 1.59 (m, 2H), 1.44 (m, 2H), 1.35 (s, 3H), 1.05 (m, 2H), 0.67 (m, 2H), 0.43 (m, 2H); ESIMS *m/z* for $(M+H)^+$

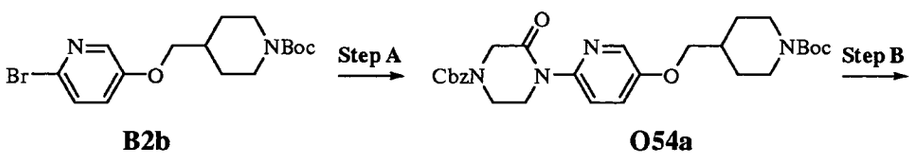
		$C_{24}H_{37}N_6O_6S$ calcd: 537.3, found: 537.3.
O44		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, J = 1.2 Hz, 1H), 7.95 (d, J = 1.2 Hz, 1H), 4.11 (d, J = 6.4 Hz, 2H), 4.08 (s, 2H), 3.98 (m, 2H), 3.62 (m, 2H), 3.04 (m, 2H), 2.68 (m, 6H), 2.50 (m, 2H), 2.33 (s, 3H), 2.17 (m, 1H), 1.91 (m, 2H), 1.72 (m, 5H), 1.62 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.79 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{39}N_6O_6S$ calcd: 551.3, found: 551.2.
O45		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 1.2 Hz, 1H), 7.94 (d, J = 1.2 Hz, 1H), 4.15 (m, 5H), 3.99 (m, 2H), 3.65 (m, 3H), 3.24 (m, 1H), 3.12 (dd, J = 4.0, 14.0 Hz, 1H), 2.99 (m, 2H), 2.68 (m, 2H), 2.04 (m, 2H), 1.85 (m, 9H), 1.48 (s, 3H), 1.20 (m, 2H), 0.80 (m, 2H), 0.56 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{37}N_6O_6S$ calcd: 537.3, found: 537.3.
O46		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 1.2 Hz, 1H), 7.95 (d, J = 1.2 Hz, 1H), 4.11 (d, J = 6.4 Hz, 2H), 4.10 (s, 2H), 3.99 (m, 2H), 3.64 (m, 2H), 2.68 (m, 2H), 2.37 (s, 2H), 2.20 (s, 2H), 1.90 (m, 1H), 1.74 (m, 4H), 1.48 (s, 3H), 1.20 (m, 2H), 0.79 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{25}H_{39}N_6O_6S$ calcd: 551.3, found: 551.2.
O47		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.95 (s, 1H), 4.16 (m, 2H), 4.12 (m, 4H), 4.02 (m, 2H), 3.97 (m, 2H), 3.82 (m, 2H), 3.66 (m, 3H), 2.68 (m, 2H), 2.04 (m, 2H), 1.91 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.80 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{33}N_6O_6S$ calcd: 509.2, found: 509.2.
O48		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 1.0 Hz, 1H), 7.95 (d, J = 1.0 Hz, 1H), 4.14 (s, 2H), 4.12 (d, J = 4.4 Hz, 2H), 3.96 (m, 2H), 3.90 (m, 1H), 3.67 (m, 2H), 3.54 (m, 2H), 3.44 (m, 2H), 2.68 (m, 2H), 2.30 (s, 3H), 1.91 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.18 (m, 2H), 0.80 (m, 2H), 0.55 (m,

		2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{35}N_6O_6S$ calcd: 523.2, found: 523.2.
O49		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 1.2 Hz, 1H), 7.94 (d, J = 1.4 Hz, 1H), 4.12 (d, J = 6.8 Hz, 2H), 4.06 (s, 2H), 3.98 (m, 2H), 3.77 (m, 2H), 3.72 (m, 1H), 3.62 (m, 2H), 3.44 (m, 2H), 3.26 (m, 2H), 3.18 (m, 1H), 2.68 (m, 2H), 1.90 (m, 1H), 1.73 (m, 2H), 1.48 (s, 3H), 1.20 (m, 3H), 0.80 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{35}N_6O_6S$ calcd: 523.2, found: 523.2.
O50		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 1.6 Hz, 1H), 7.94 (d, J = 1.6 Hz, 1H), 4.12 (d, J = 6.8 Hz, 2H), 3.98 (m, 3H), 3.72 (m, 1H), 3.62 (m, 2H), 3.43 (m, 2H), 3.23 (d, J = 7.2 Hz, 2H), 2.95 (m, 2H), 2.84 (m, 1H), 2.68 (m, 2H), 2.23 (s, 3H), 1.91 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 1.20 (m, 3H), 0.80 (m, 2H), 0.55 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{24}H_{37}N_6O_6S$ calcd: 537.3, found: 537.2.
O51		^{1}H-NMR (400MHz, $CDCl_3$) δ 8.64 (d, *J* = 1.4 Hz, 1H), 8.02 (d, *J* = 1.4 Hz, 1H), 4.23 (m, 2H), 4.19 (m, 2H), 4.06-4.06 (m, 5H), 3.84 (m, 2H), 3.76 (m, 2H), 2.74 (m, 2H), 2.33 (m, 2H), 1.98 (m, 1H), 1.80 (m, 2H), 1.55 (s, 3H), 1.26 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{23}H_{34}N_5O_7S$ $[M+H]^+$ 524.2, found 524.3.
O52		^{1}H-NMR (400MHz, $CDCl_3$) δ 8.65 (d, *J* = 1.4 Hz, 1H), 8.02 (d, *J* = 1.4 Hz, 1H), 4.21 (m, 2H), 4.18 (d, *J* = 6.5 Hz, 2H), 4.11-4.16 (m, 2H), 3.98-4.06 (m, 5H), 3.84 (m, 2H), 3.76 (m, 2H), 2.75 (dd, *J* = 12.3, 12.3 Hz, 2H), 2.33 (m, 2H), 1.97 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.26 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{23}H_{34}N_5O_7S$ $[M+H]^+$ 524.2, found 524.4.

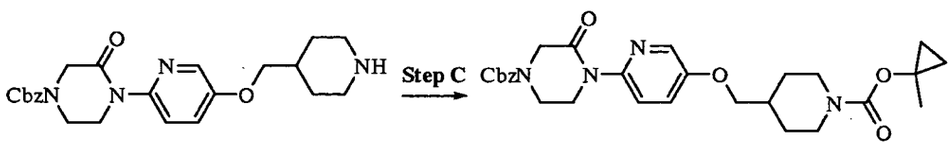
O53		^{1}H-NMR (400MHz, $CDCl_3$) δ8.65 (d, *J* = 1.4 Hz, 1H), 8.02 (d, *J* = 1.4 Hz, 1H), 4.93 (m, 4H), 4.51 (tt, *J* = 8.0, 6.4 Hz, 1H), 3.95-4.30 (m, 8H), 3.75 (m, 2H), 2.75 (m, 2H), 1.98 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.26 (m, 2H), 0.87 (m, 2H), 0.63 (m, 2H); ESIMS calcd. for $C_{22}H_{32}N_5O_7S$ $[M+H]^+$ 510.2, found 510.2.

Example O54: 1-Methylcyclopropyl 4-((5-(4-(isopropylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.

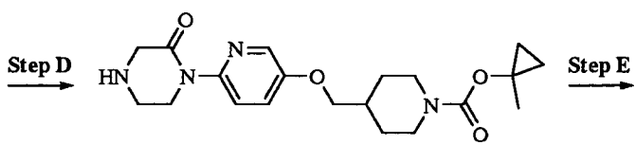




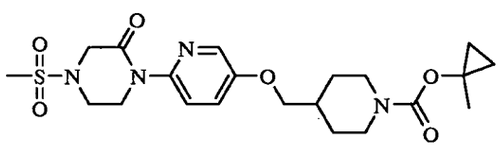
B2b **O54a**



O54b **O54c**



O54d



Example O54

[00308] **Step A: :** By following a similar procedure as the one used for preparing **O1a** from **B4b** except substituting **B2b** for **B4b**, **O54a** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{28}H_{37}N_4O_6$ calcd: 525.3, found: 525.2.

[00309] **Step B:** A sample of **O54a** (200 mg, 0.38 mmol) is treated with trifluoroacetic acid (3 mL) and aged for 30 minutes. The solvent is removed and the reaction is treated with ethyl acetate and extracted with 1 M HCl three times. The organics are discarded and the aqueous layer is made basic with solid Na_2CO_3 and extracted with ethyl acetate three times. The combined organics are dried over $MgSO_4$, filtered and evaporated to afford **O54b**; ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{29}N_4O_4$ calcd: 425.2, found: 425.2.

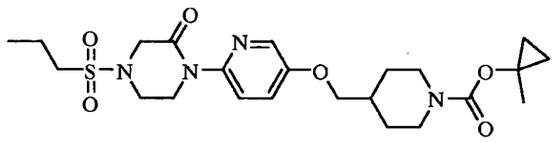
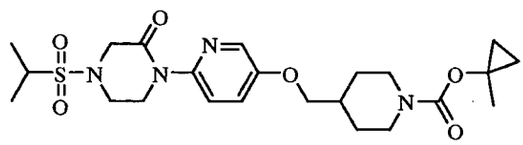
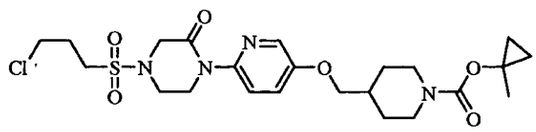
[00310] **Step C:** By following a similar procedure as the one used for preparing **O2** from **O1** except substituting **O54b** for **O1**, **O54c** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{28}H_{35}N_4O_6$ calcd: 523.3, found: 523.2.

[00311] **Step D:** By following a similar procedure as the one used for preparing **O3b** from **O3a** except substituting **O54c** for **O3a**, **O54d** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{20}H_{29}N_4O_4$ calcd: 389.2, found: 389.2.

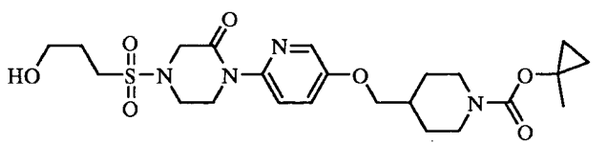
[00312] **Step E:** By following a similar procedure as the one used for preparing **O3** from **O3b** except substituting **O54d** for **O3b** and methanesulfonyl chloride for *n*-propanesulfonyl chloride, **O54** is prepared; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 2.9 Hz, 1H), 7.66 (d, J = 9.0 Hz, 1H), 7.17 (dd, J = 2.9, 9.0, 1H), 4.10 (m, 2H), 4.05 (m, 2H), 4.03 (s, 2H), 3.77 (d, J = 6.3 Hz, 2H), 3.58 (m, 2H), 2.48 (s, 3H), 2.69 (m, 2H), 1.90 (m, 1H), 1.74 (m, 2H), 1.48 (s, 3H), 1.20 (m, 2H)), 0.79 (m, 2H), 0.57 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{31}N_4O_6S$ calcd: 467.2, found: 467.2.

[00313] By following a similar procedure as the one used for preparing **O54** from **O54d** except substituting the appropriate sulfonyl chloride for methanesulfonyl chloride, the following compounds are made;

Ex.	Structure	Analytical data

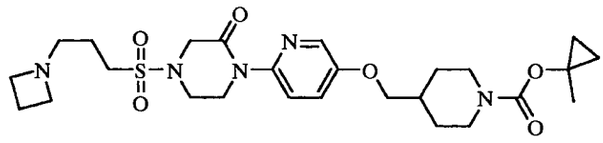
O55		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 2.9 Hz, 1H), 7.73 (d, J = 9.0 hz, 1H), 7.24 (dd, J = 9.0, 3.0 Hz, 1H), 4.20 (m, 2H), 4.13 (s, 2H), 4.09 (m, 2H), 3.84 (d, J = 6.3 Hz, 2H), 3.68 (m, 2H), 3.00 (m, 2H), 2.76 (dd, J = 12.4, 12.4 Hz, 2H), 1.98 (m, 1H), 1.89 (m, 2H), 1.82 (m, 2H), 1.55 (s, 3H), 1.27 (m, 2H), 1.08 (t, J = 7.5 Hz, 3H), 0.87 (m, 2H), 0.63 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{35}N_4O_6S$ calcd.: 495.2, found: 495.6.
O56		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 2.7 Hz, 1H), 7.73 (d, J = 9.0 Hz, 1H), 7.24 (dd, J = 9.0, 3.0 Hz, 1H), 4.18 (s, 2H), 4.16 (m, 2H), 4.08 (m, 2H), 3.84 (d, J = 6.3 Hz, 2H), 3.73 (m, 2H), 3.27 (sept., J = 6.8 Hz, 1H), 2.76 (dd, J = 12.3, 12.3 Hz, 2H), 1.97 (m, 1H), 1.82 (m, 2H), 1.55 (s, 3H), 1.40 (d, J = 6.8 Hz, 6H), 1.27 (m, 2H), 0.87 (m, 2H), 0.63 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{35}N_4O_6S$ calcd.: 495.2, found: 495.6.
O57		^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 2.8 Hz, 1H), 7.67 (d, J = 9.2 Hz, 1H), 7.17 (dd, J = 9.2, 3.2 Hz, 1H), 4.15 (m, 2H), 4.08 (m, 2H), 4.04 (m, 2H), 3.78 (d, J = 6.4 Hz, 2H), 3.63 (m, 2H), 3.15 (m, 2H), 2.69 (t, J = 12.4 Hz, 2H), 2.26 (m, 2H), 1.91 (m, 1H), 1.75 (d, J = 12.4 Hz, 2H), 1.49 (s, 3H), 1.20 (m, 2H), 0.80 (m, 2H), 0.56 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{34}ClN_4O_6S$ calcd.: 529.2, found: 529.1.

Example O58: 1-Methylcyclopropyl 4-((6-(4-(3-hydroxypropylsulfonyl)-2-oxopiperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate.



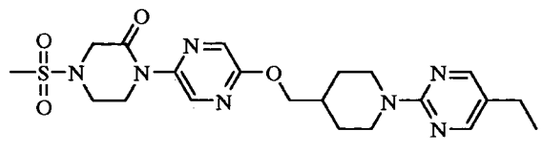
By following a similar procedure as the one used for preparing **O21** from **O5** except substituting **O57** for **O5**, **O58** is prepared; ^{1}H NMR (400 MHz, CD_3CN) δ 8.09 (d, J = 2.1 Hz, 1H), 7.65 (d, J = 6.9 Hz, 1H), 7.34 (dd, J = 3.0, 6.6 Hz, 1H), 4.02 (s, 2H), 4.01 (m, 2H), 3.96 (m, 2H), 3.90 (d, J = 4.8 Hz, 2H), 3.63 (m, 2H), 3.59 (dd, J = 4.5, 9.0 Hz, 2H), 3.16 (m, 2H), 2.79 (m, 3H), 1.92 (m, 1H), 1.77 (m, 2H), 1.49 (s, 3H), 1.19 (m, 2H), 0.80 (m, 2H), 0.59 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{23}H_{54}N_4O_7S$ calcd.: 511.2, found: 511.1.

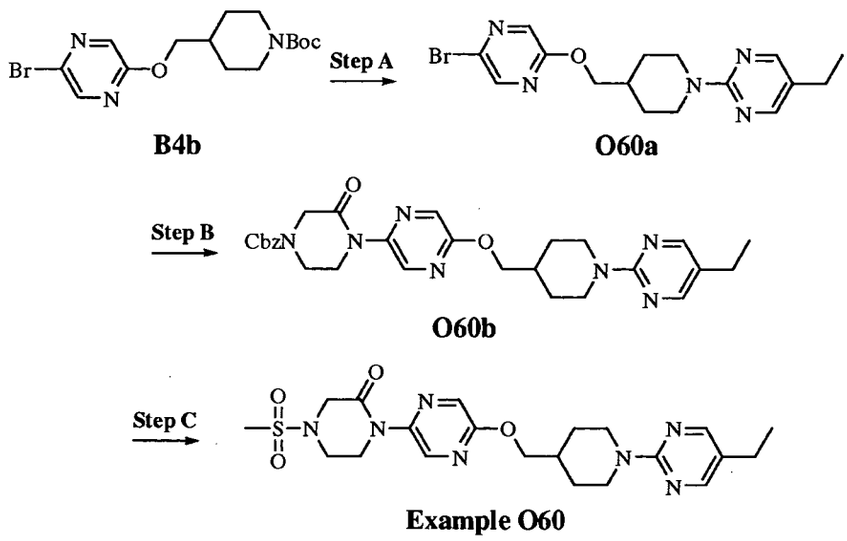
Example O59: 1-Methylcyclopropyl 4-((6-(4-(3-(azetidin-1-yl)propylsulfonyl)-2-oxopiperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate.



By following a similar procedure as the one used for preparing **O16** from **O5** except substituting **O57** for **O5**, **O59** is prepared; ^{1}H NMR (400 MHz, CD_3CN) δ 8.09 (d, J = 3.2 Hz, 1H), 7.66 (d, J = 9.2 Hz, 1H), 7.33 (dd, J = 9.2, 3.2 Hz, 1H), 4.02 (m, 2H), 4.01 (m, 2H), 3.97 (m, 2H), 3.90 (d, J = 6.4 Hz, 2H), 3.63 (m, 2H), 3.41 (m, 2H), 3.19 (m, 2H), 2.70 (m, 4H), 2.10 (m, 4H), 1.80 (m, 4H), 1.49 (s, 3H), 1.20 (m, 2H), 0.80 (m, 2H), 0.59 (m, 2H); ESIMS *m/z* for $(M+H)^+$ $C_{26}H_{40}N_5O_6S$ calcd.: 550.3, found: 550.1.

Example O60: 1-(5-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)pyrazin-2-yl)-4-(methylsulfonyl)piperazin-2-one.



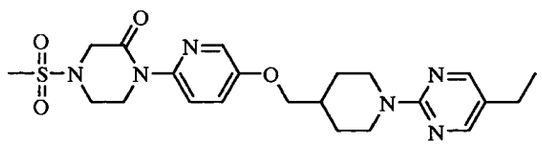


[00314] **Step A:** By following a procedure similar to the one used for preparing **E1** from **E1a**, except substituting **B4b** for **E1a**, **O60a** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{16}H_{21}BrN_5O$ calcd: 378.1, found: 378.1.

[00315] **Step B:** By following a procedure similar to the one used for preparing **O1a** from **B4b**, except substituting **O60a** for **B4b**, **O60b** is prepared; ESIMS *m/z* for $(M+H)^+$ $C_{28}H_{34}N_7O_4$ calcd: 532.3, found: 532.2.

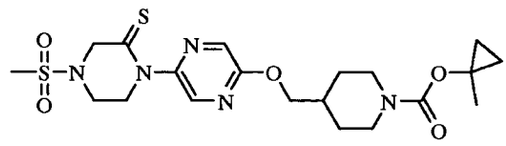
[00316] **Step C:** By following a procedure similar to the one used for preparing **O3** from **O3b**, except substituting **O60b** for **O3b**, and methanesulfonyl chloride for *n*-propanesulfonyl chloride, **O60** is prepared; ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 1.4 Hz, 1H), 8.41 (s, 2H), 8.04 (d, J = 1.4 Hz, 1H), 4.72 (m, 2H), 4.25 (d, J = 6.4, 2H), 4.14 (s, 2H), 4.09 (m, 2H), 3.68 (m, 2H), 3.21 (m, 2H), 2.94 (s, 3H), 2.60 (dd, J = 15.2, 7.6, 2H), 2.22 (m, 1H), 2.05 (m, 2H), 1.48 (m, 2H), 1.26 (dd, J = 7.6, 7.6, 3H); ESIMS *m/z* for $(M+H)^+$ $C_{21}H_{29}N_7O_4S$ calcd: 476.2, found: 476.3.

Example O61: 1-(5-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)pyridin-2-yl)-4-(methylsulfonyl)piperazin-2-one.



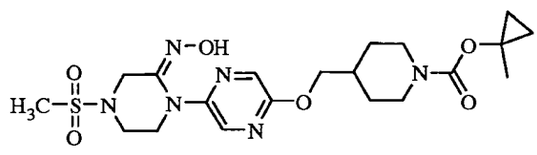
[00317] By following a procedure similar to the one used for preparing **O60** from **B4b**, except substituting **B2b** for **B4b**, **O61b** is prepared; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 2H), 8.09 (d, J = 2.9 Hz, 1H), 7.73 (d, J = 9.0 Hz, 1H), 7.25 (dd, J = 9.0, 2.9), 4.79 (m, 2H), 4.12 (m, 2H), 4.10 (s, 2H), 3.87 (d, J = 6.4, 2H), 3.64 (m, 2H), 2.92 (s, 3H), 2.91 (m, 2H), 2.46 (dd, J = 15.2, 7.6, 2H), 2.11 (m, 1H), 1.93 (m, 2H), 1.37 (m, 2H), 1.19 (dd, J = 7.6, 7.6, 3H); ESIMS *m/z* for $(M+H)^+$ $C_{22}H_{31}N_6O_4S$ calcd: 475.2, found: 475.2.

Example O62: 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)-2-thioxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



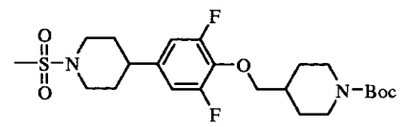
[00318] A solution of **O2** (121 mg, 0.26 mmol) in tetrahydrofuran (3 mL) is treated with Lawesson's reagent (115 mg, 0.29 mmol), sealed in a reaction vessel and stirred at 90 °C overnight. The reaction is cooled to room temperature, evaporated to dryness and purified on silica gel using a linear gradient of 0-100% ethyl acetate in hexane to afford **O62**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 1.3 Hz, 1H), 8.12 (d, J = 1.4 Hz, 1H), 4.58 (s, 2H), 4.21 (m, 2H), 4.21 (d, J = 6.5 Hz, 2H), 4.03 (m, 2H), 3.78 (m, 2H), 2.98 (s, 3H), 2.77 (m, 2H), 1.99 (m, 1H), 1.81 (m, 2H), 1.55 (s, 3H), 1.29 (m, 2H), 0.87 (m, 2H), 0.62 (m, 2H); ESIMS *m/z* for $(M+Na)^+$ $C_{20}H_{29}N_5O_5S_2Na$ calcd: 506.2, found: 506.1 ($M+Na^+$).

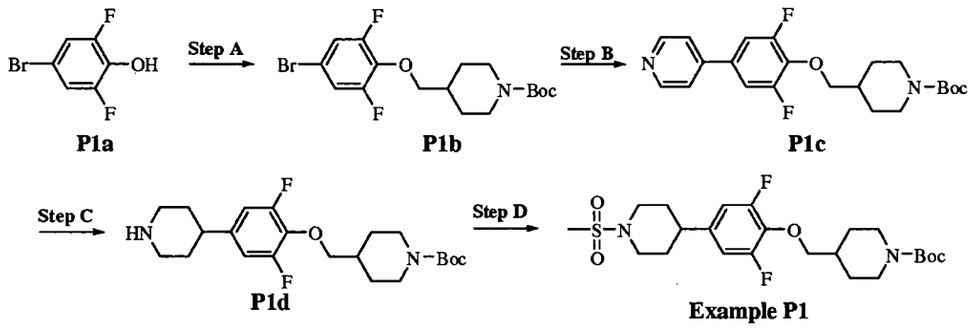
Example O63: 1-Methylcyclopropyl 4-((5-(2-(hydroxyimino)-4-(methylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



[00319] A solution of **O62** (30 mg, 0.062 mmol) in ethanol (1 mL) is treated with hydroxylamine (7 μL of a 50% solution, 0.12 mmol) sealed in a reaction vessel and stirred at 80 °C overnight. The reaction is cooled to room temperature and evaporated to dryness to afford **63**; ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.46 (d, J = 1.4 Hz, 1H), 7.96 (d, J = 1.4Hz, 1H), 4.47 (s, 2H), 4.21 (m, 2H), 4.14 (d, J = 6.5 Hz, 2H), 3.87 (m, 2H), 3.62 (m, 2H), 3.52 (m, 1H), 2.92 (s, 3H), 2.74 (m, 2H), 1.95 (m, 1H), 1.79 (m, 2H), 1.55 (s, 3H), 1.26 (m, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{20}H_{31}N_6O_6S$ $[M+H]^+$ 483.2, found 483.4.

Example P1: *tert*-Butyl 4-((2,6-difluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate.





[00320] **Step A:** A mixture of **P1a** (1.67 g, 8 mmol), *tert*-butyl 4-((methylsulfonyloxy)methyl)piperidine-1-carboxylate (2.35 g, 8 mmol), and Cs_2CO_3 (3.91 g, 12 mmol) in N,N-dimethylformamide (30 mL) is heated at 90°C overnight. The reaction mixture is poured into water (200 mL), extracted with ethyl acetate (3 x 50 mL), washed with water (2 x 30 mL), dried (Na_2SO_4) and concentrated to give **P1b;** ESIMS calcd. for $C_{17}H_{22}BrF_2NNaO_3$ $(M+Na)^+$ 428.1, found 428.2. The product is used without purification.

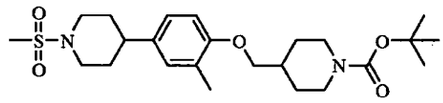
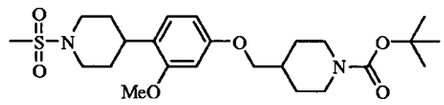
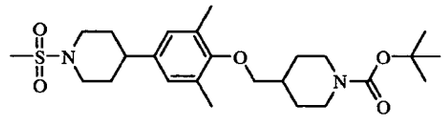
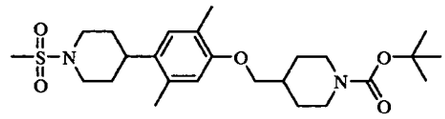
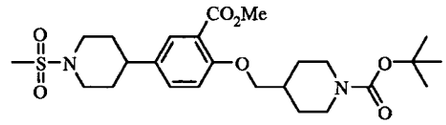
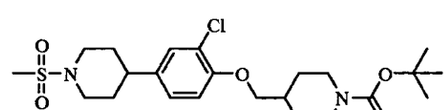
[00321] **Step B:** A mixture **P1b** (2.03 g, 5 mmol), pyridin-4-ylboronic acid (0.80 g, 6.5 mmol), Na_2CO_3 (2.65, 25 mmol), and $Pd(PPh_3)_4$ (289 mg, 0.25 mmol) in water (13

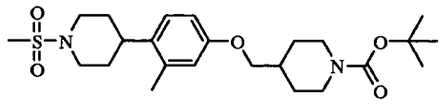
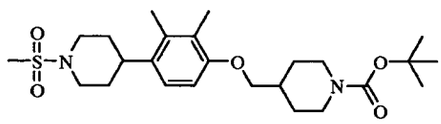
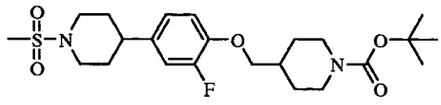
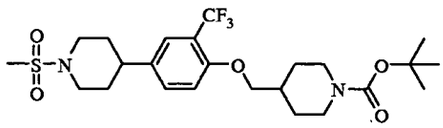
mL) and DME (52 mL)) is heated at 80°C overnight under a nitrogen atmosphere. The reaction mixture is concentrated, water (200 mL) added, extracted with ethyl acetate (3 x 100 mL), washed with water (2 x 30 mL), dried (Na_2SO_4) and concentrated. Silica gel chromatography (0% to 5% gradient of MeOH in dichloromethane) gave **P1c**; ESIMS calcd. for $C_{22}H_{27}F_2N_2O_3$ $(M+H)^+$ 405.2, found 405.2.

[00322] **Step C:** A solution **P1c** (654 mg, 1.59 mmol) and TFA (118 μL, 1.59 mmol) in EtOH (100ml) is hydrogenated using a 10% Pd/C cartridge on H-Cube (flow 1mL/min) at 70 atm and 90°C. To the resulting solution is added a saturated solution of sodiumhydrogencarbonate (1 mL) and the EtOH is evaporated. To the residue is added water (50 mL) and dichloromethane (30 mL). The aqueous phase is further extracted with dichloromethane (2 x 30 mL) and discarded. The combined organics are dried over Na_2SO_4 and concentrated to yield **P1d**; ESIMS calcd. for $C_{22}H_{33}F_2N_2O_3$ $(M+H)^+$ 411.2, found 411.2.

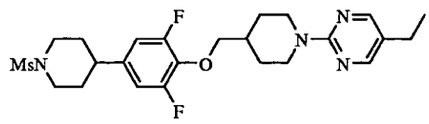
[00323] **Step D:** Methanesulfonyl chloride (117 μL, 1.5 mmol) is added dropwise to a cold (ice/water bath) solution **P1d** (411 mg, 1 mmol) and Et_3N (418 μL, 3 mmol) in dry dichloromethane (6 mL). The resulting solution is stirred at room temperature for 2 hours. The reaction mixture is added to water (40 mL) and extracted with dichloromethane (3 x 40 mL). The combined organic layers are dried (Na_2SO_4) and concentrated to yield **P1**; ^{1}H-NMR (600MHz, $CDCl_3$) δ6.74 (m, 2H), 4.14 (m, 2H), 3.94 (m, 4H), 2.82 (s, 3H), 2.75 (td, J = 12.1, 2.5 Hz, 4H), 2.53 (tt, J = 12.1, 3.6 Hz, 1H), 1.93 (m, 3H), 1.84 (m, 2H), 1.74 (m, 2H), 1.46 (s, 9H), 1.25 (qd, J = 12.4, 4.2 Hz, 2H). ESIMS calcd. for $C_{18}H_{27}F_2N_2O_3S$ $(M\text{-}Boc+H)^+$ 389.2, found 389.2.

[00324] By following a procedure similar to the one used for preparing **P1** from **P1a**, except substituting the appropriate commercially available halophenol for **P1a**, the follwing examples are prepared;

P2		^{1}H-NMR (600MHz, $CDCl_3$) δ 6.97 (m, 2H), 6.73 (d, J = 8.2 Hz, 1H), 4.15 (m, 2H), 3.92 (dt, J = 11.7, 2.1 Hz, 2H), 3.79 (d, J = 6.2 Hz, 2H), 2.81 (s, 3H), 2.75 (m, 4H), 2.52 (tt, J = 12.1, 3.6 Hz, 1H), 2.21 (s, 3H), 1.98 (m, 1H), 1.92 (m, 2H), 1.80 (m, 4H), 1.47 (s, 9H), 1.30 (qd, J = 12.4, 4.2 Hz, 2H). ESIMS calcd. for $C_{19}H_{31}N_2O_3S$ $(M\text{-}Boc+H)^+$ 367.2, found 367.2.
P3		^{1}H-NMR (600MHz, $CDCl_3$) δ 7.02 (d, J = 8.1 Hz, 1H), 6.43 (m, 2H), 4.15 (m, 2H), 3.91 (m, 2H), 3.79 (m, 5H), 2.94 (tt, J = 12.2, 3.4 Hz, 1H), 2.91 (s, 3H), 2.77 (m, 4H), 1.95 (m, 1H), 1.89 (m, 2H), 1.83 (m, 2H), 1.77 (m, 2H), 1.47 (s, 9H), 1.28 (qd, J = 12.4, 4.2 Hz, 2H). ESIMS calcd. for $C_{19}H_{31}N_2O_4S$ $(M\text{-}Boc+H)^+$ 383.2, found 383.2.
P4		^{1}H-NMR (600MHz, $CDCl_3$) δ 7.26 (s, 2H), 4.17 (m, 2H), 3.92 (m, 2H), 3.58 (d, J = 6.3 Hz, 2H), 2.81 (s, 3H), 2.75 (m, 4H), 2.48 (tt, J = 12.2, 3.6 Hz, 1H), 2.24 (s, 6H), 1.98 (m, 1H), 1.90 (m, 4H), 1.79 (m, 2H), 1.47 (s, 9H), 1.33 (qd, J = 12.4, 4.1 Hz, 2H). ESIMS calcd. for $C_{20}H_{33}N_2O_3S$ $(M\text{-}Boc+H)^+$ 381.2, found 381.2.
P5		^{1}H-NMR (600MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.58 (s, 1H), 4.15 (m, 2H), 3.94 (m, 2H), 3.77 (d, J = 6.2 Hz, 2H), 2.82 (s, 3H), 2.75 (m, 5H), 2.29 (s, 3H), 2.17 (s, 3H), 1.97 (m, 1H), 1.81 (m, 6H), 1.47 (s, 9H), 1.29 (m, 2H). ESIMS calcd. for $C_{20}H_{33}N_2O_3S$ $(M\text{-}Boc+H)^+$ 381.2, found 381.2.
P6		^{1}H-NMR (400MHz, $CDCl_3$) δ 7.63 (d, J = 2.4 Hz, 1H), 7.28 (dd, J = 8.7, 2.5 Hz, 1H), 6.89 (d, J = 8.6 Hz, 1H), 4.16 (m, 2H), 3.93 (m, 2H), 3.88 (s, 3H), 3.85 (d, J = 6.2 Hz, 2H), 2.82 (s, 3H), 2.75 (m, 4H), 2.58 (tt, J = 12.1, 3.6 Hz, 1H), 1.74-2.07 (m, 7H), 1.46 (s, 9H), 1.29 (m, 2H). ESIMS calcd. for $C_{20}H_{31}N_2O_5S$ $(M\text{-}Boc+H)^+$ 411.2, found 410.8.
P7		^{1}H-NMR (400MHz, $CDCl_3$) δ 7.20 (d, J = 2.2 Hz, 1H), 7.03 (dd, J = 8.4, 2.2 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 4.16 (m, 2H), 3.93 (m, 2H), 3.84 (d, J = 6.4 Hz, 2H), 2.82 (s, 3H), 2.75 (m, 4H), 2.53 (tt, J = 12.1, 3.6 Hz, 1H), 2.02 (m, 1H), 1.92 (m, 2H), 1.71 (m,4H), 1.46 (s, 9H), 1.29 (m, 2H). ESIMS calcd. for $C_{18}H_{28}ClN_2O_3S$ $(M\text{-}Boc+H)^+$ 387.2,

		found 386.8.
P8		^{1}H-NMR (400MHz, $CDCl_3$) δ 7.08 (d, J = 8.2 Hz, 1H), 6.71 (m, 2H), 4.14 (m, 2H), 3.94 (m, 2H), 3.77 (d, J = 6.4 Hz, 2H), 2.82 (s, 3H), 2.76 (m, 5H), 2.31 (s, 3H), 1.93 (m, 1H), 1.81 (m, 6H), 1.46 (s, 9H), 1.25 (m, 2H). ESIMS calcd. for $C_{19}H_{31}N_2O_3S$ $(M\text{-}Boc+H)^+$ 367.2, found 367.2.
P9		^{1}H-NMR (400MHz, $CDCl_3$) δ 6.99 (d, J =8.8 Hz, 1H), 6.69 (d, J = 8.7 Hz, 1H), 4.16 (m, 2H), 3.95 (m, 2H), 3.78 (d, J = 6.2 Hz, 2H), 2.72-2.84 (m, 8H), 2.24 (s, 3H), 2.18 (s, 3H), 1.83 (m, 7H), 1.47 (s, 9H), 1.30 (m, 2H). ESIMS calcd. for $C_{20}H_{33}N_2O_3S$ $(M\text{-}Boc+H)^+$ 381.2, found 381.2.
P10		^{1}H-NMR (400MHz, $CDCl_3$) δ 6.90 (m, 3H), 4.15 (m, 2H), 3.93 (m, 2H), 3.84 (d, J = 6.5 Hz, 2H), 2.82 (s, 3H), 2.75 (m, 4H), 2.54 (tt, J = 12.1, 3.6 Hz, 1H), 1.99 (m, 1H), 1.93 (m, 1H), 1.84 (m, 2H), 1.77 (m, 2H), 1.46 (s, 9H), 1.26 (m, 2H). ESIMS calcd. for $C_{18}H_{28}FN_2O_3S$ $(M\text{-}Boc+H)^+$ 371.2, found 371.2.
P11		^{1}H-NMR (400MHz, $CDCl_3$) δ 7.39 (d, J = 2.1 Hz, 1H), 7.30 (dd, J = 8.6, 2.1 Hz, 1H), 6.92 (d, J = 8.6 Hz, 1H), 4.16 (m, 2H), 3.94 (m, 2H), 3.85 (d, J = 6.1 Hz, 2H), 2.82 (s, 3H), 2.76 (m, 4H), 2.60 (tt, J = 12.1, 3.6 Hz, 1H), 2.00(m, 1H), 1.94 (m, 2H), 1.82 (m, 4H), 1.46 (s, 9H), 1.27 (m, 2H). ESIMS calcd. for $C_{19}H_{28}F_3N_2O_3S$ $(M\text{-}Boc+H)^+$ 421.2, found 421.1.

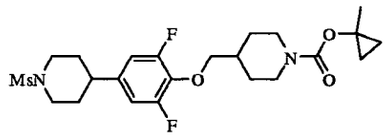
Example P12: 2-(4-((2,6-Difluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)-5-ethylpyrimidine.



[00325] By following a procedure similar to the one used for preparing **E1** from **B2**, except substituting **P1** for **B2**, **P12** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.18 (s, 2H), 6.67 (d, J = 9.2 Hz, 2H), 4.70 (m, 2H), 2.91 (dt, J = 2.0, 12.4 Hz, 2H), 2.75 (s, 3H), 2.68 (dt, J = 2.4, 12.4 Hz, 2H), 2.43 (m, 3H), 2.01 (m, 3H), 1.70 (m, 2H), 1.31 (m,

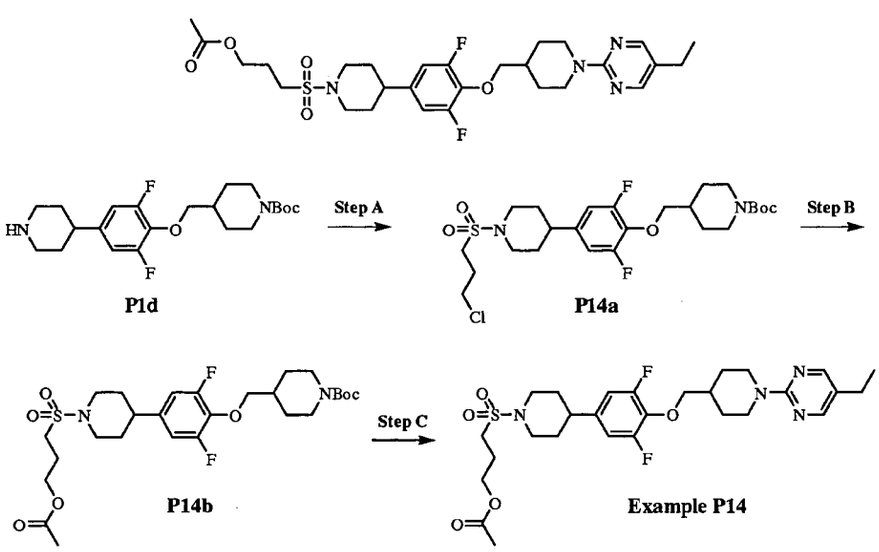
2H), 1.13 (t, J = 7.6 Hz, 3H); ESIMS calcd. for $C_{24}H_{33}F_2N_4O_3S$ $[M+H]^+$ 495.2, found 495.2.

Example P13: 1-Methylcyclopropyl 4-((2,6-difluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate.



[00326] By following a procedure similar to the one used for preparing **E3** from **B4**, except substituting **P1** for **B4**, **P12** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 6.74 (d, *J* = 8.8 Hz, 2H), 4.22 (m, 2H), 3.95 (m, 4H), 2.83 (s, 3H), 2.76 (dt, J = 2.4, 12.0 Hz, 4H), 2.55 (tt, *J* = 3.6, 12.4 Hz, 1H), 1.94 (m, 3H), 1.85 (m, 2H), 1.78 (m, 2H), 1.56 (s, 3H), 1.26 (m, 2H), 0.87 (m, 2H), 0.63 (m, 2H); ESIMS calcd. for $C_{23}H_{33}F_2N_2O_5S$ $[M+H]^+$ 487.2, found 487.2.

Example P14: 3-(4-(4-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-3,5-difluorophenyl)piperidin-1-ylsulfonyl)propyl acetate.

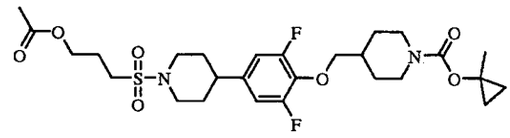


[00327] **Step A:** A solution of **P1d** (200 mg, 0.49 mmol) and 3-chloropropanesulfonyl chloride (65 μL, 0.54 mmol) in dichloromethane (10 mL) is treated with triethylamine (75 μL, 0.54 mmol) and the mixture is stirred at room temperature for 1 hour. The mixture is diluted with water (10 mL), extracted with dichloromethane, dried over $MgSO_4$, filtered and concentrated. The residue is purified on silica gel using a linear gradient of 0 to 100% ethyl acetate in hexane to afford **P14a**: ^{1}H-NMR (400MHz, $CDCl_3$) δ 6.74 (d, J = 9.2 Hz, 2H), 4.06 (m, 2H), 3.87 (m, 4H), 3.64 (t, J = 6.0 Hz, 2H), 3.04 (t, J = 6.0 Hz, 2H), 2.80 (dt, J = 2.4, 12.4 Hz, 2H), 2.65 (m, 2H), 2.49 (tt, J = 3.6, 12.4 Hz, 1H), 2.25 (m, 2H), 1.85 (m, 2H), 1.77 (m, 2H), 1.65, m, 2H), 1.39 (s, 9H), 1.18 (m, 2H); ESIMS calcd. for $C_{21}H_{30}ClF_2N_2O_5S$ $[M+H - C_4H_8]^+$ 495.2, found 495.2.

[00328] **Step B:** A solution of **P14a** (138 mg, 0.25 mmol), NaOAc (62 mg, 0.75 mmol) and NaI (38 mg, 0.25 mmol) in N,N-dimethylformamide (1 mL) is heated at 120 °C for 2 hours. The mixture is cooled, diluted with water (10 mL) and extracted with ethyl acetate (10 mL). The organic layer is washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated to provide **P14b** which is used without further purification; ESIMS calcd. for $C_{23}H_{33}F_2N_2O_7S$ $[M+H - C_4H_8]^+$ 519.2, found 519.2.

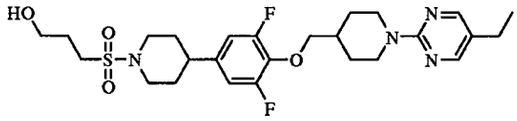
[00329] **Step C:** By following a procedure similar to the one used for preparing **E1** from **B2**, except substituting **P14b** for **B2**, **P14** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.36 (s, 2H), 6.76 (m, 2H), 4.76 (m, 2H), 4.22 (t, J = 6.4 Hz, 2H), 3.96 (m, 4H), 3.06 (m, 4H), 2.88 (dt, J = 2.4, 12.0 Hz, 2H), 2.56 (m, 3H), 2.17 (m, 3H), 2.11 (s, 3H), 2.04 (m, 2H), 1.97 (m, 2H), 1.71 (m, 2H), 1.42 (m, 2H), 1.24 (t, J = 7.6 Hz, 3H); ESIMS calcd. for $C_{28}H_{39}F_2N_4O_5S$ $[M+H]^+$ 581.3, found 581.2.

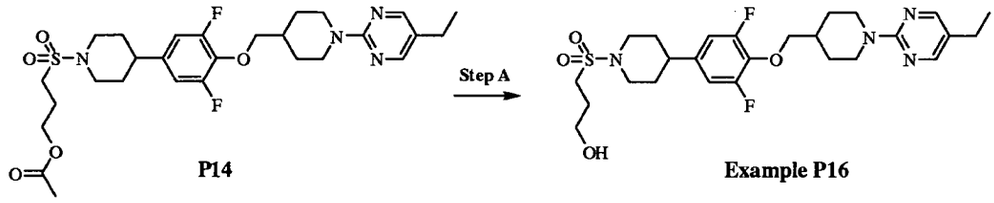
Example P15: 1-Methylcyclopropyl 4-((4-(1-(3-acetoxypropylsulfonyl)piperidin-4-yl)-2,6-difluorophenoxy)methyl)piperidine-1-carboxylate.



[00330] By following a procedure similar to the one used for preparing **P14** from **P1d**, except substituting the procedure for preparing **P13** from **P1** for **step C**, **P15** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 6.75 (m, 2H), 4.22 (t, J = 6.0 Hz, 2H), 3.95 (m, 4H), 3.03 (m, 2H), 2.88 (dt, J = 2.4, 12.4 Hz, 2H), 2.76 (m, 2H), 2.57 (m, 1H), 2.17 (m, 2H), 2.09 (s, 3H), 1.92 (m, 2H), 1.88 (m, 2H), 1.72 (m, 2H), 1.56 (s, 3H), 1.25 (m, 2H), 0.87 (m, 2H), 0.63 (m, 2H); ESIMS calcd. for $C_{27}H_{39}F_2N_2O_7S$ $[M+H]^+$ 573.2, found 573.2.

Example P16: 3-(4-(4-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-3,5-difluorophenyl)piperidin-1-ylsulfonyl)propan-1-ol.

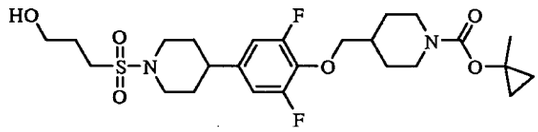




P14 **Example P16**

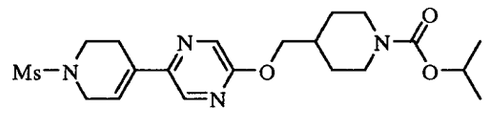
[00331] A solution of **P14** (30 mg, 0.05 mmol) in tetrahydrofuran (3 mL) is treated with LiOH hydrate (50 mg, 1.2 mmol) and the mixture is heated at 90 °C for 12 hours. The mixture is filtered, concentrated and purified by mass triggered reverse phase HPLC to afford **P16**; ^{1}H-NMR (400MHz, $CDCl_3$) δ 8.36 (s, 2H), 6.67 (m, 2H), 4.68 (m, 2H), 3.88 (m, 5H), 3.74 (t, J = 5.6 Hz, 2H), 3.00 (m, 4H), 2.78 (dt, J = 2.4, 12.0 Hz, 2H), 2.45 (m, 3H), 2.17 (m, 3H), 2.11 (s, 3H), 2.04 (m, 4H), 1.97 (m, 2H), 1.84 (m, 2H), 1.65 (m, 2H), 1.31 (m, 2H), 1.47 (t, J = 7.6 Hz, 3H); ESIMS calcd. for $C_{26}H_{37}F_2N_4O_4S$ $[M+H]^+$ 539.3, found 539.2.

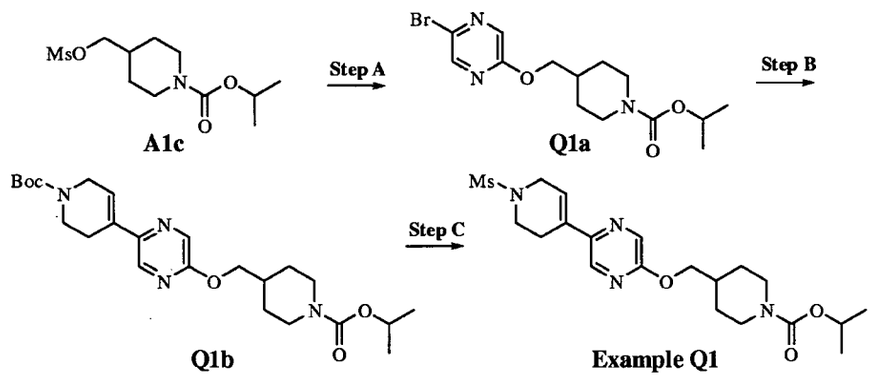
Example P17: 1-Methylcyclopropyl 4-((2,6-difluoro-4-(1-(3-hydroxypropylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate.



[00332] By following a procedure similar to the one used for preparing **P16** from **P14**, except substituting **P15** for **P14**, **P17** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 6.66 (m, 2H), 3.85 (m, 4H), 3.74 (t, *J* = 6.0 Hz, 2H), 3.02 (m, 2H), 2.79 (dt, *J* = 2.4, 12.0 Hz, 2H), 2.71 (m, 2H), 2.48 (m, 2H), 2.03 (m, 2H), 1.80 (m, 5H), 1.69 (m, 2H), 1.48 (s, 3H), 1.19 (m, 2H), 0.87 (m, 2H), 0.63 (m, 2H); ESIMS calcd. for $C_{25}H_{37}F_2N_2O_6S$ $[M+H]^+$ 531.2, found 531.2.

Example Q1: Isopropyl 4-((5-(1,2,3,6-tetrahydro-1-methanesulfonylpyridin-4-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.





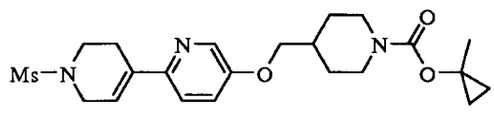
[00333] **Step A**: A solution of **A1c** (0.86 g, 3.1 mmol) and 2-bromo-5-hydroxypyrazine (0.52 g, 3.0 mmol) in dry acetonitrile (7 mL) is treated with powdered cesium carbonate (1.62 g, 5 mmol) and the mixture is stirred at 60 °C for 24 hours.

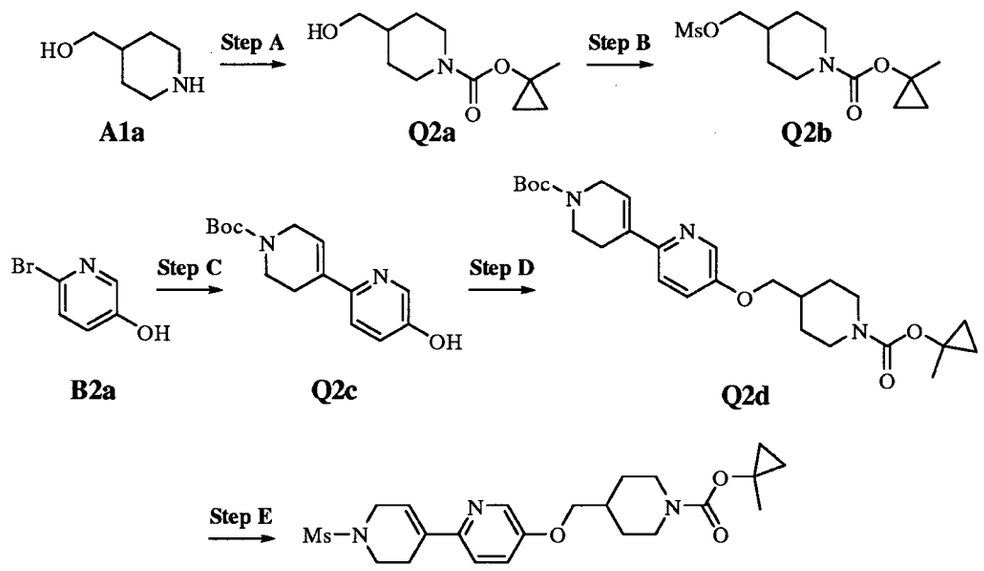
Filtration, concentration, and purification on silica gel using a linear gradient of 0 to 100% ethyl acetate in hexane affords **Q1a**; ESIMS calcd. for $C_{14}H_{21}BrN_3O_3$ ($M+H^+$) 358.1, found 358.0.

[00334] **Step B**: To a solution of **Q1a** (83.5 mg, 0.2 mmol) in 1,2-dimethoxyethane (1.5mL) are added *tert*-butyl 5,6-dihydro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-1(2*H*)-carboxylate (66.7 mg, 0.2 mmol), powdered potassium carbonate (0.10 g, 0.7 mmol), and water (0.5 g). The mixture is degassed using argon, then tetrakis-(triphenylphosphino)palladium(0) (0.08g, 0.07 mmol) is added and the mixture is heated to 180 °C for 5 min in a microwave reactor. Cooling, extraction with ethyl acetate, washing with water and brine, drying over Na_2SO_4 and concentration, followed by purification on silica gel using a linear gradient of 5 to 70% ethyl acetate in hexane affords **Q1b**; ESIMS calcd. for $C_{24}H_{37}N_4O_5$ ($M+H^+$) 461.3, found 461.1.

[00335] **Step C**: To a solution of **Q1b** (0.2 mmol) in dioxane (2 mL) is added hydrogen chloride in dioxane (4N, 1 mL), slowly, with stirring. The resulting solution is stirred at room temperature for 4 hours. After removing the solvent, the residue is dissolved in dichloromethane (3 mL) and treated with triethylamine (0.2 mL, 1.4 mmol). Then methanesulfonyl chloride (0.04 mL, 0.5 mmol) is added dropwise, with stirring, over 5 minutes. The resulting solution is stirred at room temperature for 2 hours. The solvent is removed and the resiude is purified using mass-triggered reverse phase HPLC to yield **Q1**; ESIMS calcd. for $C_{20}H_{31}N_4O_5S$ ($M+H^+$) 439.2, found 439.1.

Example Q2: 1-Methylcyclopropyl 4-((6-(1,2,3,6-tetrahydro-1-methanesulfonylpyridin-4-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate.





Example Q2

[00336] **Step A**: A solution of **A1a** (0.51 g, 4.4 mmol) in dichloromethane (7 mL) is treated with triethylamine (0.9 mL, 6.4 mmol) in one portion, followed by **E3b** (0.96 g, 4 mmol). The suspension is stirred at room temperature for 24 hours, diluted with more dichloromethane (25 mL), washed with water, saturated aqueous sodiumhydrogencarbonate (3 x 25 mL), and saturated aqueous ammonium chloride, dried over $MgSO_4$ and concentrated to yield **Q2a**; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 4.13 (br. s, 1H), 4.03 (br. s, 1H), 3.50 (m, 2H), 2.71 (t, J = 12 Hz, 2H), 1.67 (m, 3H), 1.38 (br. s, 1H), 1.54 (s, 3H), 1.14 (br. s, 2H), 0.86 (m, 2H), 0.62 (m, 2H); ESIMS calcd. for $C_{11}H_{20}NO_3$ ($M+H^+$) 214.1, found 214.1.

[00337] **Step B**: To a solution of **Q2a** (0.71 g, 3.4 mmol) in dichloromethane (20 mL) is added triethylamine (0.9 mL, 6.4 mmol) in one portion. The resulting mixture is cooled in an ice/water bath and methanesulfonyl chloride (0.35 mL, 4.5 mmol) is added slowly, with stirring. The bath is removed and the resulting solution is stirred at room temperature for 2 hours. The reaction mixture is diluted with more dichloromethane (20 mL), washed with water and saturated aqueous ammonium chloride, dried over $MgSO_4$ and concentrated to yield **Q2b**; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 4.22 (br. s, 2H), 4.07 (s, 2H), 3.23 (m, 1H), 3.17 (s, 3H), 2.72 (m, 2H), 1.92 (m, 1H), 1.74 (m, 2H), 1.54 (s,

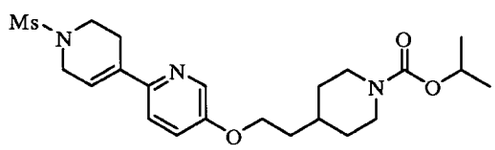
3H), 1.22 (br. s, 2H), 0.86 (m, 2H), 0.63 (m, 2H); ESIMS calcd. for $C_{12}H_{22}NO_5S$ ($M+H^+$) 292.1, found 292.0.

[00338] **Step C**: To a solution of **B2a** (0.1 g, 0.6 mmol) in 1,2-dimethoxyethane (1.5mL) is added *tert*-butyl 5,6-dihydro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-1(2*H*)-carboxylate (0.13 g, 0.4 mmol), powdered potassium carbonate (0.15 g, 1.1 mmol), and water (0.5 g). The mixture is degassed using argon, then tetrakis-(triphenylphosphino)palladium(0) (0.08g, 0.07 mmol) is added and the mixture is heated to 180 °C for 5 min in a microwave reactor. Cooling, extraction with ethyl acetate, washing with water and brine, drying over Na_2SO_4 and concentration, followed by purification on silica gel using a linear gradient of 5 to 100% ethyl acetate in hexane affords **Q2c**. ESIMS calcd. for $C_{15}H_{21}N_2O_3$ ($M+H^+$) 277.2, found 277.0.

[00339] **Step D**: A solution of **Q2b** (0.05 g, 0.17 mmol) and **Q2c** (0.04 g, 0.15 mmol) in dry acetonitrile (2 mL) is treated with powdered cesium carbonate (0.1 g, 0.3 mmol) and the mixture is stirred at 60 °C for 24 hours. Filtration, concentration, and purification on silica gel using a linear gradient of 0 to 100% ethyl acetate in hexane affords **Q2d**; ESIMS calcd. for $C_{26}H_{38}N_3O_5$ ($M+H^+$) 472.3, found 472.0.

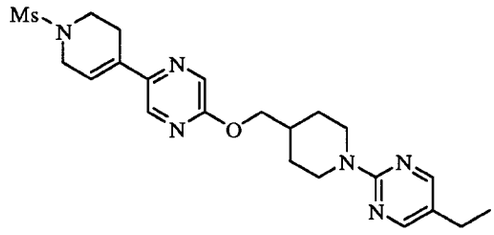
[00340] **Step E**: To a solution of **Q2d** (0.15 mmol) in dioxane (2 mL) is added hydrogen chloride in dioxane (4N, 0.5 mL), slowly, with stirring. The resulting solution is stirred at room temperature for 4 hours. The solvent is removed and the residue is dissolved in dichloromethane (3 mL) and treated with triethylamine (0.1 mL, 0.7 mmol) followed by methanesulfonyl chloride (0.025 mL, 0.3 mmol) dropwise, with stirring, over 5 minutes. The resulting solution is stirred at room temperature for 2 hours. The solvent is removed and the resulting residue is purified by mass triggered HPLC to afford **Q2**; ESIMS calcd. for $C_{22}H_{32}N_3O_5S$ ($M+H^+$) 450.2, found 450.1.

Example Q3: Isopropyl 4-(2-(6-(1,2,3,6-tetrahydro-1-methanesulfonylpyridin-4-yl)pyridin-3-yloxy)ethyl)piperidine-1-carboxylate.

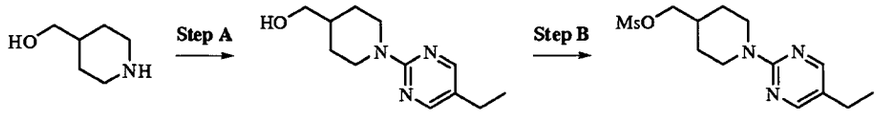


[00341] By following a procedure similar to the one used for preparing **Q1** from **A1c**, except substituting isopropyl 4-(2-(methylsulfonyloxy)ethyl)piperidine-1-carboxylate for **A1c**, **Q3** is prepared; ESIMS calcd. for $C_{22}H_{34}N_3O_5S$ ($M+H^+$) 452.2, found 452.1.

Example Q4: 2-(4-((5-(1,2,3,6-Tetrahydro-1-methanesulfonylpyridin-4-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine.



[00342] By following a procedure similar to the one used for preparing **Q2** from **A1a**, except substituting **B4a** for **B2a** in **Step A** and **Q4b** (see scheme below) for **Q2b** in **Step D**, **Q4** is prepared; ESIMS calcd. for $C_{22}H_{31}N_6O_3S$ ($M+H^+$) 459.2, found 459.1.



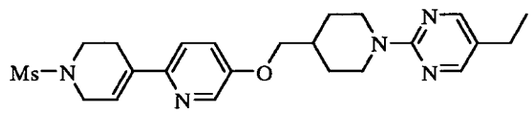
A1a **Q4a** **Q4b**

[00343] **Step A**: A solution of **A1a** (1.03 g, 9 mmol) and 2-chloro-5-ethylpyrimidine (1.1 mL, 9 mmol) in dimethylacetamide (7 mL) is treated with powdered cesium carbonate (4 g, 12.3 mmol) and the suspension is stirred at 75 °C for 48 hours. The reaction is then diluted with water (150 mL) and extracted with ethyl acetate/diethyl ether (1:1) (2 x 100 mL). The combined extracts are washed with water, saturated aqueous ammonium chloride, and brine, dried over Na_2SO_4 and concentrated to yield **Q4a**; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 8.16 (s, 2H), 4.74 (m, 2H), 3.53 (t, J = 5.9 Hz, 2H), 2.87 (td, J = 13.2, 2.4 Hz, 2H), 2.45 (q, J =7.6 Hz, 2H), 1.85 (m, 2H), 1.77 (m, 1H),

1.44 (t, J = 5.5 Hz, 1H), 1.23 (m, 2H), 1.18 (t, J = 7.6 Hz, 3H); ESIMS calcd. for $C_{12}H_{20}N_3O$ ($M+H^+$) 222.2, found 222.1.

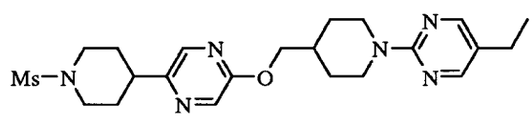
[00344] **Step B**: To a solution of **Q4a** (0.92 g, 4.2 mmol) in dichloromethane (20 mL) is added triethylamine (1.0 mL, 7.1 mmol) in one portion. The resulting mixture is cooled in an ice/water bathand methanesulfonyl chloride (0.45 mL, 5.8 mmol) is added slowly, with stirring. The bath is removed and the resulting solution is stirred at room temperature for 2 hours. The reaction mixture is diluted with more dichloromethane (20 mL), washed with water and saturated aqueous ammonium chloride, dried over $MgSO_4$ and concentrated to yield **Q4b**; ^1H NMR ($CDCl_3$, 400.13 MHz): ^1H NMR ($CDCl_3$, 400.13 MHz): δ 8.17 (s, 2H), 4.78 (m, 2H), 4.09 (d, J = 6.6 Hz, 2H), 3.02 (s, 3H), 2.88 (td, J = 13.2, 2.6 Hz, 2H), 2.46 (q, J =7.6 Hz, 2H), 2.05 (m, 2H), 1.84 (m, 1H), 1.29 (ddd, J = 4.4, 12.4, 12.7 Hz, 2H), 1.19 (t, J = 7.6 Hz, 3H); ESIMS calcd. for $C_{13}H_{22}N_3O_3S$ ($M+H^+$) 300.1, found 300.0.

Example Q5: 2-(4-((6-(1,2,3,6-Tetrahydro-1-methanesulfonylpyridin-4-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine.

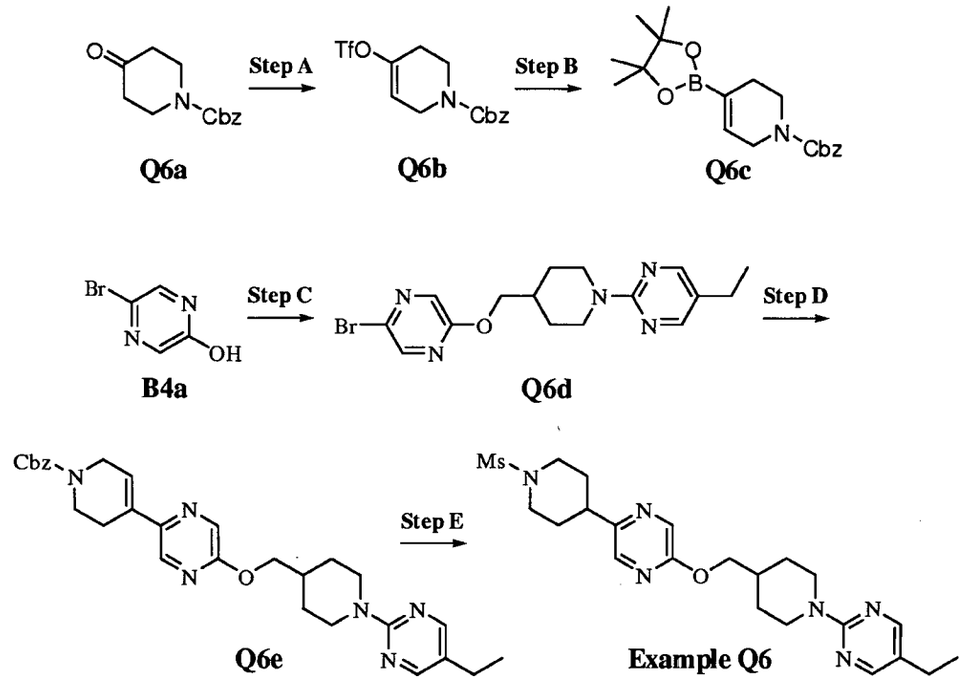


[00345] By following a procedure similar to the one used for preparing **Q2** from **Q2b**, except substituting **Q4b** for **Q2b**, **Q5** is prepared; ESIMS calcd. for $C_{23}H_{32}N_5O_3S$ ($M+H^+$) 458.2, found 458.1.

Example Q6: 2-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-5-(1-methanesulfonylpiperidin-4-yl)pyrazine.



[00346] Example Q6 may be made from Q5 above, by hydrogenation with palladium on carbon. However, an alternate synthesis is as follows:



[00347] **Step A**: A solution of diisopropylamine (2 mL, 14.2 mmol) in dry tetrahydrofuran (10 mL) at –78 °C under nitrogen is treated with *n*-Butyllithium (2.46 M solution in hexanes; 5 mL, 12.25 mmol) and the mixture is stirred for 15 min at –78 °C. A solution of **Q6a** (2.55 g, 10.9 mmol) in dry tetrahydrofuran (25 mL) is slowly added and stirring is continued at –78 °C for 2 hours. N-Phenyltriflimide (4.42 g, 12.4 mmol) in dry tetrahydrofuran (25 mL) is added dropwise at –78 °C. The mixture is stirred at –78 °C for 2.5 hours and at room temperature for 30 minutes. Dilution with ethyl acetate (200 mL) and saturated aqueous ammonium chloride (50 mL), washing with water and brine, drying over Na_2SO_4 and concentration followed by purification on silica gel using a linear gradient of 0 to 40% ethyl acetate in hexane affords **Q6b**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.3 - 7.4 (m, 5H), 5.78 (m, 1H), 5.16 (s, 2H), 4.13 (br. s, 2H), 3.72 (br. s, 2H), 2.47 (br. s, 2H); ^{19}F NMR ($CDCl_3$, 376 MHz): δ –75.32; ESIMS calcd. for $C_{14}H_{15}F_3NO_5S$ ($M+H^+$) 366.1, found 366.1.

[00348] **Step B**: To a solution of **Q6a** (1.22 g, 3.3 mmol) in 1,4-dioxane (25 mL) is added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.02 g, 4 mmol), 1,1'-bis(diphenylphosphino)ferrocene (0.08 g, 0.14 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (0.11 g, 0.13 mmol) and potassium acetate powder (1.26 g, 12.8 mmol). The mixture is degassed using argon and stirred at 80 °C for 18 hours. Cooling, diluting with water (50 mL), extraction with ethyl acetate, washing with water and brine, drying over Na_2SO_4 and concentration, followed by by purification on silica gel using a linear gradient of 0 to 50% ethyl acetate in hexane affords **Q6b**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.3 - 7.4 (m, 5H), 6.5 (m, 1H), 5.16 (s, 2H), 4.05 (m, 2H), 3.54 (m, 2H), 2.27 (br. s, 2H), 1.28 (s, 12H); ESIMS calcd. for $C_{19}H_{27}BNO_4$ ($M+H^+$) 344.2, found 344.1.

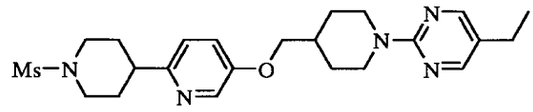
[00349] **Step C**: A solution of **B4a** (0.84 g, 4.8 mmol) and intermediate **Q4b** (1.28 g, 4.3 mmol) in dry dimethylacetamide (25 mL) is treated with powdered cesium carbonate (2.31 g, 7.1 mmol) and the mixture is stirred at 65 °C for 24 hours. Filtration, concentration, and by purification on silica gel using a linear gradient of 10 to 50% ethyl acetate in hexane affords **Q4d**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 8.17 (s, 2H), 8.16 (d, J = 1.4 Hz, 1H), 8.02 (d, J = 1.4 Hz, 1H), 4.77 (m, 2H), 4.17 (d, J = 6.6 Hz, 2H), 2.88 (td, J = 13.1, 2.6 Hz, 2H), 2.46 (q, J =7.6 Hz, 2H), 2.10 (m, 2H), 1.89 (m, 1H), 1.34 (ddd, J = 4.3, 12.4, 12.6 Hz, 2H), 1.19 (t, J = 7.6 Hz, 3H); ESIMS calcd. for $C_{16}H_{21}BrN_5O$ ($M+H^+$) 378.1, found 378.1.

[00350] **Step D**: To a solution of **Q6d** (0.8 g, 2.1 mmol) in 1,2-dimethoxyethane (5 mL) is added intermediate **Q6c** (0.91 g, 2.7 mmol), powdered potassium carbonate (0.72 g, 5.2 mmol), and water (0.5 g). The mixture is degassed using argon, then tetrakis-(triphenylphosphino)palladium(0) (0.23 g, 0.2 mmol) is added and the mixture is heated to 180 °C for 20 min in a microwave reactor. Cooling, dilution with ethyl acetate, drying over Na_2SO_4 and concentration, followed by purification on silica gel using a linear gradient of 10 to 50% ethyl acetate in hexane affords **Q6e**; ESIMS calcd. for $C_{29}H_{35}N_6O_3$ ($M+H^+$) 515.3, found 515.1.

[00351] **Step E**: A solution of **Q6e** (0.6 g, 1.2 mmol) in ethyl acetate (100 mL) and ethanol (40 mL) is treated with palladium on carbon (5%; 0.85 g, 0.4 mmol) and the mixture is saturated with hydrogen gas and is then stirred at room temperature under 1

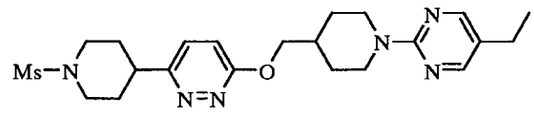
atmosphere of hydrogen for 3 hours. After filtration of the reaction through a pad of Celite® and concentration the residue is dissolved in dichloromethane (10 mL) and triethylamine (0.6 mL, 4.3 mmol). Methanesulfonyl chloride (0.15 mL, 1.9 mmol) is then slowly added, with stirring. After 2 hours, the mixture is concentrated and purified on silica gel using a linear gradient of 10 to 65% ethyl acetate in hexane to afford **Q6**. ESIMS calcd. for $C_{22}H_{33}N_6O_3S$ ($M+H^+$) 461.2, found 461.1.

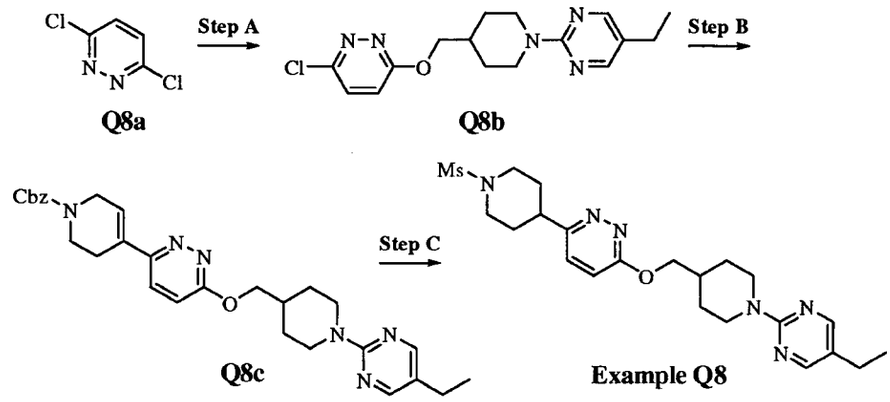
Example Q7: 2-(4-((6-(1-Methanesulfonylpiperidin-4-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine.



[00352] By following a procedure similar to the one used for preparing **Q6** from **B4a**, except substituting **B2a** for **B4a** in **Step C**, **Q7** is prepared; ESIMS calcd. for $C_{23}H_{34}N_5O_3S$ ($M+H^+$) 460.2, found 460.1.

Example Q8: 3-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-6-(1-methanesulfonylpiperidin-4-yl)pyridazine.





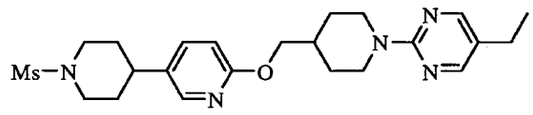
[00353] **Step A**: A solution of **Q8a** (0.64 g, 2.9 mmol) and **Q4a** (0.49 g, 3.3 mmol) in dry dimethylacetamide (6 mL) is treated with powdered potassium carbonate (0.7 g, 5.0 mmol) and the mixture is stirred at 150 °C for 2 days. Cooling, dilution with water (100 mL), extraction with ethyl acetate (2 x 100 mL), drying over Na_2SO_4, filtration, concentration, and purification on silica gel using a linear gradient of 10 to 100% ethyl acetate in hexane affords **Q8b**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 8.17 (s, 2H), 7.67 (d, J = 9.2 Hz, 1H), 6.96 (d, J = 9.2 Hz, 1H), 4.77 (m, 2H), 4.37 (d, J = 6.6 Hz, 2H), 2.90 (td, J = 13.1, 2.6 Hz, 2H), 2.46 (q, J =7.6 Hz, 2H), 2.15 (m, 2H), 1.89 (m, 1H), 1.36 (ddd, J = 4.3, 12.4, 12.6 Hz, 2H), 1.19 (t, J = 7.6 Hz, 3H); ESIMS calcd. for $C_{16}H_{21}ClN_5O$ ($M+H^+$) 334.1, found 334.1.

[00354] **Step B**: To a solution of **Q8b** (0.11 g, 0.3 mmol) in 1,2-dimethoxyethane (2 mL) is added intermediate **Q6b** (0.15 g, 0.4 mmol), powdered potassium carbonate (0.18 g, 1.3 mmol), and water (0.5 g). The mixture is degassed using argon, then tetrakis-(triphenylphosphino)palladium(0) (0.05 g, 0.04 mmol) is added and the mixture is heated to 180 °C for 20 min in a microwave reactor. Cooling, dilution with ethyl acetate, drying over Na_2SO_4 and concentration, followed by purification on silica gel using a linear gradient of 10 to 75% ethyl acetate in hexane affords **Q8c**; ESIMS calcd. for $C_{29}H_{35}N_6O_3$ ($M+H^+$) 515.3, found 515.1.

[00355] **Step C**: A solution of **Q8c** (0.15 g, 0.3 mmol) in ethyl acetate (20 mL) and ethanol (20 mL) is treated with palladium black on carbon (5%; 0.4 g, 0.2 mmol), saturated with hydrogen and then stirred at room temperature under 1 atmosphere of

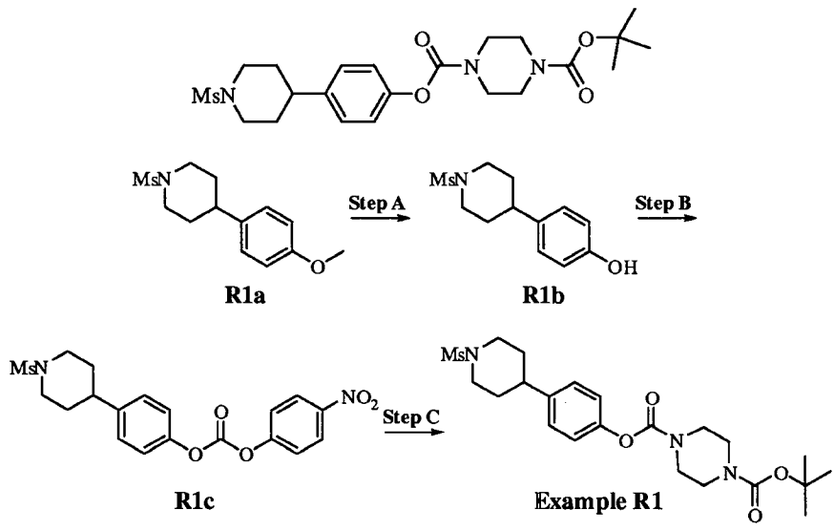
hydrogen for 6 hours. After exchanging the atmosphere for N_2, the reaction is filtered through a pad of Celite® and concentrated. The resulting oil is dissolved in dichloromethane (10 mL) and triethylamine (0.3 mL, 2.1 mmol). Methanesulfonyl chloride (0.05 mL, 0.6 mmol) is then slowly added, with stirring. After 2 hours, the mixture is concentrated and purified using mass-triggered reverse phase HPLC to afford **Q8**; ESIMS calcd. for $C_{22}H_{33}N_6O_3S$ ($M+H^+$) 461.2, found 461.1.

Example Q9: 2-(4-((5-(1-Methanesulfonylpiperidin-4-yl)pyridin-2-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine.



By following a procedure similar to the one used for preparing **Q8** from **Q8a**, except substituting **C1a** for **8a**, **Q9** is prepared; ESIMS calcd. for $C_{23}H_{34}N_5O_3S$ ($M+H^+$) 460.2, found 460.2.

Example R1: 1-*tert*-Butyl 4-(4-(1-(methylsulfonyl)piperidin-4-yl)phenyl) piperazine-1,4-dicarboxylate.

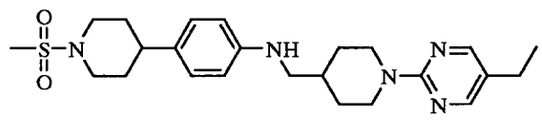


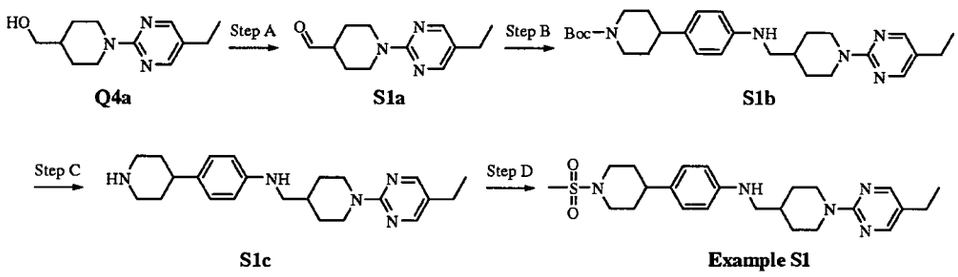
[00356] **Step A:** A solution of **R1a** (2.2 g, 8.2 mmol) in dichloromethane (10 mL) is cooled in an ice/water bath and treated with neat BBr_3 (9.21 g, 37 mmol). The reaction is stirred at ice bath temperature for 10 minutes and at room temperature for 1 hour. The reaction is then poured on to crushed ice and allowed to quenchours. The resulting solid is collected and dried to afford **R1b**; ESIMS calcd. for $C_{12}H_{17}NO_3S$ ($M+H^+$) 256.1, found 256.1.

[00357] **Step B:** A solution of **R1b** (100 mg, 0.39 mmol) and nitrophenyl chloroformate (87 mg, 0.43 mmol) in acetonitrile (5 mL) is treated with K_2CO_3 (108 mg, 0.78 mmol) and the mixture is stirred at room temperature for 2 hours, then is filtered, concentrated, and purified on silica gel using a linear gradient of 0 to 100% ethyl acetate in hexane to afford **R1c**; ESIMS calcd. for $C_{19}H_{21}N_2O_7S$ $[M+H]^+$ 421.1, found 421.1.

[00358] **Step C:** A solution of **R1c** (41 mg, 0.10 mmol), 1-Boc-piperazine (20 mg, 0.11 mmol) and triethylamine (68 μL, 0.50 mmol) in 1,2-dichloroethane (5 mL) is heated at 50 °C for 12 hours. The mixture is concentrated *in vacuo* and purified purified using mass-triggered reverse phase HPLC to afford **R1**; ^{1}H-NMR (400MHz, $CDCl_3$) δ 7.12 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 3.87 (m, 3H), 3.56 (m, 2H), 3.45 (m, 6H), 2.75 (s, 3H), 2.70 (m, 3H), 2.55 (m, 2H), 1.90 (m, 3H), 1.77 (m, 3H), 1.42 (s, 9H); ESIMS calcd. for $C_{22}H_{33}N_3NaO_6S$ $[M+Na]^+$ 490.2, found 490.1.

Example S1: *N*-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methyl)-4-(1-(methylsulfonyl)piperidin-4-yl)aniline.





[00359] **Step A:** A solution of **Q4a** (444 mg, 2mmol) in anhydrous dichloromethane (5 mL) is added to a solution of Dess-Martin periodinane (1.018 g, 2.4 mmol) in anhydrous dichloromethane (10 mL) and stirred overnight at room temperature. Additional dichloromethane (30 mL) is added and the reaction is filtered through Celite® and concentrated. Purification on silica gel using a linear gradient of 0 to 50% ethyl acetate in hexane to affords **S1a**; ESIMS calcd. for $C_{12}H_{18}N_3O$ ($M+H^+$) 220.1, found 220.1.

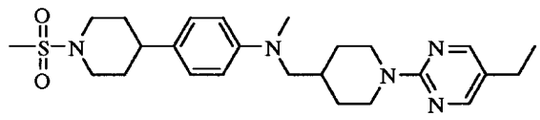
[00360] **Step B:** A mixture of **S1a** (318 mg, 1.5 mmol), *tert*-butyl 4-(4-aminophenyl)piperidine-1-carboxylate (482 mg, 1.74 mmol), and $NaBH(OAc)_3$ (636 mg, 3 mmol) in dichloromethane (7 mL) is stirred at room temperature for 5 hours. The reaction is quenched with water (20 mL) and extracted with dichloromethane (3 x 20 mL), washed with water (20 mL), dried (Na_2SO_4), and concentrated. Purification on silica gel using a linear gradient of 0 to 50% ethyl acetate in hexane to affords **S1b**; ESIMS calcd. for $C_{28}H_{42}N_5O_2$ ($M+H^+$) 480.3, found 480.4.

[00361] **Step C:** A solution of **S1b** (600 mg, 1.25 mmol) in MeOH (10 mL) is treated with a 4 M solution of HCl in dioxane (25 mL, 100 mmol) and stirred at room temperature overnight. The reaction mixture is concentrated, dioxane (20 mL) added and concentrated again to form the hydrochloride salt of **S1c**; ESIMS calcd. for $C_{23}H_{34}N_5$ ($M+H^+$) 380.3, found 380.3.

[00362] **Step D:** A cold (0°C) mixture of **S1c** (810 mg, 1.25 mmol) and triethylamine (0.892 mL, 6.4 mmol) in dichloromethane (30 mL) is treated with methanesulfonyl chloride (0.152 mL, 1.96 mmol) dropwise and stirred at room temperature for 3 hours. Additional triethylamine (0.5 mL, 3.6 mmol) and methanesulfonyl chloride (0.076 mL, 0.98 mmol) are added and the reaction is stirred at

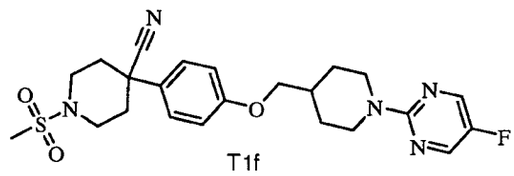
room temperature for another 30 minutes. The reaction is quenched with water (20 mL), extracted with dichloromethane (3 x 20 mL), washed with water (20 mL), dried over Na_2SO_4, and concentrated. Purification using mass-triggered reverse phase HPLC affords **S1**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (s, 2H), 7.05 (m, 2H), 6.70 (m, 2H), 4.61 (m, 2H), 3.64 (m, 2H), 2.96 (m, 2H), 2.88 (s, 3H), 2.80 (m, 4H), 2.42 (q, J = 7.6 Hz, 2H), 1.84 (m, 5H), 1.60 (m, 2H), 1.12 (m, 5H); ESIMS calcd. for $C_{24}H_{36}N_5O_2S$ ($M+H^+$) 458.3, found 458.3.

Example S2: *N*-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methyl)-*N*-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)aniline.

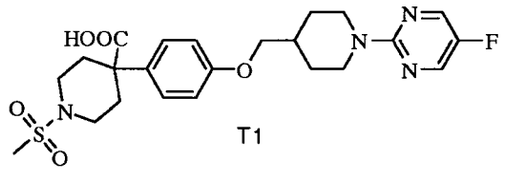


[00363] A solution of **S1** (46 mg, 0.1 mmol) in tetrahydrofuran (1 mL) is added dropwise to an ice-cold solution of 10% aqueous H_2SO_4 (0.2 mL) and 37% aqueous formaldehyde (0.1 mL, 1.2 mmol) in tetrahydrofuran (0.5 mL). $NaBH_4$ (30 mg, 0.79 mmol) is added and the reaction mixture is warmed to room temperature. After stirring for 30 minutes the reaction is quenched with 0.2 M NaOH (10 mL) and extracted with ethyl acetate (3 x 15 mL), washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The compound is purified using mass-triggered reverse phase HPLC to afford **S2**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23 (s, 2H), 7.08 (m, 2H), 6.68 (m, 2H), 4.60 (m, 2H), 3.64 (m, 2H), 3.19 (m, 2H), 2.92 (bs, 3H), 2.88 (s, 3H), 2.78 (m, 4H), 2.42 (q, J = 7.6 Hz, 2H), 1.93 (m, 1H), 1.81 (m, 2H), 1.62 (m, 4H), 1.12 (m, 5H); ESIMS calcd. for $C_{25}H_{38}N_5O_2S$ ($M+H^+$) 472.3, found 472.3.

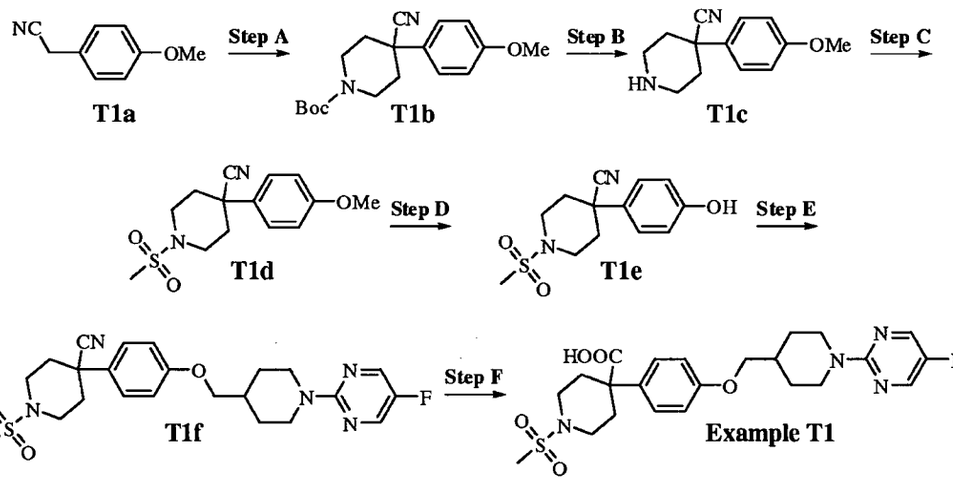
Examples T1f and T1: 4-(4-((1-(5-fluoropyrimidin-2-yl)piperidin-4-yl)methoxy)phenyl)-1-(methylsulfonyl)piperidine-4-carbonitrile and 4-(4-((1-(5-fluoropyrimidin-2-yl)piperidin-4-yl)methoxy)phenyl)-1-(methylsulfonyl)piperidine-4-carboxylic acid



T1f



T1



[00364] **Step A:** To an ice-cold suspension of NaH (60% in oil, 120 mg, 3 mmol) in anhydrous N, N-dimethylformamide (2 mL) is added **T1a** (142 μL, 1.05 mmol) and stirred for 30 minutes under a nitrogen atmosphere. To the resulting brown solution is added *tert*-butyl bis(2-chloroethyl)carbamate (242 mg, 1 mmol) in N,N-dimethylformamide (0.2 mL) and the cooling bath is removed after 15 min. The reaction mixture is heated overnight at 75 °C, cooled to room temperature and quenched with water (1 mL). More water is added (50 mL) and the reaction is extracted with dichlormethane (3 x 30 mL), dried over Na_2SO_4 and concentrated. Purification on silica gel using a linear gradient of 0 to 50% ethyl acetate in hexane to affords **T1b;** ^{1}H-NMR

(400MHz, $CDCl_3$) δ 7.38 (m, 2H), 6.93 (m, 2H), 4.26 (m, 2H), 3.82 (s, 3H), 3.19 (m, 2H), 2.08 (d, J = 12.9 Hz, 2H), 1.90 (td, J = 13.0, 4.0 Hz, 2H), 1.48 (s, 9H); ESIMS calcd. for $C_{18}H_{24}N_2NaO_3$ ($M+Na^+$) 339.2, found 388.8.

[00365] **Step B:** To a solution of **T1b** (218 mg, 0.69 mmol) in dioxane (1 mL) is added 4 M solution of HCl in dioxane (2 mL, 8 mmol) and the reaction is stirred for 2 hours at room temperature. The solvent is removed and the residue is coevaporated with dioxane (10 mL) to afford **T1c**; ESIMS calcd. for $C_{13}H_{17}N_2O$ ($M+H^+$) 217.1, found 216.9.

[00366] **Step C:** A cold (ice/water bath) solution of **T1c** (0.69 mmol) and triethylamine (385 μL, 2.76 mmol) in dry dichloromethane (10 mL) is treated with methanesulfonyl chloride (64 μL, 0.83 mmol) dropwise. The resulting solution is stirred at room temperature overnight. The reaction mixture is added to water (40 mL) and extracted with dichloromethane (3 x 40 mL). The combined organic layers are dried over Na_2SO_4 and concentrated to yield **T1d**; ESIMS calcd. for $C_{14}H_{19}N_2O_3S$ ($M+H^+$) 295.1, found 295.0.

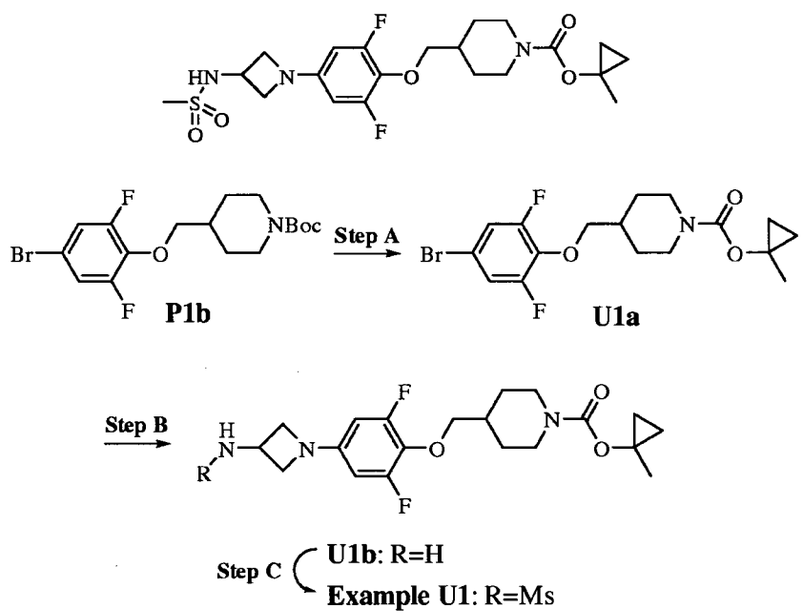
[00367] **Step D:** A solution of **T1d** (208 mg, 0.7 mmol) in anhydrous dichloromethane (3.5 mL) is cooled to -78 °C under nitrogen atmosphere and a 1M solution of BBr_3 (3.5 mL, 3.5 mmol) in dichloromethane is added dropwise. The reaction is stirred at room temperature overnight, then cooled to 0 °C and quenched with MeOH (2 mL). The reaction mixture is repeatedly concentrated with MeOH (3 x 20 mL) to afford **T1e**; ESIMS calcd. for $C_{13}H_{17}N_2O_3S$ ($M+H^+$) 281.1, found 281.0.

[00368] **Step E:** A mixture of **T1e** (196 mg, 0.7 mmol), (1-(5-fluoropyrimidin-2-yl)piperidin-4-yl)methyl methanesulfonate (202 mg, 0.7 mmol; prepared by following the procedure for **Q4a** except using 2-chloro-5-fluoropyrimidine as the electrophile), and Cs_2CO_3 (456 mg, 1.4 mmol) in acetonitrile (10 mL) is heated to 70 °C for 48 hours. The reaction mixture is concentrated and partitioned between water (20 mL) and ethyl acetate, the aqueous phase is extracted with ethyl acetate (2 x 20 mL). The combined organics are washed with water (2 x 10), dried over Na_2SO_4 and concentrated. Purification on silica gel using a linear gradient of 0 to 60% ethyl acetate in hexane to affords **T1f**; ^{1}H-NMR (400MHz, DMSO) δ 8.43 (d, J = 0.8 Hz, 2H), 7.46 (m, 2H), 7.00 (m, 2H), 4.61 (m, 2H), 3.87 (d, J = 6.4 Hz, 2H), 3.74 (m, 2H), 3.00 (m, 5H), 2.92 (m,

2H), 2.24 (m, 2H), 2.05 (m, 3H), 1.83 (m, 2H), 1.23 (m, 2H); ESIMS calcd. for $C_{23}H_{29}FN_5O_3S$ ($M+H^+$) 474.2, found 474.2.

[00369] **Step F:** A solution of **T1f** (30 mg, 0.063 mmol) and KOH (105 mg, 2.6 mmol) in 2-methoxyethanol (1 mL) and water (0.5 mL) is heated to 110 °C for 72 hours. The reaction mixture is acidified with 1N HCl to pH 2-3 and extracted with ethyl acetate (3 x 20 mL). The combined organics are dried over Na_2SO_4, and concentrated. The residue is purified using mass-triggered reverse phase HPLC to afford **T1**; ^{1}H-NMR (400MHz, DMSO-d6) δ 8.42 (d, J = 0.8 Hz, 2H), 7.30 (m, 2H), 6.92 (m, 2H), 4.60 (m, 2H), 3.83 (d, J = 6.4 Hz, 2H), 2.88 (m, 7H), 2.48 (m, 2H), 2.04 (m, 1H), 1.83 (m, 4H), 1.22 (m, 2H). ESIMS calcd. for $C_{23}H_{30}FN_4O_5S$ ($M+H^+$) 493.2, found 493.1

Example U1: 1-methylcyclopropyl 4-((2,6-difluoro-4-(3-(methylsulfonamido)azetidin-1-yl)phenoxy)methyl)piperidine-1-carboxylate.



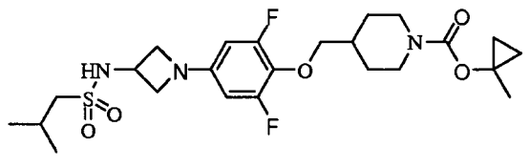
[00370] **Step A:** By following a similar procedure as that used to prepare **E3** from **E3a**, except substituting **P1b** for **E3a**, **U1a** is prepared; ESIMS calcd. for $C_{17}H_{21}BrF_2NO_3$ $[M+H]^+$: 404.1, found: 404.0.

[00371] **Step B:** By following a similar procedure as that used to prepare **B2** from **B2b**, except substituting benzyl azetidin-3-ylcarbamate for benzyl piperazine-1-

carboxylate, **U1b** is prepared; It is observed that the Cbz group is removed under reaction conditions; ESIMS calcd. for $C_{20}H_{28}F_2N_3O_3$ [M+H$^+$] 396.2, found 369.3.

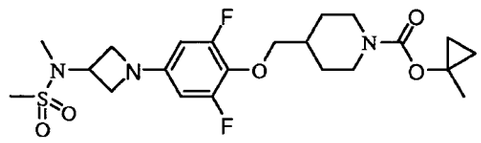
[00372] **Step C:** By following a similar procedure as that used to prepare **G1** from **G1a**, except substituting **U1b** for **G1a**, **U1** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 5.95 (d, *J* = 9.7 Hz, 2H), 4.85 (d, *J* = 9.4 Hz, 1H), 4.40 (m, 1H), 4.20 (t, *J* = 7.5 Hz, 2H), 4.29-3.94 (m, 2H), 3.80 (d, *J* = 6.0 Hz, 2H), 3.65 (dd, *J* = 5.3, 8.0 Hz, 2H), 3.00 (s, 3H), 2.74 (t, *J* = 12.4 Hz, 2H), 1.9 (m, 1H), 1.82 (d, *J* = 13.1 Hz, 2H), 1.54 (s, 3H), 1.22 (m, 2H), 0.86 (t, *J* = 6.4 Hz, 2H), 0.62 (t, *J* = 6.4 Hz, 2H). ESIMS calcd. for $C_{21}H_{30}F_2N_3O_5S$ [M+H$^+$] 474.2, found 474.1.

Example U2: 1-methylcyclopropyl 4-((2,6-difluoro-4-(3-(2-methylpropylsulfonamido)azetidin-1-yl)phenoxy)methyl)piperidine-1-carboxylate.



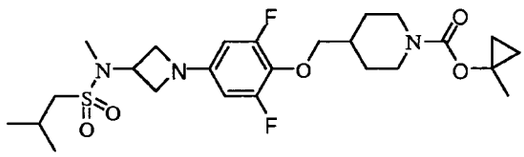
[00373] By following a similar procedure as that used to prepare **U1** from **U1c**, except substituting isobutanesulfonyl chloride for methanesulfonyl chloride, **U2** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 5.96 (d, *J* = 9.6 Hz, 2H), 4.87 (d, *J* = 9.5 Hz, 1H), 4.40 (m, 1H), 4.20 (t, *J* = 7.5 Hz, 2H), 4.29-3.94 (m, 2H), 3.82 (d, *J* = 4.8 Hz, 2H), 3.65 (dd, *J* = 7.9, 5.4 Hz, 2H), 2.93 (d, *J* = 6.4 Hz, 2H), 2.75 (m, 2H), 2.28 (septet, *J* = 6.7 Hz, 1H), 1.92 (m, 1H), 1.83 (d, *J* = 12.6 Hz, 2H), 1.56 (s, 3H), 1.24 (m, 2H), 1.13 (d, *J* = 6.7 Hz, 6H), 0.87 (t, *J* = 6.3 Hz, 2H), 0.63 (t, *J* = 6.3 Hz, 2H). ESIMS calcd. for $C_{24}H_{36}F_2N_3O_5S$ [M+H$^+$] 516.2, found 516.2.

Example U3: 1-methylcyclopropyl 4-((2,6-difluoro-4-(3-(N-methylmethylsulfonamido)azetidin-1-yl)phenoxy)methyl)piperidine-1-carboxylate.



[00374] To a solution of **U1** (25 mg, 0.05 mmol) and iodomethane (4 uL, 0.06 mmol) in dry N,N-dimethylformamide (1 mL) at 0 °C is added sodium hydride (5 mg, 0.2 mmol) in one portion. The mixture is allowed to warm slowly to room temperature and stirred an additional 1 hour. The mixture is partitioned between water and dichloromethane, and the organics washed with brine, dried over $MgSO_4$, filtered, evaporated and purified on silica gel using 0-50% ethyl acetate in dichloromethane to afford **U3**; ^{1}H-NMR (400MHz, $CDCl_3$) δ 5.97 (d, J = 9.6 Hz, 2H), 4.71 (m, 1H), 4.06 (t, J = 7.8 Hz, 2H), 4.29-3.95 (m, 2H), 3.88 (dd, J = 8.0, 5.6 Hz, 2H), 3.81 (d, J = 5.8 Hz, 2H), 2.97 (s, 3H), 2.83 (s, 3H), 2.74 (m, 2H), 1.91 (m, 1H), 1.83 (d, J = 13.4 Hz, 2H), 1.54 (s, 3H), 1.24 (m, 2H), 0.86 (t, J = 6.3 Hz, 2H), 0.62 (t, J = 6.3 Hz, 2H). ESIMS calcd. for $C_{22}H_{32}F_2N_3O_5S$ [M+H$^+$] 488.2, found 488.2.

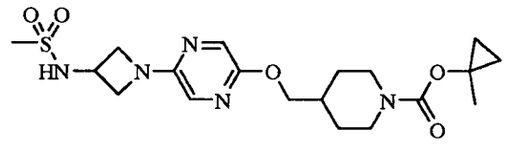
Example U4: 1-methylcyclopropyl 4-((4-(3-(N,2-dimethylpropylsulfonamido)azetidin-1-yl)-2,6-difluorophenoxy)methyl)piperidine-1-carboxylate.



[00375] By following a similar procedure as that used to prepare **U3** from **U1**, except substituting **U2** for **U1**, **U2** is prepared; ^{1}H-NMR (400MHz, $CDCl_3$) δ 5.96 (d, J = 9.7 Hz, 2H), 4.77 (m, 1H), 4.04 (t, J = 7.9 Hz, 2H), 4.25-3.96 (m, 2H), 3.87 (dd, J = 5.6, 7.8 Hz, 2H), 3.81 (d, J = 6.3 Hz, 2H), 2.97 (s, 3H), 2.77 (d, J = 6.7 Hz, 2H), 2.74 (m, 2H), 2.24 (septet, J = 6.6 Hz, 1H), 1.91 (m, 1H), 1.83 (d, J = 13.3 Hz, 2H), 1.54 (s, 3H),

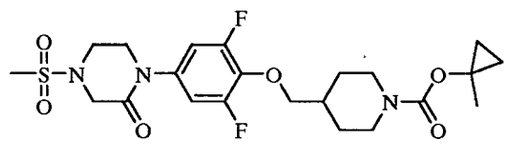
1.24 (m, 2H), 1.11 (d, J = 6.5 Hz, 6H), 0.86 (t, J = 6.3 Hz, 2H), 0.61 (t, J = 6.3 Hz, 2H). ESIMS calcd. for $C_{25}H_{38}F_2N_3O_5S$ [M+H$^+$] 530.3, found 530.2.

Example U5: 1-Methylcyclopropyl 4-((5-(3-(methylsulfonamido)azetidin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate.



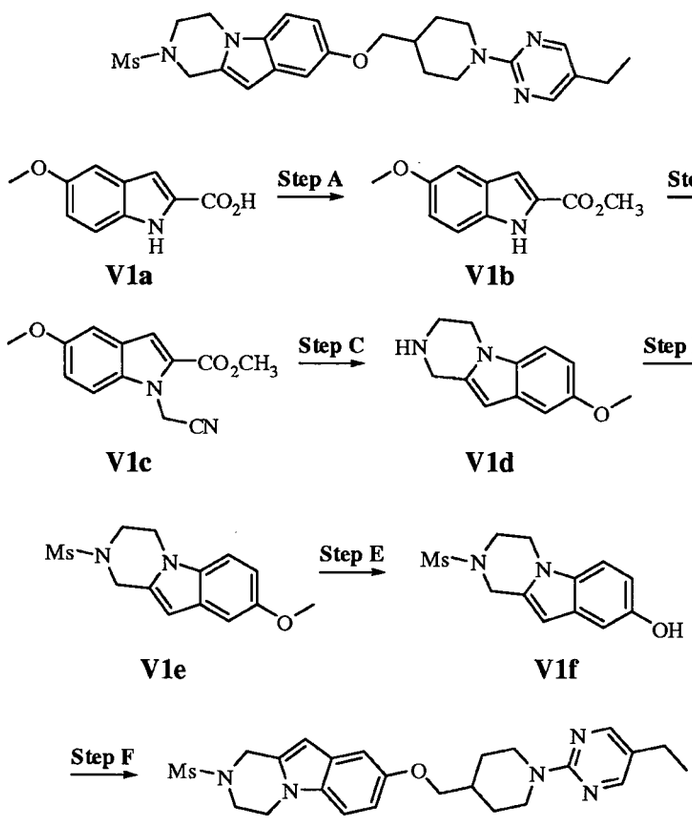
By following a similar procedure as that used to prepare **M1** from **M1a**, except substituting benzyl azetidin-3-ylcarbamate for benzyl piperazine-1-carboxylate **in step A** and methanesulfonyl chloride for methyl 3-(chlorosulfonyl)propanoate in **step d**, **U5** is prepared; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 1.4 Hz, 1H), 7.24 (d, J = 1.4 Hz, 1H), 4.73 (d, J = 9.2 Hz, 1H), 4.37 (m, 1H), 4.28 (m, 2H), 3.97 (d, J = 6.4 Hz, 2H), 3.75 (m, 2H), 3.27 (s, 3H), 2.65 (m, 2H), 1.85 (m, 1H), 1.70 (m, 2H), 1.46 (s, 3H), 1.17 (m, 3H), 0.77 (m, 2H), 0.53 (m, 2H); ESIMS *m/z* for (M+H)$^+$ $C_{19}H_{30}N_5O_5S$ calcd: 440.2, found: 440.2.

Example U6: 1-Methylcyclopropyl 4-((2,6-difluoro-4-(4-(methylsulfonyl)-2-oxopiperazin-1-yl)phenoxy)methyl)piperidine-1-carboxylate.



By following a similar procedure as that used to prepare **O2** from **B4b**, except substituting **P1b** for **B4b**, **U6** is prepared; ^{1}H-NMR (400MHz, DMSO-d6) δ 7.28 (m, 2H), 3.94 (m, 6H), 3.77 (m, 2H), 3.53 (m, 2H), 3.05 (s, 3H), 2.75 (m, 2H), 1.88 (m, 2H), 1.74 (m, 2H), 1.46 (s, 3H), 1.14 (m, 2H), 0.76 (m, 2H), 0.59 (m, 2H); ESIMS calcd. for $C_{22}H_{30}F_2N_3O_6S$ [M+H]$^+$ 502.2, found 502.2.

Example V1: 8-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-2-(methylsulfonyl)-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole.



Example V1

Step A: A suspension of **V1a** (2.26 g, 11.8 mmol) in methanol (20 mL) is treated with thionyl chloride (1.0 mL, 13.8 mmol) dropwise, with stirring. The resulting mixture is stirred at room temperature for 18h, and then concentrated to dryness. The resulting solid is triturated with 1:1 water/aqueous saturated sodiumhydrogencarbonate, filtered, washed with water and dried to afford **V1b**; ^{1}H NMR (DMSO-d_6, 400.13 MHz): δ 11.80 (s, 1H), 7.37 (d, J = 8.9 Hz, 1H), 7.11 (d, J = 2.2 Hz, 1H), 7.06 (d, J = 2.2 Hz, 1H), 6.92 (dd, J = 2.4, 8.9 Hz, 1H), 3.86 (s, 3H), 3.76 (s, 3H); ESIMS calcd. for $C_{11}H_{12}NO_3$ ($M+H^+$) 206.1, found 206.1.

Step B: A solution of **V1b** (1.86 g, 9.1 mmol) is in *N,N*-dimethylacetamide (25 mL) is treated with powdered cesium carbonate (5.31 g, 16.3 mmol) and chloroacetonitrile (0.90 mL, 14.3 mmol) and the mixture is stirred at 65 °C for 18 hours. Cooling to room temperature, dilution with ethyl acetate, washing with water (2x), saturated aqueous ammonium chloride and brine, drying over Na_2SO_4, filtration and concentration yields a solid. The residue is purified on silica gel using 5-30% ethyl acetate in hexanes to afford **V1c**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.33 (d, J = 8.9 Hz, 1H), 7.30 (d, J = 1.0 Hz, 1H), 7.12 (m, 2H), 5.59 (s, 2H), 3.95 (s, 3H), 3.87 (s, 3H); ESIMS calcd. for $C_{13}H_{13}N_2O_3$ ($M+H^+$) 245.1, found 245.0.

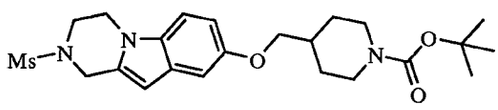
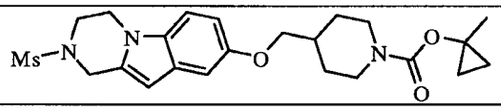
Step C: **V1d** is prepared from **V1c** according to the literature procedure described in *Bioorg. Med. Chem. Lett.* **2002**, *12*, 155-158; ESIMS calcd. for $C_{12}H_{15}N_2O$ ($M+H^+$) 203.1, found 203.1.

Step D: To a solution of **V1d** (0.58 g, 2.5 mmol) in dichloromethane (15 mL) is added triethylamine (0.7 mL, 5 mmol) in one portion. The resulting mixture is cooled in an ice/water bathand methanesulfonyl chloride (0.25 mL, 3.2 mmol) is added dropwise, with stirring, over 5 minutes. The bath is removed and the resulting solution is stirred at room temperature for 30 minutes. The reaction mixture is added to water (40 mL) and extracted with dichloromethane (2 x 40 mL). The combined organic extracts are washed with saturated aqueous ammonium chloride solution, dried over $MgSO_4$, and concentrated to yield **V1e**; ESIMS calcd. for $C_{13}H_{17}N_2O_3S$ ($M+H^+$) 281.1, found 281.2.

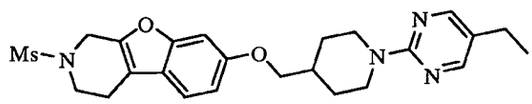
Step E: A solution of **V1e** (0.60 g, 2.1 mmol) in dichloromethane (15 mL) is treated with neat boron tribromide (0.8 mL, 8.3 mmol) at room temperature. The resulting solution is stirred at room temperature for 30 minutes. The reaction mixture is carefully added to methanol (50 mL), treated with solid Na_2CO_3 (0.4 g), filtered and concentrated to dryness. The crude **V1f** is used as such in the next step; ESIMS calcd. for $C_{12}H_{15}N_2O_3S$ ($M+H^+$) 267.1, found 267.1.

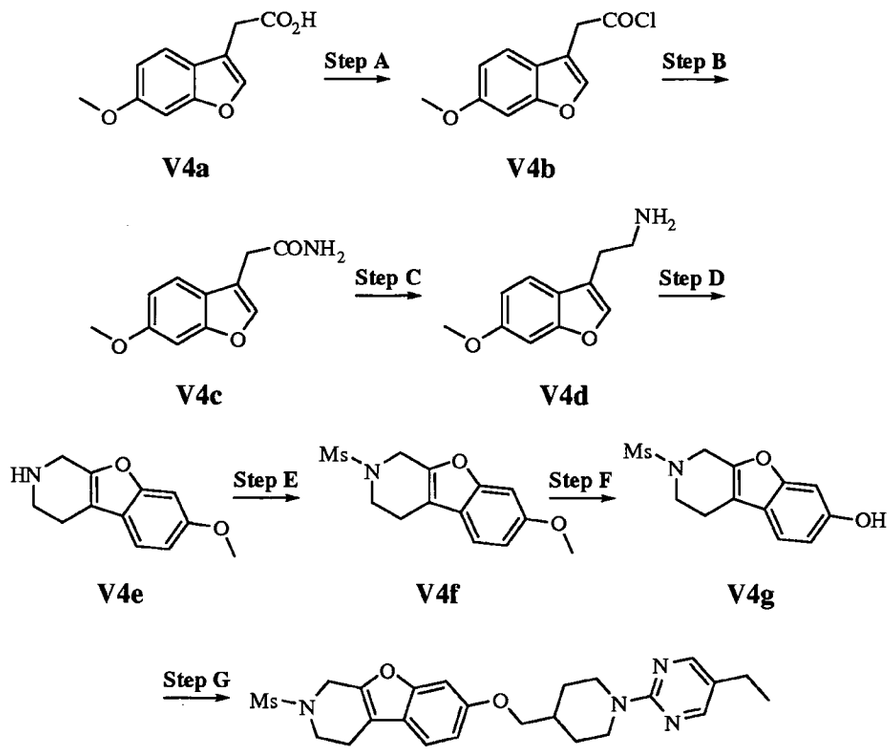
Step F: A solution of **V1f** and **Q4b** (0.03 g, 0.1 mmol) in dry acetonitrile (2 mL) is treated with powdered cesium carbonate (0.1 g, 0.3 mmol) and the mixture is stirred at 75 °C for 24 hours. Filtration and mass directed reverse phase HPLC purification yields **V1**; ESIMS calcd. for $C_{24}H_{32}N_5O_3S$ ($M+H^+$) 470.2, found 470.1.

By following a similar procedure as the one used for preparing **V1** from **V1f** except substituting the appropriate mesylate for **Q4b** the following compounds are prepared;

Example	Structure	Analytical data
V2		^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.17 (d, *J* = 8.8 Hz, 1H), 7.03 (d, *J* = 2.3 Hz, 1H), 6.85 (dd, *J* = 2.3, 8.8 Hz, 1H), 6.24 (d, *J* = 0.7 Hz, 1H), 4.67 (s, 2H), 4.16 (br, 2H), 4.15 (t, *J* = 5.4 Hz, 2H), 3.84 (m, 4H), 2.87 (s, 3H), 2.76 (t, *J* = 12.2 Hz, 2H), 1.98 (m, 1H), 1.85 (t, *J* = 12.6 Hz, 2H), 1.47 (s, 9H), 1.28 (ddd, *J* = 4.7, 12.4, 12.4 Hz, 2H); ESIMS calcd. for $C_{23}H_{34}N_3O_5S$ ($M+H^+$) 464.2, found 464.1.
V3		ESIMS calcd. for $C_{23}H_{32}N_3O_5S$ ($M+H^+$) 462.2, found 462.2.

Example V4: 7-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-2-(methylsulfonyl)-1,2,3,4-tetrahydrobenzofuro[2,3-*c*]pyridine.





Example V4

Step A: A suspension of **V4a** (3.99 g, 19.4 mmol) is in dichloromethane (50 mL) is treated with oxalyl chloride (1.8 mL, 21.3 mmol) slowly, with stirring, followed by dimethylformamide (0.01 mL). The resulting mixture is stirred at room temperature for 1 hour, and then concentrated to dryness to yield **V4b**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.58 (t, J = 1.0 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.03 (d, J = 2.2 Hz, 1H), 6.92 (dd, J = 2.2, 8.6 Hz, 1H), 4.21 (d, J = 1.0 Hz, 2H), 3.84 (s, 3H).

Step B: A solution of **V4b** (19.4 mmol) in dichloromethane (100 mL) is treated with ammonia gas by slow bubbling through the stirring solution for 5 minutes. The resulting suspension is stirred in a closed flask for 2 hours. The resulting suspension is filtered, the collected solids are washed with more dichloromethane and air dried to yield **V4c**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.52 (t, J = 0.7 Hz, 1H), 7.43 (d, J = 8.6 Hz, 1H), 7.03 (d, J = 2.2 Hz, 1H), 6.92 (dd, J = 2.2, 8.6 Hz, 1H), 5.61 (s, 1H), 5.45 (s, 1H), 3.86 (s, 3H), 3.63 (d, J = 0.7 Hz, 2H); ESIMS calcd. for $C_{11}H_{12}NO_3$ ($M+H^+$) 206.1, found 206.1.

Step C: A solution of **V4c** (2.79 g, 13.6 mmol) in dry tetrahydrofuran (100 mL) is treated with borane solution in tetrahydrofuran (1.0 N; 50 mL, 50 mmol) and the resulting solution is stirred in a closed flask overnight. The reaction mixture is carefully treated with methanol (50 mL) and concentrated to dryness. The residue is purified by silica gel chromatography using a linear gradient of 20 to 100% ethyl acetate in hexanes to afford **V4d**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.46 (s, 1H), 7.38 (d, J = 8.6 Hz, 1H), 7.02 (d, J = 2.2 Hz, 1H), 6.90 (dd, J = 2.2, 8.6 Hz, 1H), 3.85 (s, 3H), 3.63 (br. s, 2H), 3.14 (tt, J = 6.4, 6.8 Hz, 2H), 3.02 (t, J = 6.4 Hz, 2H); ESIMS calcd. for $C_{11}H_{14}NO_2$ ($M+H^+$) 192.1, found 192.1.

Step D: **V4e** acetic acid salt is prepared from **V4d** according to the procedure described in WO2000/020421, p. 15; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.30 (d, J = 8.5 Hz, 1H), 6.99 (d, J = 2.2 Hz, 1H), 6.86 (dd, J = 2.2, 8.5 Hz, 1H), 3.88 (br. s, 2H), 3.85 (s, 3H), 3.06 (t, J = 5.8 Hz, 2H), 2.85 (m, 2H), 2.72 (m, 1H); ESIMS calcd. for $C_{12}H_{14}NO_2$ ($M+H^+$) 204.1, found 204.1.

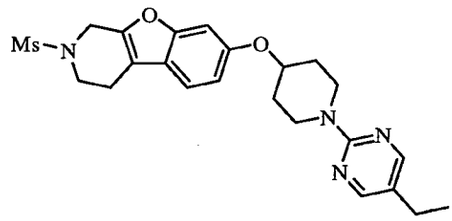
Step E: A solution of **V4e** acetic acid salt (0.18 g, 0.7 mmol) in dichloromethane (5 mL) is treated with triethylamine (0.2 mL, 1.4 mmol) and methanesulfonic anhydride (0.15 g, 0.86 mmol) and the mixture is stirred at room temperature for 1 hour. Washing with water, drying over $MgSO_4$ and concentration yields **V4f**; ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ 7.29 (d, J = 8.5 Hz, 1H), 6.98 (d, J = 2.2 Hz, 1H), 6.84 (dd, J = 2.2, 8.5 Hz, 1H), 3.84 (s, 3H), 2.77 (m, 2H), 2.73 (m, 2H), 2.54 (s, 3H); ESIMS calcd. for $C_{13}H_{16}NO_4S$ ($M+H^+$) 282.1, found 282.0.

Step F: A solution of **V4f** (0.15 g, 0.5 mmol) in dichloromethane (5 mL) is treated with neat boron tribromide (0.2 mL, 2.1 mmol) at room temperature. The resulting solution is stirred at room temperature for 30 minutes. The reaction mixture is carefully added to methanol (50 mL), treated with solid Na_2CO_3 (0.4 g), filtered and concentrated to dryness to afford **V4g**; ESIMS calcd. for $C_{12}H_{14}NO_4S$ ($M+H^+$) 268.1, found 268.1.

Step G: A solution of **V4g** and **Q4b** (0.03 g, 0.1 mmol) in dry acetonitrile (2 mL) is treated with powdered cesium carbonate (0.08 g, 0.2 mmol) and the mixture is stirred at 75 °C for 24 hours. Filtration and mass directed HPLC purification yields **V4**; ESIMS calcd. for $C_{24}H_{31}N_4O_4S$ ($M+H^+$) 471.2, found 471.2.

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Example V5: 7-(1-(5-Ethylpyrimidin-2-yl)piperidin-4-yloxy)-2-(methylsulfonyl)-1,2,3,4-tetrahydrobenzofuro[2,3-c]pyridine.



By following a similar procedure as the one used for preparing **V4** from **V4g** except substituting 1-(5-ethylpyrimidin-2-yl)piperidin-4-yl methanesulfonate for **Q4b** the **V5** is prepared; ESIMS calcd. for $C_{23}H_{29}N_4O_4S$ ($M+H^+$) 457.2, found 457.1.

Biological Assays

Generation of Stable Cell Line

[00376] Flp-In-CHO cells (Invitrogen, Cat.# R758-07) are maintained in Ham's F12 medium supplemented with 10% fetal bovine serum, 1% antibiotic mixture and 2 mM L-glutamine. The cells are transfected with a DNA mixture containing human GPR119 (hGPR119) or mouse GPR119 (mGPR119) in the pcDNA5/FRT vector (Invitrogen) and the pOG44 vector (Invitrogen) in a 1:9 ratio using Fugene6 (Roche), according to the manufacturer's instructions. After 48 hours, the medium is changed to medium supplemented with 400 μg/mL hygromycin B to initiate the selection of stably transfected cells. The resultant cell lines are designated CHO-hGPR119 and CHO-mGPR119 respectively.

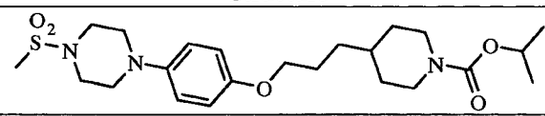
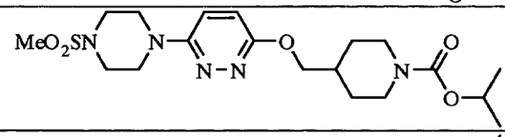
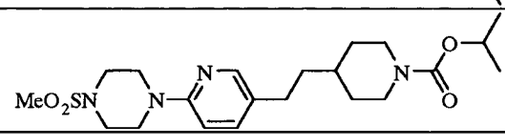
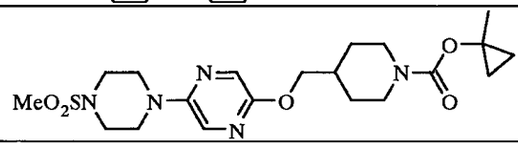
Cyclic AMP Assays

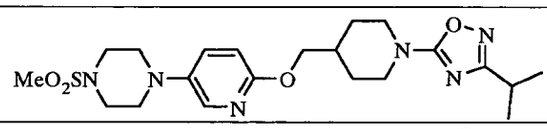
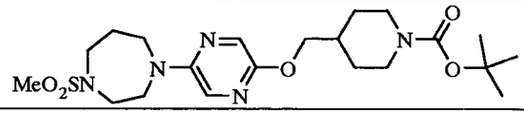
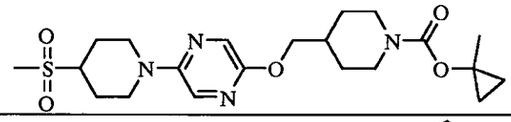
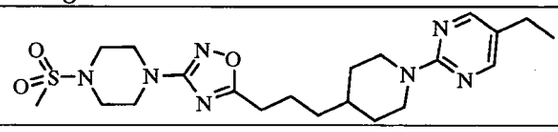
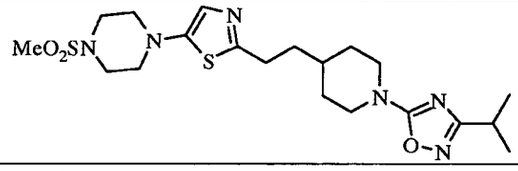
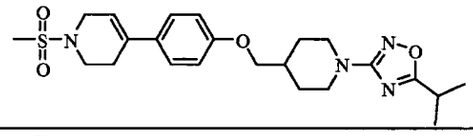
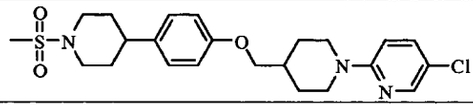
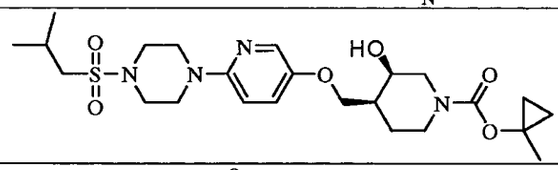
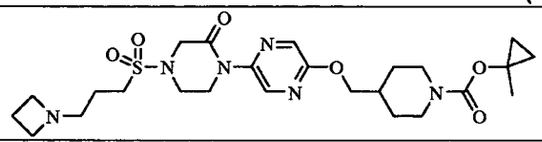
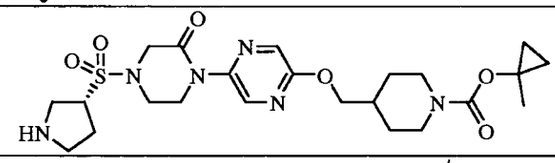
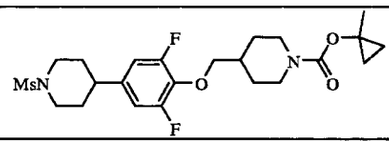
[00377] To test the activity of compounds of the invention on human GPR119, CHO-hGPR119 cells are harvested and resuspended at 300,000 cells/mL in assay media (Ham's F12 medium plus 3% lipid-depleted fetal bovine serum, 1 mM 3-isobutyl-1-methyl-xanthine (IBMX)). Cells (5 μl) are placed in each well of a white 1536-well plate. A compound of the invention (50 nL) diluted in 100% dimethyl sulfoxide (DMSO) is added to each well and the plates are incubated at 37°C for 30 minutes. cAMP concentrations are then measured

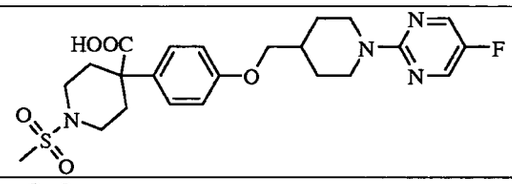
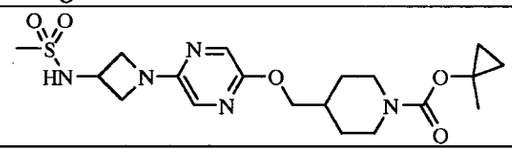
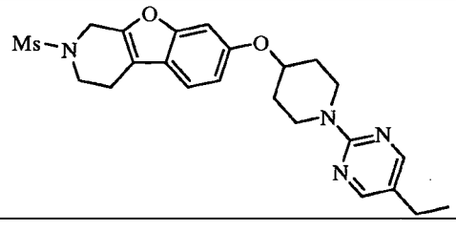
using the cAMP dynamic 2 kit (Cisbio Bioassays) according to the manufacturer's instructions. 2.5 μL of diluted cAMP-XL665 is added to each well, followed by 2.5 μL diluted anti-cAMP-Cryptate. The plate is covered and incubated for one hour at room temperature, then read on an Envision plate reader (Perkin Elmer) using the HTRF method with excitation at 337 nm, and emissions measured at 620 nm and 655 nm.

[00378] Activity of compounds of the invention on mouse GPR119 is measured by a similar method in 384-well plates. CHO-mGPR119 cells are harvested and resuspended in assay media at 500,000 cells/mL. 50 μl cells are placed in each well of a white 384-well plate. A compound of the invention (500 nL) diluted in 100% DMSO is added to each well and the plates are incubated at 37°C for 30 minutes. cAMP concentrations are measured as above except that 20 μL of diluted cAMP-XL665 followed by 20 μL diluted anti-cAMP-Cryptate is added to each well.

[00379] Compounds of the invention, in free form or in pharmaceutically acceptable salt form, produced a concentration-dependent increase in intracellular cAMP level. Compounds of the invention show an EC_{50} of between $1x10^{-5}$ and $1x\ 10^{-10}M$, preferably less than 500nM, more preferably less than 100nM. The following table shows a non-limiting sample of EC_{50} measurements for compounds of the invention whereby +, ++ and +++ represent EC_{50} ranges of >800nM, 200-800nM and <200nM, respectively:

Compound	Structure	EC_{50} Activity
A3		+
C2		+
D2		++
E3		+++

E9		++
G1		+
G4		+++
H3		+++
I1		+++
J7		+++
J22		+++
K3		+++
O9		+++
O41		+++
P13		+++

T1		++
U5		+++
V5		+++

GLUTag GLP-1 assay

[00380] The effect of compounds of the invention on GLP-1 secretion can be studied in GLUTag cells (a mouse entereoendocrine cell line that secretes GLP-1). GLUTag cells are plated in poly-D-lysine-coated 96-well plates on day one in complete medium (DMEM/10% FBS). On day two, the culture medium is replaced with a low glucose medium (DMEM/5.5 mM glucose/10% FBS). One day three, cells are washed twice and pre-incubated in glucose free EBSS buffer (100 mM NaCl, 5 mM KCl, 0.8 mM $MgSO_4 \cdot 7H_2O$, 1.65 mM $NaH_2PO_4 \cdot 2H_2O$, 26 mM $NaHCO_3$, 1.6 mM $CaCl_2$, 0.1% fatty acid-free bovine serum albumin, pH 7.35) for two hours at 37 °C with 5% CO_2. After this pre-incubation period, the cells are washed again with glucose free EBSS buffer, and then stimulated with a compound of the invention at various concentrations in EBSS buffer plus 10 mM glucose and a DPP-4 inhibitor at 37 °C in the presence of 5% CO_2. At the end of the incubation, the supernatants are then collected and transferred to a HEK293 cell line that over expresses human GLP-1 receptor and a CRE-luciferase reporter construct. The CRE-luciferase construct expresses luciferase gene under the control of a cAMP response element (CRE). GLP-1-stimulated GLP-1 receptor leads to cAMP production, which in turn, up regulates luciferase expression. The HEK293-GLP-1R reporter cells are plated the night before in white 384-well plates. After incubation with the supernatants from GLUTag cells treated with a compound of the invention, the HEK293-GLP-1R reporter cells are incubated at 37 °C in the presence of 5%

CO_2 for 18 hours. Luciferase produced from the treatment is measured by the addition of Steady-Glo reagent (Promega, Cat. # E2550). The EC_{50} values are calculated with nonlinear regression using Graphpad Prism.

HIT-T15 insulin assay

[00381] The effect of GPR119 agonist on insulin secretion is studied in HIT-T15 cells (a hamster beta cell line that secrets insulin). HIT-T15 cells are obtained from ATCC and are cultured in Ham's F12 Kaighn's medium plus 10% horse serum and 2.5% fetal bovine serum. On day one, HIT-T15 cells are plated in 96-well plates and cultured for 24 hours and then the medium is replaced with a low-glucose medium (RPMI 1640 medium supplemented with 10% horse serum, 2.5% fetal bovine serum and 3.0 mM D-(+)-glucose). On day three, the cells are washed twice and then pre-incubated with glucose-free Krebs–Ringer bicarbonate buffer (KRBB) that contains 119 mM NaCl, 4.74 mM KC1, 2.54 mM $CaCl_2$, 1.19 mM KH_2PO_4, 1.19 mM $MgCl_2$, 25 mM $NaHCO_3$, 10 mM HEPES and 0.1% fatty-acid-free bovine serum albumin at pH 7.4. One hour later, the cells are washed again for three times and incubated with a compound of the invention in KRBB plus 16.5 mM glucose for 3 hours at 37 °C. After a 5 minute centrifugation at 1,000 rpm, supernatant is removed from each well and transferred into a separate plate for insulin measurement following the instructions for Cisbio insulin HTRF assay kit (Cisbio, Cat. # 62INSPEC). The EC_{50} values are calculated with nonlinear regression using Graphpad Prism.

GLP-1 Assay

[00382] Adult male wild-type C57BL/6J mice (age 9 weeks, JAX) are used as the experimental animals. In all experiments, mice are housed in a 12 hour light/dark cycle facility (light on from 5:00 a.m. to 5:00 p.m) and have access to food (Purina 5001) and water ad libitum. Mice (8 per group) are randomized into treatment groups based on their initial body weight. They are orally dosed with vehicle, DPP4 inhibitor alone, or DPP4 inhibitor and a compound of the invention, in a single dose. A glucose bolus (2 g/kg) is delivered sixty minutes post dosing. A sample is collected 2 minutes post glucose bolus.

[00383] Plasma active GLP-1 is measured in C57BL/6 mice following a single oral administration of increasing doses of a compound of the invention (3, 10 and 30 mg/kg).

Animals are fasted for 16 hours prior to compound administration. Oral doses are administered at approximately 10:00 am in a 75%PEG300:25%D5W suspension. Blood is obtained (via retro-orbital bleeding) to measure plasma levels of active GLP-1. Approximately 200 μL samples of blood are removed for analysis at 62 minutes post dosing (2 minutes post glucose bolus). All data are expressed as the mean ± SEM for each experimental group of mice. Statistical analysis of data is performed using a one-way ANOVA with a Bonferroni's Multiple Comparison Post Test (GraphPad Prism 4.02).

[00384] Treatment of mice with increasing doses of a compound of the invention (in combination with a DPP4 inhibitor) results in increasing levels of plasma active GLP-1. The magnitude of GLP-1 increase observed in the 10 mg/kg group demonstrate that some compounds of the invention can increase circulating levels of active GLP-1 by about 2.2X fold relative to the effect with a DPP4 inhibitor alone.

OGTT Assay

[00385] Adult male Zucker fa/fa rats (age 11 weeks, Charles River Labs) are used as the experimental animals. In all experiments, rats are housed in a 12 hour light/dark cycle facility (light on from 5:00 a.m. to 5:00 p.m) and have access to food (Purina 5001) and water ad libitum. Rats (6 per group) are randomized into treatment groups based on their initial body weight and are dosed (orally) with vehicle orally, a DPP4 inhibitor, or a compound of the invention. Sixty minutes after dosing, a 3 g/kg glucose bolus is administered.

[00386] A compound of the invention is dissolved in vehicle for dosing (orally using a gavage needle) at a final concentration of 0.2, 2 or 6mg/mL. Oral doses are administered at approximately 7:30 am in a 75%PEG300:25%D5W.

[00387] OGTT evaluations are performed in conscious rats that are 11 weeks of age. The rats are fasted by removing food at 6pm the day before. A baseline blood sample is taken at t = minus 60 minutes and the rats are then dosed orally with the a compound of the invention. A baseline blood sample is taken at t = zero minutes and the animals are then administered an oral glucose bolus (3 g/kg) immediately. Blood is obtained (via tail bleeding) to measure blood glucose (using a glucometer). A single drop of blood from the

tail is measured for glucose using a glucometer at t = -60, 0, 10, 30, 60, 90, 120 and 180 minutes.

[00388] The area under the curve (AUC) is calculated using the trapezoidal rule. All data are expressed as the mean ± sem for each experimental group of rats. Statistical analysis of data is performed using a one-way ANOVA with a Bonferroni's Multiple Comparison Post Test (GraphPad Prism 4.02).

[00389] Some compounds of the invention exhibit a clear dose-dependent effect on improved glucose clearance at 3, 10, and 30 mg/kg (about 31%, about 48%, and about 56% reduction in glucose AUC, respectively) when dosed in a 75% PEG300 / 25% D5W formulation. The results demonstrate that some compounds of the invention can lower blood glucose in response to glucose challenge.

[00390] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.

yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(2-(piperidin-1-yl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(2-morpholinoethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(2-(dimethylamino)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((5-(4-(3-chloropropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((5-(4-(3-acetoxypropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-aminopropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(2-ethoxyethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-(pyrrolidin-1-yl)propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-(2-methyl-1H-imidazol-1-yl)propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-(dimethylamino)propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(isopropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(isobutylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(sec-butylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-acetoxy-2,2-dimethylpropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((5-(4-(3-hydroxy-2,2-dimethylpropylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-(2-(pyridin-3-yl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-(2-(pyridin-4-yl)ethylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-sulfamoylpiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; tert-Butyl 4-((5-(4-(morpholinosulfonyl)piperazin-1-yl)pyrazin-2-

yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(ethylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-fluoro-6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; tert-Butyl 4-((5-(4-(methylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-(methylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(2-oxo-4-(propylsulfonyl)piperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-(isopropylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((5-(4-(isopropylsulfonyl)-2-oxopiperazin-1-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(2-oxo-4-(propylsulfonyl)piperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-((6-(4-(isopropylsulfonyl)-2-oxopiperazin-1-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; 1-(5-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)pyrazin-2-yl)-4-(methylsulfonyl)piperazin-2-one; 1-(5-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)pyridin-2-yl)-4-(methylsulfonyl)piperazin-2-one; tert-Butyl 4-((2,6-difluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((3-methoxy-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2,6-dimethyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2,5-dimethyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2-(methoxycarbonyl)-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2-chloro-4-(1-

(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((3-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2,3-dimethyl-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((2-fluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; tert-butyl 4-((4-(1-(methylsulfonyl)piperidin-4-yl)-2-(trifluoromethyl)phenoxy)methyl)piperidine-1-carboxylate; 2-(4-((2,6-Difluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidin-1-yl)-5-ethylpyrimidine; 1-Methylcyclopropyl 4-((2,6-difluoro-4-(1-(methylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; 3-(4-(4-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-3,5-difluorophenyl)piperidin-1-ylsulfonyl)propyl acetate; 1-Methylcyclopropyl 4-((4-(1-(3-acetoxypropylsulfonyl)piperidin-4-yl)-2,6-difluorophenoxy)methyl)piperidine-1-carboxylate; 3-(4-(4-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-3,5-difluorophenyl)piperidin-1-ylsulfonyl)propan-1-ol; 1-Methylcyclopropyl 4-((2,6-difluoro-4-(1-(3-hydroxypropylsulfonyl)piperidin-4-yl)phenoxy)methyl)piperidine-1-carboxylate; Isopropyl 4-((5-(1,2,3,6-tetrahydro-1-methanesulfonylpyridin-4-yl)pyrazin-2-yloxy)methyl)piperidine-1-carboxylate; 1-Methylcyclopropyl 4-((6-(1,2,3,6-tetrahydro-1-methanesulfonylpyridin-4-yl)pyridin-3-yloxy)methyl)piperidine-1-carboxylate; Isopropyl 4-(2-(6-(1,2,3,6-tetrahydro-1-methanesulfonylpyridin-4-yl)pyridin-3-yloxy)ethyl)piperidine-1-carboxylate; 2-(4-((5-(1,2,3,6-Tetrahydro-1-methanesulfonylpyridin-4-yl)pyrazin-2-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine; 2-(4-((6-(1,2,3,6-Tetrahydro-1-methanesulfonylpyridin-4-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine; 2-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-5-(1-methanesulfonylpiperidin-4-yl)pyrazine; 2-(4-((6-(1-Methanesulfonylpiperidin-4-yl)pyridin-3-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine; 3-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methoxy)-6-(1-methanesulfonylpiperidin-4-yl)pyridazine; 2-(4-((5-(1-Methanesulfonylpiperidin-4-yl)pyridin-2-yloxy)methyl)piperidin-1-yl)-5-ethylpyrimidine; 1-tert-Butyl 4-(4-(1-(methylsulfonyl)piperidin-4-yl)phenyl) piperazine-1,4-dicarboxylate; N-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methyl)-4-(1-(methylsulfonyl)piperidin-4-yl)aniline; N-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)methyl)-N-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)aniline; 4-(4-((1-(5-fluoropyrimidin-2-yl)piperidin-4-yl)methoxy)phenyl)-1-(methylsulfonyl)piperidine-4-carboxylic acid; 2-[(2-{4-

[5-({1-[(1-methylcyclopropoxy)carbonyl]piperidin-4-yl}methoxy)pyrazin-2-yl]-3-oxopiperazine-1-sulfonyl}ethyl)amino]acetic acid; 1-methylcyclopropyl 4-{[(5-{4-[(2-carbamimidamidoethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-methyl-3-nitrobutane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(1-benzylpyrrolidine-3-sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(carbamoylmethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(1-carbamoyl-1-methylethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(2-oxo-4-{[2-(pyrrolidin-1-yl)ethane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(morpholin-4-yl)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(dimethylamino)propane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(dimethylcarbamoyl)methane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[1-(2-methylpropyl)pyrrolidine-3-sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(2-oxo-4-{[3-(1H-pyrazol-1-yl)propane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[2-oxo-4-(pyrrolidine-3-sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(2-amino-2-methylpropane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-methylpyrrolidin-3-yl)methane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(azetidin-1-yl)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(2-oxo-4-{[2-(1H-pyrazol-1-yl)ethane]sulfonyl}piperazin-1-yl)pyrazin-2-

yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(1-methylpyrrolidine-3-sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[1-(dimethylcarbamoyl)-1-methylethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(3,3-difluoroazetidin-1-yl)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(dimethylamino)-3-methylbutane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(2-{[2-(tert-butoxy)-2-oxoethyl]amino}ethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(azetidine-3-sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(3,3-difluoroazetidin-1-yl)propane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(azetidin-1-yl)propane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(3S)-pyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3S)-1-methylpyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3R)-1-methylpyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3S)-pyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3R)-pyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(azetidine-3-sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(pyrrolidin-3-ylmethane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(1-hydroxy-2-methylpropane-2-sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(2-hydroxyethane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(azetidin-3-ylmethane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-

methylpyrrolidin-2-yl)methane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(3R)-pyrrolidine-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(1-methylazetidine-3-sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(1-methylazetidine-3-sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-methylazetidin-3-yl)methane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-methylazetidin-3-yl)methane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({3-[(3S,4S)-3,4-dihydroxypyrrolidin-1-yl]propane}sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({2-[(3S,4S)-3,4-dihydroxypyrrolidin-1-yl]ethane}sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(azetidin-3-ylmethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(pyrrolidin-2-ylmethane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-aminopropane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(2-aminoethane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(3-methanesulfonamidoazetidin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(dimethylamino)ethane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(2-oxo-4-{[3-(pyrrolidin-1-yl)propane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(morpholin-4-yl)propane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(3-methyloxetan-3-yl)methane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(acetyloxy)propane]sulfonyl}-2-oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3,3,3-trifluoropropane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[(2E)-2-

(hydroxyimino)-4-methanesulfonylpiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-chloropropane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-hydroxypropane)sulfonyl]-2-oxopiperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({[1-(dimethylamino)cyclopropyl]methane}sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({[1-(dimethylamino)cyclopropyl]methane}sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-hydroxy-3-methylbutane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(3R)-oxolane-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{2-oxo-4-[(3S)-oxolane-3-sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(acetyloxy)-3-methylbutane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({6-[4-({[1-(azetidin-1-yl)cyclopropyl]methane}sulfonyl)piperazin-1-yl]pyridin-3-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({[1-(benzylamino)cyclopropyl]methane}sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({[1-(azetidin-1-yl)cyclopropyl]methane}sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-hydroxycyclopropyl)methane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(1-hydroxycyclopropyl)ethane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({2-[1-(acetyloxy)cyclopropyl]ethane}sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-({[1-(benzyloxy)cyclopropyl]methane}sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[(1-aminocyclopropyl)methane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(1-hydroxycyclopropyl)ethane]sulfonyl}-2-

oxopiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{2,6-difluoro-4-[3-(N-methylmethanesulfonamido)azetidin-1-yl]phenoxymethyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-[2,6-difluoro-4-(3-methanesulfonamidoazetidin-1-yl)phenoxymethyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-{2,6-difluoro-4-[3-(2-methylpropane-1-sulfonamido)azetidin-1-yl]phenoxymethyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{4-[3-(N,2-dimethylpropane-1-sulfonamido)azetidin-1-yl]-2,6-difluorophenoxymethyl}piperidine-1-carboxylate; 5-ethyl-2-{4-[({2-methanesulfonyl-1H,2H,3H,4H-pyrazino[1,2-a]indol-8-yl}oxy)methyl]piperidin-1-yl}pyrimidine; 11-{[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]oxy}-5-methanesulfonyl-8-oxa-5-azatricyclo[7.4.0.0{2,7}]trideca-1(13),2(7),9,11-tetraene; 11-{[1-(5-ethylpyrimidin-2-yl)piperidin-4-yl]methoxy}-5-methanesulfonyl-8-oxa-5-azatricyclo[7.4.0.0{2,7}]trideca-1(13),2(7),9,11-tetraene; tert-butyl 4-[({2-methanesulfonyl-1H,2H,3H,4H-pyrazino[1,2-a]indol-8-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({2-methanesulfonyl-1H,2H,3H,4H-pyrazino[1,2-a]indol-8-yl}oxy)methyl]piperidine-1-carboxylate; propan-2-yl 4-{3-[3-(1-methanesulfonylpiperidin-4-yl)phenoxy]propyl}piperidine-1-carboxylate; propan-2-yl 4-{2-[3-(1-methanesulfonylpiperidin-4-yl)phenoxy]ethyl}piperidine-1-carboxylate; propan-2-yl 4-[3-(1-methanesulfonylpiperidin-4-yl)phenoxymethyl]piperidine-1-carboxylate; propan-2-yl 4-{3-[3-(1-methanesulfonyl-1,2,3,6-tetrahydropyridin-4-yl)phenoxy]propyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-methanesulfonyl-2-sulfanylidenepiperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl (3S,4S)-3-hydroxy-4-{[(6-{4-[(2-methylpropane)sulfonyl]piperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl (3R,4S)-3-hydroxy-4-{[(6-{4-[(2-methylpropane)sulfonyl]piperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-hydroxy-4-{[(6-{4-[(2-methylpropane)sulfonyl]piperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(6-{4-[(2-hydroxy-2-methylpropane)sulfonyl]piperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl (3S,4R)-3-methoxy-4-{[(6-{4-[(2-methylpropane)sulfonyl]piperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(3,3-difluoroazetidin-1-yl)propane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-

1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[3-(azetidin-1-yl)propane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(5-{4-[(3-methoxypropane)sulfonyl]piperazin-1-yl}pyrazin-2-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(6-{4-[(3-chloropropane)sulfonyl]-2-oxopiperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(azetidin-1-yl)ethane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[6-(4-{[3-(azetidin-1-yl)propane]sulfonyl}piperazin-1-yl)pyridin-3-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[({5-[4-(pyrrolidine-3-sulfonyl)piperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[5-(4-{[2-(3,3-difluoroazetidin-1-yl)ethane]sulfonyl}piperazin-1-yl)pyrazin-2-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-{[(6-{4-[(3-hydroxypropane)sulfonyl]-2-oxopiperazin-1-yl}pyridin-3-yl)oxy]methyl}piperidine-1-carboxylate; 1-methylcyclopropyl 4-({[6-(4-{[3-(azetidin-1-yl)propane]sulfonyl}-2-oxopiperazin-1-yl)pyridin-3-yl]oxy}methyl)piperidine-1-carboxylate; 1-methylcyclopropyl 4-[2,6-difluoro-4-(4-methanesulfonyl-2-oxopiperazin-1-yl)phenoxymethyl]piperidine-1-carboxylate; and 1-methylcyclopropyl 4-[({5-[4-(oxetane-3-sulfonyl)-2-oxopiperazin-1-yl]pyrazin-2-yl}oxy)methyl]piperidine-1-carboxylate.

8. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable excipient.

9. A method for modulating GPR119 activity, comprising administering to a system or a subject in need thereof, a therapeutically effective amount of the compound of claim 1 or pharmaceutically acceptable salts or pharmaceutical compositions thereof, thereby modulating said GPR119 activity.

10. The method of claim 9, wherein the compound of claim 1 directly contacts GPR119.

11. The method of claim 10, wherein the contacting occurs in vitro or in vivo.

12. A method for treating a disease or condition wherein modulation of GPR119 activity can prevent, inhibit or ameliorate the pathology and/or symptomology of the disease or condition, comprising administering to a subject a therapeutically effective amount of the compound of claim 1 or pharmaceutically acceptable salts or pharmaceutical compositions thereof.

13. The method of claim 12, wherein said disease or condition is selected from obesity, type 1 diabetes, type 2 diabetes mellitus, hyperlipidemia, idiopathic type 1 diabetes, latent autoimmune diabetes in adults, early-onset type 2 diabetes, youth-onset atypical diabetes, maturity onset diabetes of the young, malnutrition-related diabetes and gestational diabetes.

14. The method of claim 12, wherein said disease or condition is selected from coronary heart disease, ischemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, myocardial infarction, dyslipidemia, post-prandial lipemia, conditions of impaired glucose tolerance, conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, osteoporosis, hypertension, congestive heart failure, left ventricular hypertrophy, peripheral arterial disease, diabetic retinopathy, macular degeneration, cataract, diabetic nephropathy, glomerulosclerosis, chronic renal failure, diabetic neuropathy, metabolic syndrome, syndrome X, premenstrual syndrome, coronary heart disease, angina pectoris, thrombosis, atherosclerosis, myocardial infarction, transient ischemic attacks, stroke, vascular restenosis, hyperglycemia, hyperinsulinemia, hyperlipidemia, hypertrygliceridemia, insulin resistance, impaired glucose metabolism, conditions of impaired glucose tolerance, conditions of impaired fasting plasma glucose, obesity, erectile dysfunction, skin and connective tissue disorders, foot ulcerations and ulcerative colitis, endothelial dysfunction and impaired vascular compliance.

INTERNATIONAL SEARCH REPORT

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PCT/US2008/075145

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/10 C07D401/14 C07D413/06 C07D413/14 C07D417/14
C07D487/04 C07D491/048 A61K31/44 A61K31/496 A61K31/4965
A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/003964 A (PROSIDION LTD [GB]; BARBA OSCAR [GB]; BRADLEY STUART EDWARD [GB]; FYFE) 11 January 2007 (2007-01-11) page 1, line 1 - page 2, line 2 page 21 - page 55; examples 1-4,11,42-89 claim 1	1-14
A	WO 2007/003960 A (PROSIDION LTD [GB]; BRADLEY STUART EDWARD [GB]; DAWSON GRAHAM JOHN [GB) 11 January 2007 (2007-01-11) page 1, line 1 - page 2, line 4 page 34 - page 66; examples 1-238 claim 1	1-14

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 December 2008	15/12/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bissmire, Stewart

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/075145

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/061489 A (PROSIDION LTD [GB]; FYFE MATTHEW [GB]; GARDNER LISA [GB]; KING-UNDERWO) 7 July 2005 (2005-07-07) page 1, line 1 - page 2, line 10 page 31 - page 149; examples 1-149 claim 1	1-14
A	WO 2007/003962 A (PROSIDION LTD [GB]; BRADLEY STUART EDWARD [GB]; FYFE MATTHEW COLIN THO) 11 January 2007 (2007-01-11) page 1, line 1 - page 2, line 4 page 18 - page 76; examples 1-265 claim 1	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/075145

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		CA 2549955 A1	07-07-2005
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		EP 1711491 A1	18-10-2006
		JP 2007517010 T	28-06-2007
		KR 20060127011 A	11-12-2006
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		KR 20080027908 A	28-03-2008
		NO 20080010 B	30-01-2008

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COMPUESTOS Y COMPOSICIONES COMO MODULADORES DE LA ACTIVIDAD DE GPR119

REFERENCIA CRUZADA A SOLICITUDES RELACIONADAS

La presente solicitud reivindica el beneficio de prioridad de la Solicitud de Patente Provisoria de los Estados Unidos Número 60/974.064, presentada el 20 de septiembre de 2007 y de la Solicitud de Patente Provisoria de los Estados Unidos Número 61/045.263, presentada el 15 de abril de 2008. Las memorias descriptivas completas de estas solicitudes se incorporan a la presente como referencia en su totalidad y para todo fin.

ANTECEDENTES DE LA INVENCIÓN

Campo de la Invención

La invención da a conocer compuestos, composiciones farmacéuticas que comprenden dichos compuestos y métodos para utilizar dichos compuestos para el tratamiento o prevención de enfermedades o trastornos asociados con la actividad de GPR119.

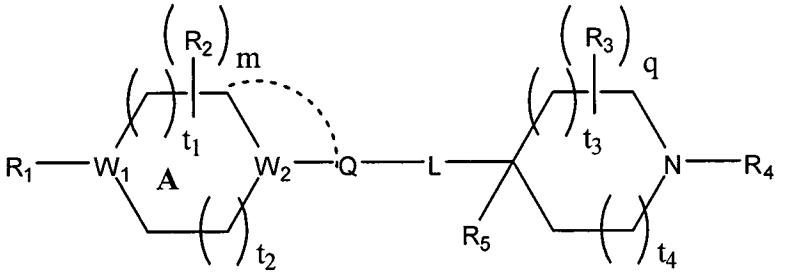
Antecedentes

GPR119 es un receptor acoplado a la proteína G (GPCR) que se expresa principalmente en el páncreas, intestino delgado, colon y tejido adiposo. El perfil de expresión del GPR119 humano indica su potencial utilidad como blanco para el tratamiento de la obesidad y la diabetes. Los novedosos compuestos de la presente invención modulan la actividad de GPR119 y, por lo tanto, se estima que son de utilidad en el tratamiento de las enfermedades o trastornos asociados a GPR119 tales como, aunque no a modo de limitación, diabetes, obesidad y trastornos metabólicos asociados.

C. 218.740
M. B.

SÍNTESIS DE LA INVENCIÓN

En un aspecto, la presente invención da a conocer un compuesto de la Fórmula I:



en la cual:

Q es un radical bivalente o trivalente seleccionado entre arilo C_{6-10}, heteroarilo C_{1-10}, cicloalquilo C_{3-8} y heterocicloalquilo C_{3-8}; donde dicho arilo, heteroarilo, cicloalquilo o heterocicloalquilo de Q está optativamente sustituido con hasta 3 radicales independientemente seleccionados entre halo, alquilo C_{1-6}, alquilo C_{1-6} sustituido con halo, alcoxi C_{1-6}, alcoxi C_{1-6} sustituido con halo, $-C(O)R_{20}$ y $-C(O)OR_{20}$; donde R_{20} es seleccionado entre hidrógeno y alquilo C_{1-6}; y que optativamente conecta a un carbono adyacente a W_2 a través de una CR_{31}, O, S o NR_{31} con un carbono de Q (indicado por la línea de puntos) para formar un anillo de 5 miembros fusionado a los anillos A y Q (tales como los anillos fusionados en los ejemplos V1–V5, más adelante); donde R_{31} es seleccionado entre hidrógeno y alquilo C_{1-6};

W_1 y W_2 son independientemente seleccionados entre CR_{21} y N; donde R_{21} es seleccionado entre hidrógeno, ciano, alquilo C_{1-6} y $-C(O)OR_{25}$; donde R_{25} es seleccionado entre hidrógeno y alquilo C_{1-6}; el anillo A puede tener hasta 2 carbonos del anillo sustituidos con un grupo seleccionado entre –C(O)–, –C(S)– y $-C(=NOR_{30})-$ y puede estar parcialmente insaturado con hasta 2 enlaces dobles, donde R_{30} es seleccionado entre hidrógeno y alquilo C_{1-6};

L es seleccionado entre alquileno C_{1-6}, alquenileno C_{2-6}, $-(CH_2)_nO-$, $-OC(O)(CH_2)_n-$, $-C(O)O(CH_2)_n-$, $-NR_{26}(CH_2)_n-$ y $-O(CH_2)_n-$; donde R_{26} es seleccionado

entre hidrógeno y alquilo C_{1-6} y n es seleccionado entre 0, 1, 2, 3, 4 y 5; donde cualquier alquilo de L puede estar optativamente sustituido con 1 a 3 radicales independientemente seleccionados entre halo, alquilo C_{1-6}, alquilo C_{1-6} sustituido con halo, alcoxi C_{1-6}, alcoxi C_{1-6} sustituido con halo, $-C(O)R_{22}$ y $-C(O)OR_{22}$; donde R_{22} es seleccionado entre hidrógeno y alquilo C_{1-6};

m es seleccionado entre 0, 1, 2, 3 y 4;

q es seleccionado entre 0, 1, 2, 3 y 4;

cada uno de t_1, t_2, t_3 y t_4 es independientemente seleccionado entre 0, 1 y 2;

R_1 es seleccionado entre $-X_1S(O)_{0-2}X_2R_{6a}$, $-X_1S(O)_{0-2}X_2OR_{6a}$, $-X_1S(O)_{0-2}X_2C(O)R_{6a}$, $-X_1S(O)_{0-2}X_2C(O)OR_{6a}$, $-X_1S(O)_{0-2}X_2OC(O)R_{6a}$ y $-X_1S(O)_{0-2}NR_{6a}R_{6b}$; donde X_1 es seleccionado entre un enlace, O, $NR_{7a}R_{7b}$ y alquileno C_{1-4}; X_2 es seleccionado entre un enlace y alquileno C_{1-4}; R_{6a} es seleccionado entre hidrógeno, halo, alquilo C_{1-6}, alquenilo C_{2-6}, arilo C_{6-10}, heteroarilo C_{1-10}, heterocicloalquilo C_{3-8} y cicloalquilo C_{3-8}; donde dicho arilo, heteroarilo, cicloalquilo y heterocicloalquilo de R_{6a} está optativamente sustituido con 1 a 3 radicales independientemente seleccionados entre hidroxi, halo, alquilo C_{1-6}, alquilo C_{1-6} sustituido con halo, alquilo C_{1-6} sustituido con hidroxi, alquilo C_{1-6} sustituido con ciano, alcoxi C_{1-6}, alcoxi C_{1-6} sustituido con halo y aril C_{6-10}– alcoxi C_{1-4}; R_{6b} es seleccionado entre hidrógeno y alquilo C_{1-6}; y R_{7a} y R_{7b} son independientemente seleccionados entre hidrógeno y alquilo C_{1-6};

R_2 y R_3 son independientemente seleccionados entre hidrógeno, halo, hidroxi, alquilo C_{1-6}, alquilo C_{1-6} sustituido con halo, alquilo C_{1-6} sustituido con hidroxi, alcoxi C_{1-6}, alcoxi C_{1-6} sustituido con halo, $-C(O)R_{23}$, y $-C(O)OR_{23}$; donde R_{23} es seleccionado entre hidrógeno y alquilo C_{1-6};

R_4 es seleccionado entre R_8 y $-C(O)OR_8$; donde R_8 es seleccionado entre alquilo C_{1-6}, arilo C_{6-10}, heteroarilo C_{1-10}, cicloalquilo C_{3-8} y heterocicloalquilo C_{3-8}; donde dicho arilo, heteroarilo, cicloalquilo o heterocicloalquilo de R_8 está optativamente sustituido con 1 a 3 radicales independientemente seleccionados entre halo, alquilo C_{1-6},

cicloalquilo C_{3-12}, heterocicloalquilo C_{3-8}, alquilo C_{1-6} sustituido con halo, alquilo C_{1-6} sustituido con hidroxi, alcoxi C_{1-6} y alcoxi C_{1-6} sustituido con halo;

R_5 es seleccionado entre hidrógeno, alquilo C_{1-6}, alquilo C_{1-6} sustituido con halo, alquilo C_{1-6} sustituido con hidroxi, alcoxi C_{1-6} y alcoxi C_{1-6} sustituido con halo.

En un segundo aspecto, la presente invención da a conocer una composición farmacéutica que contiene un compuesto de la fórmula I o un derivado N–óxido del mismo, los isómeros individuales y mezclas de isómeros del mismo, o una sal aceptable para uso farmacéutico del mismo, mezclada con uno o más excipientes.

En un tercer aspecto, la presente invención da a conocer un método para el tratamiento de una enfermedad en un animal en el cual la modulación de la actividad de GPR119 puede prevenir, inhibir o mitigar la patología y/o sintomatología de las enfermedades, método que comprende administrar a un animal una cantidad terapéuticamente efectiva de un compuesto de la Fórmula I o un derivado N–óxido del mismo, los isómeros individuales y mezclas de isómeros del mismo, o una sal aceptable para uso farmacéutico del mismo.

En un cuarto aspecto, la presente invención da a conocer el uso de un compuesto de la fórmula I en la elaboración de un medicamento para el tratamiento de una enfermedad en un animal en el cual la actividad de GPR119 contribuye a la patología y/o sintomatología de la enfermedad.

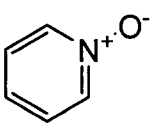
En un quinto aspecto, la presente invención da a conocer un proceso para la preparación de compuestos de la fórmula I y los derivados N–óxido, derivados profármacos, derivados protegidos, isómeros individuales y mezcla de isómeros de los mismos, así como las sales aceptables para uso farmacéutico de los mismos.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Definiciones

"Alquilo" como grupo y como elemento estructural de otros grupos, por ejemplo alquilo sustituido con halo y alcoxi, puede ser de cadena recta, ramificada, cíclica o espiro. Alcoxi C_{1-6} incluye metoxi, etoxi, y demás. Alquilo sustituido con halo incluye trifluorometilo, pentafluoroetilo, y demás.

"Arilo" se refiere a un conjunto de anillos monocíclicos o bicíclicos fusionados que contienen de seis a diez átomos de anillo. Por ejemplo, arilo puede ser fenilo o naftilo, preferentemente fenilo. "Arileno" se refiere a un radical bivalente derivado de un grupo arilo. "Heteroarilo" es como se define con respecto a arilo, donde uno o más de los miembros del anillo son heteroátomos. Por ejemplo, heteroarilo C_{1-10} incluye piridilo, indolilo, indazolilo, quinoxalinilo, quinolinilo, benzofuranilo, benzopiranilo, benzothiopiranilo, benzo[1,3]dioxol, imidazolilo, benzo–imidazolilo, pirimidinilo, furanilo, oxazolilo, isoxazolilo, triazolilo, tetrazolilo, pirazolilo, tienilo, 1H–piridin–2–onilo, 6–oxo–1,6–dihidro–piridin–3–ilo, etc. "aril C_{6-10}alquilo C_{0-4}" se refiere a un arilo de acuerdo con lo descripto anteriormente, conectado por medio de un agrupamiento alquileno. Por ejemplo, aril C_{6-10}alquilo C_{0-4} incluye fenetilo, bencilo, etc. Heteroarilo también incluye los derivados N–óxido, por ejemplo, los derivados N–óxido de piridina con la siguiente estructura:



"Cicloalquilo" se refiere a un conjunto de anillos monocíclicos, bicíclicos fusionados o enlazados saturados o parcialmente insaturados que contiene el número de átomos de anillo indicado. Por ejemplo, cicloalquilo C_{3-10} incluye ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, etc. "Heterocicloalquilo" significa cicloalquilo, según lo definido en esta solicitud, siempre que uno o más de los carbonos indicados del anillo haya sido reemplazado por una porción seleccionada entre –O–, –N=, –NR–, –C(O) –, –S–, –S(O) – o $–S(O)_2–$, donde R es hidrógeno, alquilo C_{1-4} o un grupo protector de nitrógeno.

Por ejemplo, en el contexto de esta solicitud el término heterocicloalquilo C_{3-8} utilizado para describir los compuestos de la presente invención, incluye morfolino, pirrolidinilo, piperazinilo, piperidinilo, piperidinilona, 1,4–dioxa–8–aza–espiro[4.5]dec–8–ilo, 2–oxo–pirrolidin–1–ilo, 2–oxo–piperidin–1–ilo, etc.

GPR119 se refiere al receptor 119 acoplado a la proteína G (GenBank® No. de Acceso AAP72125) al que también se hace referencia en la literatura como RUP3 y GPR116. El término GPR119 empleado en este contexto incluye las secuencias humanas que se encuentran en el número de acceso de GeneBank AY288416, variantes alélicas de origen natural, ortólogos de mamíferos y mutantes recombinantes de los mismos.

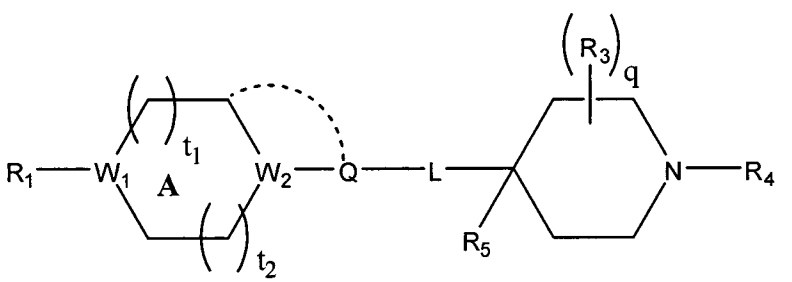
"Halógeno" (o halo) representa preferentemente cloro o flúor, aunque también puede ser bromo o yodo.

"Tratar", "tratando" y "tratamiento" se refieren a un método para mitigar o vencer una enfermedad y/o sus síntomas asociados.

Descripción de las Realizaciones Preferidas

La presente invención da a conocer compuestos, composiciones y métodos para el tratamiento de enfermedades en las cuales la modulación de la actividad de GPR119 puede prevenir, inhibir o mejorar la patología y/o sintomatología de las enfermedades, método que comprende administrar al animal una cantidad terapéuticamente efectiva de un compuesto de la fórmula I.

En una realización, con referencia a los compuestos de la Fórmula Ia:



en la cual:

Q es un radical bivalente o trivalente seleccionado entre arilo C_{6-10}, heteroarilo C_{1-10}, cicloalquilo C_{3-8} y heterocicloalquilo C_{3-8}; donde dicho arilo, heteroarilo, cicloalquilo o heterocicloalquilo de Q está optativamente sustituido con hasta 3 radicales independientemente seleccionados entre halo, alquilo C_{1-6}, alquilo C_{1-6} sustituido con halo, alcoxi C_{1-6}, alcoxi C_{1-6} sustituido con halo, $-C(O)R_{20}$ y $-C(O)OR_{20}$; donde R_{20} es seleccionado entre hidrógeno y alquilo C_{1-6}; y que optativamente conecta un carbono adyacente a W_2 a través de un CR_{31} u O con un carbono de Q (indicado por la línea de puntos en la Fórmula Ia) para formar un anillo de 5 miembros fusionado a los anillos A y Q (tal como los anillos fusionados de los ejemplos V1–V5, expuestos más adelante); donde R_{31} es seleccionado entre hidrógeno y alquilo C_{1-6};

W_1 y W_2 son independientemente seleccionados entre CR_{21} y N, donde R_{21} es seleccionado entre hidrógeno, ciano, alquilo C_{1-6} y $-C(O)OR_{25}$; donde R_{25} es seleccionado entre hidrógeno y alquilo C_{1-6}; el anillo A puede tener hasta 2 carbonos del anillo sustituidos con un grupo seleccionado entre –C(O)–, –C(S)– y $-C(=NOR_{30})-$ y puede estar parcialmente insaturado con hasta 2 enlaces dobles, donde R_{30} es seleccionado entre hidrógeno y alquilo C_{1-6};

L es seleccionado entre alquileno C_{1-6}, alquenileno C_{2-6}, $-(CH_2)_nO-$, $-NR_{26}CH_2)_n-$, $-OC(O)(CH_2)_n-$, $-C(O)O(CH_2)_n-$ y $-O(CH_2)_n-$; donde R_{26} es seleccionado entre hidrógeno y alquilo C_{1-6}; donde n es seleccionado entre 0, 1, 2, 3, 4 y 5; donde cualquier alquilo de L puede estar optativamente sustituido con 1 a 3 radicales independientemente seleccionados entre halo, alquilo C_{1-6}, alquilo C_{1-6} sustituido con halo, alcoxi C_{1-6}, alcoxi C_{1-6} sustituido con halo, $-C(O)R_{22}$ y $-C(O)OR_{22}$; donde R_{22} es seleccionado entre hidrógeno y alquilo C_{1-6};

cada uno de t_1 y t_2 es independientemente seleccionado entre 0, 1 y 2;

q es seleccionado entre 0, 1, 2, 3 y 4;

R_1 es seleccionado entre$-X_1S(O)_{0-2}X_2R_{6a}$, $-X_1S(O)_{0-2}X_2OR_{6a}$, $-X_1S(O)_{0-2}X_2C(O)R_{6a}$, $-X_1S(O)_{0-2}X_2C(O)OR_{6a}$, $-X_1S(O)_{0-2}X_2OC(O)R_{6a}$ y $-X_1S(O)_{0-2}NR_{6a}R_{6b}$; donde X_1 es seleccionado entre un enlace, O, $NR_{7a}R_{7b}$ y alquileno C_{1-4}; X_2 es seleccionado entre un enlace y alquileno C_{1-4}; R_{6a} es seleccionado entre hidrógeno, halo, alquilo C_{1-6}, alquenilo C_{2-6}, arilo C_{6-10}, heteroarilo C_{1-10}, heterocicloalquilo C_{3-8} y cicloalquilo C_{3-8};

donde dichos arilo, heteroarilo, cicloalquilo y heterocicloalquilo de R_{6a} están optativamente sustituidos con 1 a 3 radicales independientemente seleccionados entre hidroxi, halo, alquilo C_{1-6}, alquilo C_{1-6} sustituido con halo, alquilo C_{1-6} sustituido con hidroxi, alquilo C_{1-6} sustituido con ciano, alcoxi C_{1-6}, alcoxi C_{1-6} sustituido con halo y aril–C_{6-10}alcoxi C_{1-4}; R_{6b} es seleccionado entre hidrógeno y alquilo C_{1-6}; y R_{7a} y R_{7b} son independientemente seleccionados entre hidrógeno y alquilo C_{1-6};

R_3 es seleccionado entre hidrógeno, halo, hidroxi, alquilo C_{1-6}, alquilo C_{1-6} sustituido con halo, alquilo C_{1-6} sustituido con hidroxi, alcoxi C_{1-6}, alcoxi C_{1-6} sustituido con halo, $-C(O)R_{23}$, y $-C(O)OR_{23}$; donde R_{23} es seleccionado entre hidrógeno y alquilo C_{1-6};

R_4 es seleccionado entre R_8 y $-C(O)OR_8$; donde R_8 es seleccionado entre alquilo C_{1-6}, arilo C_{6-10}, heteroarilo C_{1-10}, cicloalquilo C_{3-8} y heterocicloalquilo C_{3-8}; donde dichos arilo, heteroarilo, cicloalquilo o heterocicloalquilo de R_8 están optativamente sustituidos con 1 a 3 radicales independientemente seleccionados entre halo, alquilo C_{1-6}, cicloalquilo C_{3-12}, heterocicloalquilo C_{3-8}, alquilo C_{1-6} sustituido con halo, alquilo C_{1-6} sustituido con hidroxi, alcoxi C_{1-6}, y alcoxi C_{1-6} sustituido con halo;

R_5 es seleccionado entre hidrógeno, alquilo C_{1-6}, alquilo C_{1-6} sustituido con halo, alquilo C_{1-6} sustituido con hidroxi, alcoxi C_{1-6} y alcoxi C_{1-6} sustituido con halo.

En otra realización, Q es un radical bivalente o trivalente seleccionado entre fenilo, piridinilo, pirazinilo, piridazinilo, pirimidinilo, 1,2,4–oxadiazolilo, y tiazolilo; donde dichos fenilo, piridinilo, pirazinilo, piridazinilo, pirimidinilo y tiazolilo de Q están optativamente sustituidos con hasta 3 radicales independientemente seleccionados entre halo, alquilo C_{1-6}, alcoxi C_{1-6}, alquilo C_{1-6} sustituido con halo, $-C(O)OR_{20}$ y $-C(O)R_{20}$; donde R_{20} es seleccionado entre hidrógeno y alquilo C_{1-6}; y que optativamente conectan un átomo de carbono adyacente a W_2 a través de un CR_{31} u O con un carbono de Q para formar un anillo de 5 miembros fusionado a los anillos A y Q; donde R_{31} es seleccionado entre hidrógeno y alquilo C_{1-6}.

En otra de las realizaciones, W_1 y W_2 son independientemente seleccionados entre CR_{21} y N; donde R_{21} es seleccionado entre hidrógeno, ciano, alquilo C_{1-6} y $-C(O)OR_{25}$; donde R_{25} es seleccionado entre hidrógeno y alquilo C_{1-6}; el anillo A puede contener una sustitución de un carbono del anillo con un grupo seleccionado entre –C(O)–, –

C(S)– y –C(=NOR$_{30}$)– y puede estar parcialmente insaturado con un doble enlace; donde R$_{30}$ es seleccionado entre hidrógeno y alquilo C$_{1-6}$; y L es seleccionado entre –O(CH$_2$)$_{0-4}$–, –(CH=CH)–, –OC(O)–, –NH(CH$_2$)$_{0-4}$–, –NCH$_3$(CH$_2$)$_{0-4}$– y –(CH$_2$)$_{1-4}$–.

En otra realización, R$_1$ es seleccionado entre –X$_1$S(O)$_{0-2}$X$_2$R$_{6a}$, –X$_1$S(O)$_{0-2}$X$_2$OR$_{6a}$, –X$_1$S(O)$_{0-2}$X$_2$C(O)OR$_{6a}$, –X$_1$S(O)$_{0-2}$X$_2$OC(O)R$_{6a}$ y –X$_1$S(O)$_{0-2}$NR$_{6a}$R$_{6b}$; donde X$_1$ es seleccionado entre un enlace y O; X$_2$ es seleccionado entre un enlace y alquileno C$_{1-4}$; R$_{6a}$ es seleccionado entre hidrógeno, halo, ciano, metilo, etilo, propilo, isopropilo, etenilo, piridinilo, pirrolidinilo, piperidinilo, morfolino, isoxazolilo, tetrazolilo, fenilo y imidazolilo; donde dichos piperidinilo, piridinilo, pirrolidinilo, morfolino, isoxazolilo, tetrazolilo, fenilo o imidazolilo de R$_{6a}$ están optativamente sustituidos con 1 a 3 radicales independientemente seleccionados entre hidroxi, halo, alquilo C$_{1-6}$ y benzoxi; y R$_{6b}$ es seleccionado entre hidrógeno, metilo y etilo.

En otra realización, R$_4$ es seleccionado entre R$_8$ y –C(O)OR$_8$; donde R$_8$ es seleccionado entre isopropilo, ciclopropilo, t–butilo, 1,2,4–oxadiazolilo, pirimidinilo, piridinilo, piridazinilo, tetrahidro–2H–piranilo, tetrahidrofuranilo, oxetanilo, 2H–tetrazolilo y tiazolilo; donde dichos ciclopropilo, 1,2,4–oxadiazolilo, pirimidinilo, piridinilo, piridazinilo, tetrahidro–2H–piranilo, tetrahidrofuranilo, oxetanilo, 2H–tetrazolilo o tiazolilo de R$_8$ están optativamente sustituidos con 1 a 3 radicales independientemente seleccionados entre halo, trifluorometilo, isopropilo, t–butilo, metilo, etilo y ciclopropilo optativamente sustituido con metilo; y R$_5$ es seleccionado entre hidrógeno y metoxi.

En otra realización se presentan compuestos seleccionados entre: isopropil 4–((4–((4–metansulfonilpiperazin)–1–il)fenoxi)metil)piperidin–1–carboxilato, isopropil 4–(2–(4–(4–(metilsulfonil)piperazin–1–il)fenoxi)etil)piperidin–1–carboxilato, isopropil 4–(3–(4–(4–(metilsulfonil)piperazin–1–il)fenoxi)propil)piperidin–1–carboxilato, isopropil 4–(4–(4–(4–(metilsulfonil)piperazin–1–il)fenoxi)butil)piperidin–1–carboxilato, Isopropil 4–((6–(4–(metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato, *terc*–Butil 4–((6–(4–(metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato, Isopropil 4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, *terc*–Butil 4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, 3–Ciclopropil–5–(4–((5–(4–(metilsulfonil)piperazin–

1–il)pirazin–2–iloxi)metil)piperidin–1–il)–1,2,4–oxadiazol, 5–Ciclopropil–3–(4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–il)–1,2,4–oxadiazol, 2–(4–(Metilsulfonil)piperazin–1–il)–5–((1–(5–(trifluorometil)piridin–2–il)piperidin–4–il)metoxi)pirazina, 5–Isopropil–3–(4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–il)–1,2,4–oxadiazol, Tetrahidro–2H–piran–4–il 4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, (S)–Tetrahidrofuran–3–il 4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, (R)–Tetrahidrofuran–3–il 4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, 2–Isopropil–5–(4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–il)tiazol, 2–((1–(2–metil–2H–tetrazol–5–il)piperidin–4–il)metoxi)–5–(4–(metilsulfonil)piperazin–1–il)pirazina, Oxetan–3–il 4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, Isopropil 4–((5–(4–(metilsulfonil)piperazin–1–il)piridin–2–iloxi)metil)piperidin–1–carboxilato, Isopropil 4–((6–(4–(metilsulfonil)piperazin–1–il)piridazin–3–iloxi)metil)piperidin–1–carboxilato, Isopropil 4–((5–(4–(metilsulfonil)piperazin–1–il)pirimidin–2–iloxi)metil)piperidin–1–carboxilato, (E)–isopropil 4–(2–(6–(4–(metilsulfonil)piperazin–1–il)piridin–3–il)vinil)piperidin–1–carboxilato, Isopropil 4–(2–(6–(4–(metilsulfonil)piperazin–1–il)piridin–3–il)etil)piperidin–1–carboxilato, (E)–Isopropil 4–(2–(2–(4–(metilsulfonil)piperazin–1–il)pirimidin–5–il)vinil)piperidin–1–carboxilato, 5–Etil–2–(4–((6–(4–(metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–il)pirimidina, 1–(Metilsulfonil)–4–(5–((1–(5–(trifluorometil)piridin–2–il)piperidin–4–il)metoxi)piridin–2–il)piperazina, 1–Metilciclopropil 4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, 5–Etil–2–(4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–il)pirimidina, 2–((1–(5–Metilpiridin–2–il)piperidin–4–il)metoxi)–5–(4–(metilsulfonil)piperazin–1–il)pirazina, 1–Metilciclopropil 4–((5–(4–(metilsulfonil)piperazin–1–il)piridin–2–iloxi)metil)piperidin–1–carboxilato, 5–Etil–2–(4–((5–(4–(metilsulfonil)piperazin–1–il)piridin–2–iloxi)metil)piperidin–1–il)pirimidina, 3–Isopropil–5–(4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–il)–1,2,4–oxadiazol, 3–Isopropil–5–(4–((5–(4–(metilsulfonil)piperazin–1–il)piridin–2–

iloxi)metil)piperidin–1–il)–1,2,4–oxadiazol, 1–Metilciclopropil 4–((6–(4–(metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato, 5–Isopropil–3–(4–((6–(4–(metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–il)–1,2,4–oxadiazol, 2–((1–(5–Fluoropiridin–2–il)piperidin–4–il)metoxi)–5–(4–(metilsulfonil)piperazin–1–il)pirazina, 3–Isopropil–5–(4–((6–(4–(metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–il)–1,2,4–oxadiazol, *terc*–Butil 4–((5–(4–(metilsulfonil)–1,4–diazepan–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, *terc*–Butil 4–((5–(4–(metilsulfonil)–1,4–diazepan–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, *terc*–butil 4–((5–(4–(metilsulfonil)piperidin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, 1–Metilciclopropil 4–((5–(4–(metilsulfonil)piperidin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, *terc*–Butil 4–(2–(3–(4–(metilsulfonil)piperazin–1–il)–1,2,4–oxadiazol–5–il)etil)piperidin–1–carboxilato, *terc*–Butil 4–(3–(3–(4–(metilsulfonil)piperazin–1–il)–1,2,4–oxadiazol–5–il)propil)piperidin–1–carboxilato, 5–(3–(1–(5–etilpirimidin–2–il)piperidin–4–il)propil)–3–(4–(metilsulfonil)piperazin–1–il)–1,2,4–oxadiazol, Isopropil 4–(3–(3–(4–(metilsulfonil)piperazin–1–il)–1,2,4–oxadiazol–5–il)propil)piperidin–1–carboxilato, 3–Isopropil–5–(4–(2–(5–(4–(metilsulfonil)piperazin–1–il)tiazol–2–il)etil)piperidin–1–il)–1,2,4–oxadiazol, Isopropil 4–((4–(1–metansulfonil–1,2,3,6–tetrahidropiridin–4–il)fenoxi)metil)piperidin–1–carboxilato, isopropil 4–(4–(1–(metilsulfonil)–1,2,3,6–tetrahidropiridin–4–il)fenoxi)piperidin–1–carboxilato, isopropil 4–(2–(4–(1–(metilsulfonil)–1,2,3,6–tetrahidropiridin–4–il)fenoxi)etil)piperidin–1–carboxilato, isopropil 4–(3–(4–(1–(metilsulfonil)–1,2,3,6–tetrahidropiridin–4–il)fenoxi)propil)piperidin–1–carboxilato, isopropil 4–(4–(4–(1–(metilsulfonil)–1,2,3,6–tetrahidropiridin–4–il)fenoxi)butil)piperidin–1–carboxilato, 1–metilciclopropil 4–((4–(1–(metilsulfonil)–1,2,3,6–tetrahidropiridin–4–il)fenoxi)metil)piperidin–1–carboxilato, 5–isopropil–3–(4–((4–(1–(metilsulfonil)–1,2,3,6–tetrahidropiridin–4–il)fenoxi)metil)piperidin–1–il)–1,2,4–oxadiazol, Isopropil 4–((4–(1–metansulfonilpiperidin–4–il)fenoxi)metil)piperidin–1–carboxilato, isopropil 4–(4–(1–(metilsulfonil)piperidin–4–il)fenoxi)piperidin–1–carboxilato, isopropil 4–(2–(4–(1–(metilsulfonil)piperidin–4–il)fenoxi)etil)piperidin–1–carboxilato, isopropil 4–(3–(4–(1–(metilsulfonil)piperidin–4–il)fenoxi)propil)piperidin–1–

carboxilato, isopropil 4–(4–(4–(1–(metilsulfonil)piperidin–4–il)fenoxi)butil)piperidin–1–carboxilato, 1–Metilciclopropil 4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato, 2–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)–5–(trifluorometil)piridina, 5–isopropil–3–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)–1,2,4–oxadiazol, 3–cloro–2–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)–5–(trifluorometil)piridina, 5–cloro–2–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)piridina, 3–cloro–6–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)piridazina, 5–bromo–2–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)pirimidina, 5–etil–2–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)pirimidina, 5–fluoro–2–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)piridina, 3–isopropil–5–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)–1,2,4–oxadiazol, 3–terc–butil–6–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)piridazina, 5–fluoro–2–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)pirimidina, Isopropil 4–(2–(3–(1–metansulfonil–1,2,3,6–tetrahidropiridin–4–il)fenoxi)etil)piperidin–1–carboxilato, 1–Metilciclopropil 4–metoxi–4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, 1–metilciclopropil 4–((6–formil–5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, 1–Metilciclopropil 4–((6–cloro–5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, 1–Metilciclopropil 4–((5–(4–(3–metoxi–3–oxopropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, ácido 3–(4–(5–((1–((1–metilciclopropoxi)carbonil)–piperidin–4–il)metoxi)pirazin–2–il)piperazin–1–ilsulfonil)propanoico, ácido 3–(4–(5–((1–((1–metilciclopropoxi)carbonil)piperidin–4–il)metoxi)pirazin–2–il)piperazin–1–ilsulfonil)propanoico, ácido 3–(4–(5–((1–((1–metilciclopropoxi)carbonil)piperidin–4–il)metoxi)pirazin–2–il)piperazin–1–ilsulfonil)propanoico, ácido 3–(4–(5–((1–((1–metilciclopropoxi)carbonil)piperidin–4–il)metoxi)pirazin–2–il)piperazin–1–ilsulfonil)propanoico, ácido 3–(4–(5–((1–((1–metilciclopropoxi)carbonil)piperidin–4–il)metoxi)pirazin–2–il)piperazin–1–

ilsulfonil)propanoico; 1–metilciclopropil 4–((5–(4–(3–cianopropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(3–(1H–tetrazol–5–il)propilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(vinilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(2–(piperidin–1–il)etilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(2–morfolinoetilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(2–(dimetilamino)etilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; terc–butil 4–((5–(4–(3–cloropropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; terc–butil 4–((5–(4–(3–acetoxipropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(3–aminopropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(2–etoxietilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(3–(pirrolidin–1–il)propilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(3–(2–metil–1H–imidazol–1–il)propilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(3–(dimetilamino)propilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(propilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(etilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(isopropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(isobutilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(sec–butilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(3–acetoxi–2,2–dimetilpropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(3–hidroxi–2,2–dimetilpropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–Metilciclopropil 4–((5–(4–(2–(piridin–3–il)etilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–Metilciclopropil 4–((5–(4–(2–(piridin–4–

il)etilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–Metilciclopropil 4–((5–(4–sulfamoilpiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; *terc*–Butil 4–((5–(4–(morfolinosulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((6–(4–(etilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((6–(4–(etilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((6–(4–(etilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((6–(4–(etilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((6–(4–(etilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato; 1–Metilciclopropil 4–((5–fluoro–6–(4–(metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato; terc–Butil 4–((5–(4–(metilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–Metilciclopropil 4–((5–(4–(metilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–Metilciclopropil 4–((5–(2–oxo–4–(propilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–Metilciclopropil 4–((5–(4–(isopropilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–Metilciclopropil 4–((5–(4–(isopropilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((6–(2–oxo–4–(propilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((6–(4–(isopropilsulfonil)–2–oxopiperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato; 1–(5–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metoxi)pirazin–2–il)–4–(metilsulfonil)piperazin–2–ona; 1–(5–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metoxi)piridin–2–il)–4–(metilsulfonil)piperazin–2–ona; *terc*–Butil 4–((2,6–difluoro–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; terc–butil 4–((2–metil–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; terc–butil 4–((3–metoxi–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; terc–butil 4–((2,6–dimetil–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; terc–butil 4–((2,5–dimetil–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; terc–butil

4–((2–(metoxicarbonil)–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; terc–butil 4–((2–cloro–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; terc–butil 4–((3–metil–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; terc–butil 4–((2,3–dimetil–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; terc–butil 4–((2–fluoro–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; terc–butil 4–((4–(1–(metilsulfonil)piperidin–4–il)–2–(trifluorometil)fenoxi)metil)piperidin–1–carboxilato; 2–(4–((2,6–Difluoro–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)–5–etilpirimidina; 1–Metilciclopropil 4–((2,6–difluoro–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; 3–(4–(4–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metoxi)–3,5–difluorofenil)piperidin–1–ilsulfonil)propil acetato; 1–Metilciclopropil 4–((4–(1–(3–acetoxipropilsulfonil)piperidin–4–il)–2,6–difluorofenoxi)metil)piperidin–1–carboxilato; 3–(4–(4–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metoxi)–3,5–difluorofenil)piperidin–1–ilsulfonil)propan–1–ol; 1–Metilciclopropil 4–((2,6–difluoro–4–(1–(3–hidroxipropilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; Isopropil 4–((5–(1,2,3,6–tetrahidro–1–metansulfonilpiridin–4–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–Metilciclopropil 4–((6–(1,2,3,6–tetrahidro–1–metansulfonilpiridin–4–il)piridin–3–iloxi)metil)piperidin–1–carboxilato; Isopropil 4–(2–(6–(1,2,3,6–tetrahidro–1–metansulfonilpiridin–4–il)piridin–3–iloxi)etil)piperidin–1–carboxilato; 2–(4–((5–(1,2,3,6–Tetrahidro–1–metansulfonilpiridin–4–il)pirazin–2–iloxi)metil)piperidin–1–il)–5–etilpirimidina; 2–(4–((6–(1,2,3,6–Tetrahidro–1–metansulfonil–piridin–4–il)piridin–3–iloxi)metil)piperidin–1–il)–5–etilpirimidina; 2–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metoxi)–5–(1–metansulfonilpiperidin–4–il)pirazina; 2–(4–((6–(1–Metansulfonilpiperidin–4–il)piridin–3–iloxi)metil)piperidin–1–il)–5–etilpirimidina; 3–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metoxi)–6–(1–metansulfonilpiperidin–4–il)piridazina; 2–(4–((5–(1–Metansulfonilpiperidin–4–il)piridin–2–iloxi)metil)piperidin–1–il)–5–etilpirimidina; 1–*terc*–Butil 4–(4–(1–(metilsulfonil)piperidin–4–il)fenil) piperazin–1,4–dicarboxilato; *N*–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metil)–4–(1–(metilsulfonil)piperidin–4–il)anilina; *N*–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metil)–*N*–metil–4–(1–(metilsulfonil)piperidin–4–il)anilina; 4–(4–((1–(5–fluoropirimidin–2–

il)piperidin–4–il)metoxi)fenil)–1–(metilsulfonil)piperidin–4–carboxílico ácido; ácido 2–[(2–{4–[5–({1–[(1–metilciclopropoxi)carbonil]piperidin–4–il}metoxi)pirazin–2–il]–3–oxopiperazin–1–sulfonil}etil)amino]acético; 1–metilciclopropil 4–{[(5–{4–[(2–carbamimidamidoetan)sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(3–metil–3–nitrobutan)sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–(1–bencilpirrolidin–3–sulfonil)–2–oxopiperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(carbamoilmetan)sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(1–carbamoil–1–metiletan)sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(2–oxo–4–{[2–(pirrolidin–1–il)etan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[2–(morfolin–4–il)etan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[3–(dimetilamino)propan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[2–(1,3–dioxo–2,3–dihidro–1H–isoindol–2–il)etan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[(dimetilcarbamoil)metan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[1–(2–metilpropil)pirrolidin–3–sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(2–oxo–4–{[3–(1H–pirazol–1–il)propan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[2–oxo–4–(pirrolidin–3–sulfonil)piperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(2–amino–2–metilpropan)sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[(1–metilpirrolidin–3–il)metan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[2–(azetidin–1–il)etan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(2–oxo–4–{[2–(1H–pirazol–1–il)etan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–

metilciclopropil 4–[({5–[4–(1–metilpirrolidin–3–sulfonil)–2–oxopiperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[1–(dimetilcarbamoil)–1–metiletan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[2–(3,3–difluoroazetidin–1–il)etan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[3–(dimetilamino)–3–metilbutan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(2–{[2–(terc–butoxi)–2–oxoetil]amino}etan)sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–(azetidin–3–sulfonil)–2–oxopiperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[3–(3,3–difluoroazetidin–1–il)propan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[3–(azetidin–1–il)propan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{2–oxo–4–[(3S)–pirrolidin–3–sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(3S)–1–metilpirrolidin–3–sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(3R)–1–metilpirrolidin–3–sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(3S)–pirrolidin–3–sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(3R)–pirrolidin–3–sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–(azetidin–3–sulfonil)piperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{2–oxo–4–[(pirrolidin–3–ilmetan)sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–(1–hidroxi–2–metilpropan–2–sulfonil)piperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(2–hidroxietan)sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(azetidin–3–ilmetan)sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[(1–metilpirrolidin–2–il)metan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{2–oxo–4–[(3R)–pirrolidin–3–sulfonil]piperazin–1–il}pirazin–2–

il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–(1–metilazetidin–3–sulfonil)piperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–(1–metilazetidin–3–sulfonil)–2–oxopiperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[(1–metilazetidin–3–il)metan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[(1–metilazetidin–3–il)metan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–({3–[(3S,4S)–3,4–dihidroxipirrolidin–1–il]propan}sulfonil)–2–oxopiperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–({2–[(3S,4S)–3,4–dihidroxipirrolidin–1–il]etan}sulfonil)–2–oxopiperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(azetidin–3–ilmetan)sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{2–oxo–4–[(pirrolidin–2–ilmetan)sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(3–aminopropan)sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(2–aminoetan)sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(3–metansulfonamidoazetidin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[2–(dimetilamino)etan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(2–oxo–4–{[3–(pirrolidin–1–il)propan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[3–(morfolin–4–il)propan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[(3–metiloxetan–3–il)metan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[3–(acetiloxi)propan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(3,3,3–trifluoropropan)sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[(2E)–2–(hidroxiimino)–4–metansulfonilpiperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(3–cloropropan)sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato;

1–metilciclopropil 4–{[(5–{4–[(3–hidroxipropan)sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–({[1–(dimetilamino)ciclopropil]metan}sulfonil)–2–oxopiperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–({[1–(dimetilamino)ciclopropil]metan}sulfonil)piperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(3–hidroxi–3–metilbutane)sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{2–oxo–4–[(3R)–oxolan–3–sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{2–oxo–4–[(3S)–oxolan–3–sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[3–(acetiloxi)–3–metilbutan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–[({6–[4–({[1–(azetidin–1–il)ciclopropil]metan}sulfonil)piperazin–1–il]piridin–3–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–({[1–(bencilamino)ciclopropil]metan}sulfonil)piperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–({[1–(azetidin–1–il)ciclopropil]metan}sulfonil)piperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[(1–hidroxiciclopropil)metan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[2–(1–hidroxiciclopropil)etan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–({2–[1–(acetiloxi)ciclopropil]etan}sulfonil)piperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–({[1–(benciloxi)ciclopropil]metan}sulfonil)piperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[(1–aminociclopropil)metan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[2–(1–hidroxiciclopropil)etan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–{2,6–difluoro–4–[3–(N–metilmetansulfonamido)azetidin–1–il]fenoximetil}piperidin–1–carboxilato; 1–metilciclopropil 4–[2,6–difluoro–4–(3–metansulfonamidoazetidin–1–il)fenoximetil]piperidin–1–carboxilato; 1–metilciclopropil 4–{2,6–difluoro–4–[3–(2–

metilpropan–1–sulfonamido)azetidin–1–il]fenoximetil}piperidin–1–carboxilato; 1–metilciclopropil 4–{4–[3–(N,2–dimetilpropan–1–sulfonamido)azetidin–1–il]–2,6–difluorofenoximetil}piperidin–1–carboxilato; 5–etil–2–{4–[({2–metansulfonil–1H,2H,3H,4H–pirazino[1,2–a]indol–8–il}oxi)metil]piperidin–1–il}pirimidina; 11–{[1–(5–etilpirimidin–2–il)piperidin–4–il]oxi}–5–metansulfonil–8–oxa–5–azatriciclo[7.4.0.0{2,7}]trideca–1(13),2(7),9,11–tetraeno; 11–{[1–(5–etilpirimidin–2–il)piperidin–4–il]metoxi}–5–metansulfonil–8–oxa–5–azatriciclo[7.4.0.0{2,7}]trideca–1(13),2(7),9,11–tetraeno; terc–butil 4–[({2–metansulfonil–1H,2H,3H,4H–pirazino[1,2–a]indol–8–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–[({2–metansulfonil–1H,2H,3H,4H–pirazino[1,2–a]indol–8–il}oxi)metil]piperidin–1–carboxilato; propan–2–il 4–{3–[3–(1–metansulfonilpiperidin–4–il)fenoxi]propil}piperidin–1–carboxilato; propan–2–il 4–{2–[3–(1–metansulfonilpiperidin–4–il)fenoxi]etil}piperidin–1–carboxilato; propan–2–il 4–[3–(1–metansulfonilpiperidin–4–il)fenoximetil]piperidin–1–carboxilato; propan–2–il 4–{3–[3–(1–metansulfonil–1,2,3,6–tetrahidropiridin–4–il)fenoxi]propil}piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–metansulfonil–2–sulfanilidenpiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil (3S,4S)–3–hidroxi–4–{[(6–{4–[(2–metilpropan)sulfonil]piperazin–1–il}piridin–3–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil (3R,4S)–3–hidroxi–4–{[(6–{4–[(2–metilpropan)sulfonil]piperazin–1–il}piridin–3–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–hidroxi–4–{[(6–{4–[(2–metilpropan)sulfonil]piperazin–1–il}piridin–3–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(6–{4–[(2–hidroxi–2–metilpropan)sulfonil]piperazin–1–il}piridin–3–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil (3S,4R)–3–metoxi–4–{[(6–{4–[(2–metilpropan)sulfonil]piperazin–1–il}piridin–3–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[3–(3,3–difluoroazetidin–1–il)propan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[3–(azetidin–1–il)propan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(3–metoxipropan)sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(6–{4–[(3–cloropropan)sulfonil]–2–oxopiperazin–1–il}piridin–3–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[2–(azetidin–1–

il)etan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[6–(4–{[3–(azetidin–1–il)propan]sulfonil}piperazin–1–il)piridin–3–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–(pirrolidin–3–sulfonil)piperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[2–(3,3–difluoroazetidin–1–il)etan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–{[(6–{4–[(3–hidroxipropan)sulfonil]–2–oxopiperazin–1–il}piridin–3–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–({[6–(4–{[3–(azetidin–1–il)propan]sulfonil}–2–oxopiperazin–1–il)piridin–3–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–[2,6–difluoro–4–(4–metansulfonil–2–oxopiperazin–1–il)fenoximetil]piperidin–1–carboxilato; y 1–metilciclopropil 4–[({5–[4–(oxetan–3–sulfonil)–2–oxopiperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato.

En los Ejemplos y Tablas expuestos más adelante se detallas otros compuestos de la invención.

La presente invención incluye todos los compuestos con marca isotópica aceptables para uso farmacéutico de la invención, es decir, los compuestos de la Fórmula (I), en los cuales se reemplaza uno o más átomos por átomos que tengan el mismo número atómico, aunque una masa atómica o número de masa diferente de la masa atómica o número de masa habitualmente encontrado en la naturaleza.

Entre los ejemplos de isótopos adecuados para la inclusión en los compuestos de la presente invención se cuentan los isótopos de hidrógeno, como por ejemplo ^{2}H y ^{3}H, carbono, tales como ^{11}C, ^{13}C y ^{14}C, cloro, como ^{36}Cl, flúor, como por ejemplo ^{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, como por ejemplo ^{32}P, y azufre, como ^{35}S.

Ciertos compuestos con marca isotópica de la Fórmula (I), por ejemplo, los que incorporan un isótopo radiactivo, son de utilidad en estudios de distribución tisular de fármacos y/o sustratos. Los isótopos radiactivos tritio, es decir ^{3}H, y carbono–14, o sea. ^{14}C, son particularmente útiles para este fin, en vista de su facilidad de incorporación y medios de detección viables.

La sustitución con isótopos más pesados tales como deuterio, es decir ^{2}H, puede dar

lugar a ciertas ventajas terapéuticas como resultado de una mayor estabilidad metabólica, por ejemplo una mayor vida media in vivo o una reducción de los requerimientos de dosificación y, por ende, pueden ser preferibles en algunas circunstancias.

La sustitución con isótopos emisores de positrones tales como ^{11}C, ^{18}F, ^{15}O y ^{13}N, puede ser de utilidad en estudios de Topografía por Emisión de Positrones (PET) para examinar la ocupación de receptores en el sustrato.

Los compuestos con marca isotópica de la Fórmula (I) se pueden preparar, en general, por técnicas convencionales conocidas por las personas con capacitación normal en la técnica o mediante procesos análogos a los descriptos en los Ejemplos y Preparaciones adjuntas utilizando reactivos con marca isotópica adecuados en lugar de los reactivos sin marca que se utilizaban anteriormente.

Utilidad Farmacológica

Los compuestos de la invención modulan la actividad de GPR119 y, por tal motivo, son de utilidad para el tratamiento de enfermedades o trastornos en los cuales la actividad de GPR119 contribuye a la patología y/o sintomatología de la enfermedad. Esta invención presenta además los compuestos de la presente invención para usar en la preparación de medicamentos para el tratamiento de las enfermedades o trastornos en los cuales la actividad de GPR119 contribuye a la patología y/o sintomatología de la enfermedad.

Las patologías que aparecen como consecuencias de diabetes Tipo II son la señalización deteriorada de la insulina en sus tejidos diana y la incapacidad de las células productoras de insulina del páncreas para segregar un grado de insulina apropiado en respuesta a una señal hiperglucémica. Las terapias actuales para el tratamiento de esta última incluyen inhibidores del canal del potasio sensible a ATP sensible a las células β para desencadenar la liberación de reservas endógenas de insulina, o la administración de insulina exógena. Ninguna de estas obtiene una normalización precisa de los niveles de glucosa en sangre y ambas conllevan el riesgo de inducir la hipoglucemia. Por estas razones, ha existido un intenso interés en el

desarrollo de productos farmacéuticos que funcionen en una acción dependiente de la glucosa, es decir, potenciadores de la señalización de la glucosa. Los sistemas de señalización fisiológicos que funcionan de esta manera están bien caracterizados e incluyen los péptidos intestinales GLP–I, GIP y PACAP. Estas hormonas actúan a través de su receptor acoplado a la proteína G cognado para estimular la producción de cAMP en las células β pancreáticas. El aumento de cAMP no parece dar lugar a la estimulación de la liberación de insulina durante el estado de ayuno o pre–prandial. Sin embargo, una serie de blancos bioquímicos de la señalización de cAMP, entre los que se incluye el canal del potasio sensible a ATP, los canales del potasio sensibles al voltaje y la maquinaria exocitótica, se modifican de tal manera que se potencia intensamente la respuesta secretoria de insulina a un estímulo de glucosa postprandial. En consecuencia, los agonistas de los novedosos GPCRs de células β, de similar funcionamiento, incluyendo GPR119, también estimularían la liberación de insulina endógena y, en consecuencia, promoverían la normoglucemia en la diabetes Tipo II. También es un hecho reconocido que el incremento de cAMP, por ejemplo como resultado de la estimulación de GLP–I, promueve la proliferación de células β, inhibe la muerte de las células β y, de esa manera, mejora la masa de islotes. Se estima que este efecto positivo sobre la masa de células β ha de resultar beneficioso tanto en la diabetes Tipo II, en la cual se produce una cantidad insuficiente de insulina, como en la diabetes Tipo I, en la cual se destruyen las células β debido a una respuesta autoinmune inapropiada.

Algunos GPCRs de células β, entre los que se incluye el GPR119, también están presentes en el hipotálamo, donde modulan el apetito, la saciedad, reducen la ingesta de alimentos, controlando o reduciendo el peso y el gasto energético. Por ende, dada su función dentro del circuito hipotalámico, los agonistas o agonistas inversos de estos receptores mitigan el apetito, promueven la saciedad y, por lo tanto, regulan el peso.

También es un hecho reconocido que las enfermedades metabólicas ejercen una influencia negativa sobre otros sistemas fisiológicos. Por consiguiente, con frecuencia hay un codesarrollo de múltiples estados patológicos (por ejemplo, diabetes tipo I, diabetes tipo II, tolerancia insuficiente a la glucosa, resistencia a la insulina,

hiperglucemia, hiperlipidemia, hipertrigliceridemia, hipercolesterolemia, obesidad o enfermedad cardiovascular en el "Síndrome X") o enfermedades secundarias que se producen claramente como secundarias de la diabetes (por ejemplo enfermedad renal, neuropatía periférica). Por consiguiente, se estima que el tratamiento efectivo del trastorno diabético ha de ser, a su vez, provechoso para esos estados patológicos interconectados..

En una realización de la presente invención, se presenta un método para el tratamiento de una enfermedad metabólica y /o un trastorno relacionado con el metabolismo en un individuo, que comprende administrar al individuo que necesita dicho tratamiento una cantidad terapéuticamente efectiva de un compuesto de la presente invención o una composición farmacéutica del mismo. Las enfermedades metabólicas y trastornos asociados al metabolismo son seleccionados, aunque no a modo de limitación, entre hiperlipidemia, diabetes tipo 1, diabetes mellitus tipo 2, diabetes tipo 1 idiopático (Tipo Ib), diabetes autoinmune latente en adultos (DALA), diabetes tipo 2 de inicio temprano (EOD), diabetes atípica de inicio juvenil (YOAD), diabetes de inicio en la madurez (MODY), diabetes relacionada con la desnutrición, diabetes gestacional, enfermedad cardiaca coronaria, accidente cerebrovascular isquémico, restenosis posterior a la angioplastia, enfermedad vascular periférica, claudicación intermitente, infarto de miocardio (por ejemplo, necrosis y apoptosis), dislipidemia, lipemia postprandial, condiciones de tolerancia a la glucosa deteriorada (IGT), estados de glucosa plasmática deteriorada en ayunas, acidosis metabólica, cetosis, artritis, obesidad, osteoporosis, hipertensión, insuficiencia cardiaca congestiva, hipertrofia del ventrículo izquierdo, enfermedad arterial periférica, retinopatía diabética, degeneración macular, cataratas, nefropatía diabética, glomeruloesclerosis, insuficiencia renal crónica, neuropatía diabética, síndrome metabólico, síndrome X, síndrome premenstrual, enfermedad cardiaca coronaria, angina pectoris, trombosis, aterosclerosis, infarto de miocardio, ataques isquémicos transitorios, accidente cerebrovascular, restenosis vascular, hiperglucemia, hiperinsulinemia, hiperlipidemia, hipertrigliceridemia, resistencia a la insulina, metabolismo de la glucosa deteriorado, condiciones de tolerancia a la glucosa deteriorada, condiciones de glucosa plasmática en ayunas

deteriorada, obesidad, disfunción eréctil, trastornos de la piel y los tejidos conectivos, ulceraciones de los pies y colitis ulcerativa, disfunción endotelial y deterioro de la flexibilidad vascular.

En un a realización de la presente invención se presentan los beneficios terapéuticos de los moduladores de la actividad de GPR119 derivados de los niveles crecientes de GIP y PPY. Por ejemplo, neuroprotección, aprendizaje y memoria, convulsiones y neuropatía periférica.

Se ha demostrado que los agonistas del receptor GLP–1 y GLP–1 son eficaces para el tratamiento de las enfermedades neurodegenerativas y otros trastornos neurológicos. Se ha demostrado que GLP–1 y exendina–4 estimulan la excrecencia de neuritas y potencian la supervivencia de las células después del retiro del factor de crecimiento en células PC12. En un modelo de neurodegeneración en roedores, GLP–1 y exendina–4 restauran la actividad de los marcadores colinérgicos en el cerebro anterior basal. La infusión central de GLP–1 y exendina–4 también reduce los niveles del péptido β–amiloide en ratones y reduce la cantidad de proteína precursora amiloide en las células PC12 cultivadas. Se ha demostrado que los agonistas del receptor GLP–1 aumentan el aprendizaje en ratas y que los ratones con inactivación (knockout) del receptor GLP–1 exhiben deficiencias en el comportamiento del aprendizaje. Los ratones knockout también exhiben susceptibilidad a las convulsiones inducidas por cainato, que se pueden prevenir mediante la administración de agonistas del receptor GLP–1. También se ha demostrado que GLP–1 y exendina–4 son eficaces para el tratamiento de la degeneración de los nervios inducida por piridoxina, un modelo experimental de neuropatía sensorial periférica.

Asimismo, ha quedado demostrado que el polipéptido insulinotrópico dependiente de la glucosa (GIP) tiene efectos sobre la proliferación de las células progenitores del hipocampo y en el aumento de la coordinación sensoriomotriz y el reconocimiento mnemónico.

En una realización de la presente invención se dan a conocer los beneficios terapéuticos de los moduladores de la actividad de GPR119. Por ejemplo, GLP–2 y síndrome de intestino corto (SBS). Varios estudios en animales y de ensayos clínicos

han demostrado que GLP–2 es una hormona trófica que desempeña una función importante en la adaptación intestinal. Su rol en la regulación de la proliferación celular, la apoptosis y la absorción de nutrientes ha sido bien documentado. El síndrome de intestino corto se caracteriza por la mala absorción de nutrientes, agua y vitaminas como resultado de enfermedad o resección quirúrgica de partes del intestino delgado (por ejemplo, enfermedad de Crohn). Se piensa que las terapias que mejoran la adaptación intestinal son ventajosas en el tratamiento de esta enfermedad. De hecho, los estudios en fase II en pacientes con SBS han demostrado que la teglutida, un análogo del GLP–2, aumentaba modestamente la absorción de fluidos y nutrientes.

En una realización de la invención se presentan los beneficios terapéuticos de los moduladores de la actividad de GPR119 derivados de los niveles crecientes de GIP y PPY. Por ejemplo, GLP–1, GIP y osteoporosis. Se ha demostrado que GLP–1 aumenta la secreción y expresión de calcitonina y péptido derivado del gen de la calcitonina (CGRP) en una línea de células C murinas (CA–77). La calcitonina inhibe la resorción ósea por los osteoclastos y promueve la mineralización del hueso esquelético. La osteoporosis es una enfermedad que se caracteriza por una densidad mineral ósea reducida y, por consiguiente, el aumento de la calcitonina inducido por GLP–1 podría ser terapéuticamente beneficioso.

Se ha informado que el GIP estaba implicado en la regulación en ascenso de los marcadores de formación ósea en osteoblastos, incluyendo el ARNm tipo I de colágeno y en el aumento de la densidad mineral ósea. Como en el caso de GLP–1, también se ha demostrado que GIP inhibe la resorción ósea.

En una realización de la invención se encuentran los beneficios terapéuticos de los moduladores de la actividad de GPR119 derivados del aumento de los niveles de GIP y PPY. Por ejemplo, PPY y la evacuación gástrica. El GPR119 situado en las células de polipéptido pancreático (PP) de los islotes ha estado implicado en la secreción de PPY. Se ha informado que PPY tenía profundos efectos sobre diversos procesos fisiológicos, entre los que se incluye la modulación de la evacuación gástrica y la motilidad gastrointestinal. Estos efectos retardan el proceso digestivo y la captación de nutrientes y, de esa manera, previenen la elevación postprandial de la glucosa en sangre. El PPY

puede suprimir la ingesta de alimentos cambiando la expresión de los péptidos hipotalámicos reguladores de la alimentación. Los ratones con sobreexpresión de PP exhibieron el fenotipo delgado con reducción de la ingesta de alimentos y evacuación gástrica.

De acuerdo con lo expuesto, la presente invención presenta además un método para la prevención o mejoramiento de la sintomatología de cualquiera de las enfermedades o trastornos antes descriptos en un sujeto que lo necesita, método que comprende administrar a dicho sujeto una cantidad terapéuticamente efectiva (*Ver, "Administration and Pharmaceutical Compositions", citado más adelante*) de un compuesto de la Fórmula I o una sal aceptable para uso farmacéutico del mismo. Para cualquiera de los usos mencionados, la dosis necesaria varía dependiendo del modo de administración, la afección específica a tratar y el efecto pretendido.

Administración y Composiciones Farmacéuticas

En general, los compuestos de la presente invención se administran en cantidades terapéuticamente efectivas por las vías habituales y aceptables conocidas en la técnica, ya sea en forma individual o en combinación con uno o más agentes terapéuticos. Una cantidad terapéuticamente efectiva puede variar ampliamente dependiendo de la gravedad de la enfermedad, la edad y la salud relativa del sujeto, de la potencia del compuesto empleado y otros factores. En general, se indica que se pueden obtener resultados satisfactorios con dosis diarias de aproximadamente 0,03 a 2,5 mg/kg de peso corporal. Una dosis diaria indicada en un mamífero de mayor tamaño, por ejemplo en humanos, está en el rango de aproximadamente 0,5 mg a aproximadamente 100 mg, administrada en forma conveniente, por ejemplo en dosis divididas hasta cuatro veces por día o en forma retardada. Las formas de dosificación unitaria adecuadas para la administración oral comprenden de aproximadamente1 a 50 mg del ingrediente activo.

Los compuestos de la presente invención se pueden administrar en forma de composiciones farmacéuticas por cualquier vía convencional, especialmente por vía

enteral, por ejemplo oral, por ejemplo en forma de comprimidos o cápsulas, o por vía parenteral, por ejemplo en forma de soluciones o suspensiones inyectables, por vía tópica, por ejemplo en forma de lociones, geles, ungüentos o cremas, o en forma nasal o en supositorios. Las composiciones farmacéuticas que comprenden un compuesto de la presente invención en forma libre o en forma de sal aceptable para uso farmacéutico en combinación con por lo menos un vehículo o diluyente aceptable para uso farmacéutico y pueden ser elaboradas de manera convencional mediante métodos de mezclado, granulación o revestimiento. Por ejemplo, las composiciones orales pueden ser comprimidos o cápsulas de gelatina que comprenden el ingrediente activo con a) diluyentes, por ejemplo lactosa, dextrosa, manitol, sorbitol, celulosa y/o glicina; b) lubricantes, por ejemplo sílice, talco, ácido esteárico, sus sales de magnesio o calcio y/o polietilenglicol; en el caso de los comprimidos también c) aglutinantes, por ejemplo silicato de magnesio y aluminio, pasta de almidón, gelatina, tragacanto, metilcelulosa, carboximetilcelulosa sódica o polivinilpirrolidona; en caso de convenir, d) desintegrantes, por ejemplo almidones, agar, ácido algínico o su sal de sodio, o mezclas efervescentes y/o e) absorbentes, colorantes, sabores y edulcorantes. Las composiciones inyectables pueden ser soluciones o suspensiones acuosas isotónicas y los supositorios se pueden preparar a partir de emulsiones o suspensiones grasas. Las composiciones pueden ser esterilizadas y/o contener adyuvantes, tales como agentes conservantes, estabilizadores, humectantes o emulsionantes, promotores de solución, sales para regular la presión osmótica y/o buffers. Además, también pueden contener otras sustancias de valor terapéutico. Las formulaciones adecuadas para aplicaciones transdérmicas incluyen una cantidad efectiva de un compuesto de la presente invención con un vehículo. Un vehículo puede incluir solventes absorbibles aceptables para uso farmacéutico para asistir en el paso a través de la piel del huésped. Por ejemplo, los dispositivos transdérmicos se presentan en forma de ventaje que comprende una pieza de respaldo, un depósito que contiene el compuesto, optativamente con vehículos, optativamente una barrera para controlar la velocidad para administrar el compuesto a la piel del huésped a una velocidad controlada y predeterminada durante un período de tiempo prolongado y medios para asegurar el

dispositivo a la piel. También se pueden emplear Formulaciones de Matriz para administración Transdérmica. Las formulaciones adecuadas para la administración tópica, por ejemplo a la piel y los ojos son preferentemente soluciones, ungüentos, cremas o geles muy conocidos en la técnica. Estos pueden contener solubilizantes, estabilizadores, agentes potenciadores de la tonicidad, buffers y conservantes.

Los compuestos de la presente invención se pueden administrar en cantidades terapéuticamente efectivas, en combinación con uno o más agentes terapéuticos (combinaciones farmacéuticas).

Por ejemplo, se pueden producir efectos sinérgicos con otros agentes antiobesidad, agentes anorexígenos, supresores del apetito y agentes relacionados. La dieta y/o el ejercicio también pueden tener efectos sinérgicos. Entre los agentes antiobesidad se incluyen, aunque no a modo de limitación, los inhibidores de la secreción de apolipproteína–B/proteína microsomal de transferencia de triglicéridos (apo–B/MTP), agonistas de MCR–4, agonistas de colecistoquinina–A (CCK–A), inhibidores de la recaptación de serotonina y norepinefrina (por ejemplo, sibutramina), agentes simpatomiméticos, agonistas del receptor β3 adrenérgico, agonistas de la dopamina (por ejemplo, bromocriptina), análogos del receptor de la hormona estimulante de melanocitos, antagonistas del receptor cannabinoide 1 [por ejemplo, los compuestos descriptos en WO2006/047516), antagonistas de la hormona concentradora de melamina, leptonas (la proteína OB), análogos de leptina, agonistas del receptor de leptina, antagonistas de galanina, inhibidores de la lipasa (tales como tetrahidrolipstatina, es decir, Orlistat), agentes anorexígenos (como por ejemplo un agonista de bombesina), antagonistas del Neuropéptido Y, agentes tiromiméticos, deshidroepiandrosterona o un análogo de la misma, agonistas o antagonistas del receptor de glucocorticoides, antagonistas del receptor de orexina, antagonistas de la proteína de unión de urocortina, agonistas del receptor del péptido 1 tipo glucagón, factores neurotróficos ciliares (tales como Axokine^{TM}), proteínas humanas relacionadas con la proteína agouti (AGRP), antagonistas del receptor de grelina, antagonistas o agonistas inversos del receptor de histamina 3, agonistas del receptor U de

neuromedina, agentes anorexígenos noradrenérgicos (por ejemplo, fentermina, mazindol y demás) y supresores del apetito (por ejemplo, bupropión).

Cuando se administran los compuestos de la invención en combinación con otras terapias, como es natural, las dosis de los compuestos co–administrados varían dependiendo del tipo de cofármaco específico empleado, del fármaco específico utilizado, de la afección en tratamiento y demás.

Una preparación combinada o composición farmacéutica puede comprender un compuesto de la presente invención según lo definido anteriormente o una sal aceptable para uso farmacéutico del mismo y por lo menos un ingrediente activo seleccionado entre:

a) agentes antidiabéticos tales como insulina, derivados y miméticos de insulina, secretagogos de insulina tales como sulfonilureas, por ejemplo glipizida, gliburida y Amaril, ligandos insulinotrópicos del receptor de sulfonilurea tales como meglitinidas, por ejemplo, nateglinida y repaglinida; sensibilizadores a la insulina tales como inhibidores de la proteína tirosina fosfatasa–1B (PTP–1B) tales como PTP–112; inhibidores de GSK3 (glucógeno sintasa quinasa–3) tales como SB–517955, SB–4195052, SB–216763, NN–57–05441 y NN–57–05445; ligandos de RXR tales como GW–0791 y AGN–194204; inhibidores de los cotransportadores de la glucosa dependientes del sodio tales como T–1095; inhibidores de la glucógeno fosforilasa A tales como BAY R3401; biguanidas tales como metformina; inhibidores de la alfa–glucosidasa, GLP–1 (péptido similar al glucagón–1), análogos de GLP–1 tales como Exendin–4 y miméticos de GLP–1; inhibidores de la DPPIV (dipeptidil peptidasa IV) tales como DPP728, LAF237 (vildagliptina – Ejemplo 1 de WO 00/34241), MK–0431, saxagliptina, GSK23A ; un alterador de la AGE, un derivado de tiazolidona (glitazona) tal como pioglitazona, rosiglitazona, o ácido *(R)*–1–{4–[5–metil–2–(4–trifluorometil–fenil)–oxazol–4–ilmetoxi]–bencensulfonil}–2,3–dihidro–1*H*–indol–2–carboxílico descripto en la solicitud de patente WO 03/043985, como compuesto 19 del Ejemplo 43, un agonista gamma de PPAR no glitazona, por ejemplo GI–262570; inhibidores de la diacilglicerol acetiltransferasa (DGAT) tales como los descriptos en WO 2005044250, WO 2005013907, WO 2004094618 y WO 2004047755;

b) agentes hipolipidémicos tales como los inhibidores de la 3–hidroxi–3–metil–glutaril coenzima A (HMG–CoA) reductasa, por ejemplo lovastatina y compuestos relacionados tales como los descriptos en la Patente de los Estados Unidos No. 4.231,938, pitavastatina, simvastatina y compuestos relacionados tales como los descriptos en las Patentes de los Estados Unidos Nos. 4.448.784 y 4.450.171, pravastatina y compuestos relacionados tales como los descriptos en la Patente de los Estados Unidos No. 4.346.227, cerivastatina, mevastatina y compuestos relacionados, como los descriptos en la Patente de los Estados Unidos No. 3.983.140, velostatina, fluvastatina, dalvastatina, atorvastatina, rosuvastatina y compuestos de estatina relacionados descriptos en la Patente de los Estados Unidos No. 5.753.675, rivastatina, análogos de pirazol de derivados de mevalonolactona de acuerdo con lo descripto en la Patente de los Estados Unidos No. 4.613.610, análogos de indeno de derivados de mevalonolactona descriptos en la solicitud PCT WO 86/03488, 6–[2– (pirrol sustituido–1–il)–alquil)piran–2–onas y derivados de los mismos de acuerdo con lo descripto en la Patente de los Estados Unidos No. 4.647.576, SC–45355 de Searle (un derivado del ácido pentandioico 3– sustituido) dicloroacetato, análogos de imiazol de mevalonolactona de acuerdo con lo descripto en la solicitud PCT WO 86/07054, derivados del ácido 3– carboxi–2– hidroxi–propan–fosfónico descriptos en la Patente francesa No. 2.596.393, pirrol 2,3–disustituido, derivados de furano y tiofeno descriptos en la Solicitud de patente europea No. 0221025, análogos de naftilo de mevalonolactona de acuerdo con lo descripto en la Patente de los Estados Unidos No. 4.686.237, octahidronaftalenos tales como los descriptos en la Patente de los Estados Unidos No. 4. 499.289, análogos ceto de mevinolina (lovastatina) tales como los descriptos en la Solicitud de patente europea No. 0.142.146 A2, y derivados de quinolina y piridina descriptos en las Patentes de los Estados Unidos Nos. 5.506.219 y 5.691.322. Además, en GB 2205837 se describen compuestos de ácido fosfínico de utilidad para la inhibición de la HMG CoA reductasa y adecuados para usar en la presente; inhibidores de la escualeno sintasa; ligandos de FXR (receptor farnesoide X) y LXR (receptor hepático X), colesiramina, fibratos, ácido nicotínico y aspirina;

c) un agente antiobesidad o un agente regulador del apetito tal como un modulador de la actividad de CB1, agonistas del receptor de melanocortina (MC4R), antagonistas del receptor de la hormona concentradora de melanina (MCHR), antagonistas del receptor de secretagogos de la hormona de crecimiento (GHSR), moduladores del receptor de galanina, antagonistas de orexina, agonistas de CCK, agonistas de GLP–1 y otros péptidos derivados de Pre–proglucagón, antagonista de NPY1 o NPY5, moduladores de NPY2 y NPY4, agonistas del factor liberador de corticotropina, moduladores del receptor de histamina–3 (H3), inhibidores de aP2, moduladores gamma de PPAR, moduladores delta de PPAR, inhibidores de la actil–CoA carboxilasa (ACC), inhibidores de 11–β–HSD–1, moduladores del receptor de adinopectina, agonistas beta 3 adrenérgicos tales como AJ9677 (Takeda/Dainippon), L750355 (Merck), o CP331648 (Pfizer) u otros agonistas beta 3 conocidos de acuerdo con lo descripto en las Patentes de los Estados Unidos Nos. 5.541.204. 5.770.615. 5. 491.134. 5.776.983 y 5.488.064, un modulador beta del receptor tiroideo tal como el ligando del receptor tiroideo descripto en WO 97/21993 (U. Cal SF), WO 99/00353 (KaroBio) y GB98/284425 (KaroBio), un inhibidor de SCD–1 de acuerdo con lo descripto en WO2005011655, un inhibidor de la lipasa tal como orlistat o ATL–962 (Alizyme), agonistas del receptor de serotonina (por ejemplo, BVT– 933 (Biovitrum)), inhibidores de la recaptación o agentes liberadores de monoamina tales como fenfluramina, dexfenfluramina, fluvoxamina, fluoxetina, paroxetina, sertralina, clorfentermina, cloforex, clortermina, picilorex, sibutramina, dexamphetamina, fentermina, fenilpropanolamina o mazindol, agentes anorexígenos tales como topiramato (Johnson & Johnson), CNTF (factor neurotrófico ciliar)/Axokine® (Regeneron), BDNF (factor neurotrófico derivado del cerebro), moduladores de la leptina y el receptor de leptina, fentermina, leptina, bromocriptina, dexamphetamina, anfetamina, fenfluramina, dexfenfluramina, sibutramina, orlistat, dexfenfluramina, mazindol, fentermina, fendimetrazina, dietilpropión, fluoxetina, bupropión, topiramato, dietilpropión, benzofetamina, fenilpropanolamina o ecopipam, efedrina, pseudoefedrina;

d) agentes antihipertensivos tales como diuréticos de bucle tales como ácido etacrínico, furosemida y torsemida; diuréticos tales como derivados de tiazida, cloritiazida,

hidroclorotiazida, amilorida; inhibidores de la enzima convertidora de angiotensina (ACE) tales como benazeprilo, captoprilo, enalaprilo, fosinoprilo, lisinoprilo, moexiprilo, perinodoprilo, quinaprilo, ramipril y trandolapril; inhibidores de la bomba de membrana de Na–K–ATPasa tales como digoxina; inhibidores de la neutralendopeptidasa (NEP), por ejemplo tiorfán, terteo–tiorfán, SQ29072; inhibidores de la ECE, por ejemplo SLV306; inhibidores de la ACE/NEP tales como omapatrilat, sampatrilat y fasidotril; antagonistas de la angiotensina II tales como candesartán, eprosartán, irbesartán, losartán, telmisartan y valsartán, especialmente valsartán; inhibidores de la renina tales como aliskiren, terlakiren, ditekiren, RO 66–1132, RO–66–1168; bloqueantes del receptor beta–adrenérgico tales como acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol y timolol; agentes inotrópicos tales como digoxina, dobutamina y milrinona; bloqueantes de los canales del calcio tales como as amlodipina, bepridilo, diltiazem, felodipina, nicardipina, nimodipina, nifedipina, nisoldipina y verapamil; antagonistas del receptor de aldosterona; inhibidores de la aldosterona sintasa y antagonistas dobles de ET/AII tales como los descriptos en WO 00/01389.

e) un compuesto para el aumento del HDL;

f) Moduladores de la absorción de colesterol tales como Zetia® y KT6–971;

g) Análogos y miméticos de la Apo–A1;

h) inhibidores de la trombina tales como Ximelagatrán;

i) inhibidores de la aldosterona tales como anastrazol, fadrazol, eplerenona;

j) inhibidores de la agregación plaquetaria tales como aspirina, clopidogrel bisulfato;

k) estrógeno, testosterona, un modulador selectivo del receptor de estrógeno, un modulador selectivo del receptor de andrógeno;

l) un agente quimioterapéutico tal como inhibidores de la aromatasa, por ejemplo femara, anti–estrógenos, inhibidores de la topoisomerasa I, inhibidores de la topoisomerasa II, agentes activos en los microtúbulos, agentes alquilantes, antimetabolitos antineoplásicos, compuestos de platino, compuestos reductores de la actividad de proteína quinasa tales como un inhibidor del receptor de tirosina quinasa PDGF , preferentemente Imatinib ({ N–{5–[4–(4–metil–piperazino–metil)–

benzoilamido]–2–metilfenil}–4–(3–piridil)–2–pirimidin–amina }) descripto en la solicitud de Patente europea EP–A–0 564 409 como ejemplo 21 o 4–Metil–N–[3–(4–metil–imidazol–1–il)–5–trifluorometil–fenil]–3–(4–piridin–3–il–pirimidin–2–ilamino)–benzamida descripta en la solicitud de patente WO 04/005281 como ejemplo 92; y

m) un agente que interactúa con un receptor 5–HT_3 y/o un agente que interactúa con un receptor 5–HT_4 tal como tegaserod, descripto en la Patente de los Estados Unidos No. 5510353 como ejemplo 13, tegaserod hidrógeno maleato, cisapride, cilansetrón;

n) un agente para el tratamiento del abuso del tabaco, por ejemplo agonistas parciales del receptor de nicotina, bupropión clorhidrato (también conocido bajo la denominación comercial Zyban®) y terapias de reemplazo de la nicotina;

o) un agente para el tratamiento de la disfunción eréctil, por ejemplo agentes dopaminérgicos tales como apomorfina), agentes para ADD/ADHD (por espacio de, Ritalin®, Strattera®, Concerta® y Adderall®);

p) un agente para el tratamiento del alcoholismo, como por ejemplo antagonisas de opioides (por ejemplo, naltrexona (también conocido bajo la denominación comercial ReVia®) y nalmefeno), disulfiram (también conocido bajo la denominación comercial Antabuse®), y acamprosato (también conocido bajo la denominación comercial Campral®)). Además, se pueden administrar conjuntamente agentes para la reducción de los síntomas de abstinencia de alcohol tales como benzodiazepinas, beta–bloqueantes, clonidina, carbamazepina, pregabalina, y gabapentina (Neurontin®);

q) otros agentes de utilidad incluyen agentes antiinflamatorios (por ejemplo, inhibidores de la COX–2) ; antidepresivos (por ejemplo, fluoxetina clorhidrato (Prozac®)); agentes para el mejoramiento cognitivo (por ejemplo, donazepil clorhidrato (Aircept®) y otros inhibidores de la acetilcolinesterasa), agentes neuroprotectores (por ejemplo, memantina) ; medicamentos antipsicóticos (por ejemplo ziprasidona (Geodon®), risperidona (Risperdal®), y olanzapina (Zyprexa®));

o, en cada caso, una sal aceptable para uso farmacéutico del mismo y, optativamente, un vehículo aceptable para uso farmacéutico.

La invención presenta asimismo combinaciones farmacéuticas, por ejemplo un kit, que comprende a) un primer agente que es un compuesto de la presente invención de

acuerdo con lo descripto en la presente, en forma libre o en forma de sal aceptable para uso farmacéutico del mismo y b) por lo menos un coagente. El kit puede comprender instrucciones para su administración.

Los términos "co–administración" o "administración combinada" o similares, utilizados en este contexto, han de abarcar la administración de los agentes terapéuticos seleccionados a un paciente individual y se pretende que incluyan regímenes de tratamiento en los cuales los agentes no se administran necesariamente por la misma vía de administración o al mismo tiempo.

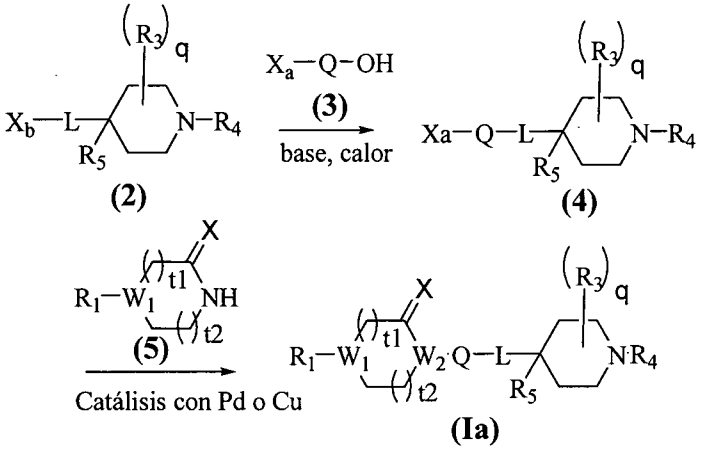
El término "combinación farmacéutica" empleado en este contexto se refiere a un producto que es el resultado de la mezcla o combinación de más de un ingrediente activo e incluye tanto combinaciones fijas como no fijas de los ingredientes activos. El término "combinación fija" significa que los ingredientes activos, por ejemplo un compuesto de la Fórmula I y un co–agente, se administran juntos a un paciente en forma simultánea en forma de una entidad o dosis única. El término "combinación no fija" se refiere a que los ingredientes activos, por ejemplo un compuesto de la Fórmula I y a co–agente, se administran a un paciente en forma de entidades separadas en forma simultánea, conjunta o consecutiva sin límites de tiempo específicos, donde dicha administración confiere los niveles efectivos de los 2 compuestos en el cuerpo del paciente. Esto último se aplica asimismo a la terapia de cocktail, por ejemplo la administración de 3 o más ingredientes activos.

Procesos para la Preparación de los Compuestos de la Invención

La presente invención incluye además procesos para la preparación de los compuestos de la presente invención. En las reacciones descriptas, puede ser necesario proteger los grupos funcionales reactivos, por ejemplo grupos hidroxi, amino, imino, tio o carboxi, donde se pretende que éstos estén en el producto final, para evitar su participación perjudicial en las reacciones. Se pueden utilizar grupos protectores convencionales de acuerdo con el uso convencional, por ejemplo, véase T.W. Greene y P. G. M. Wuts en "Protective Groups in Organic Chemistry", John Wiley y Sons, 1991.

En los siguientes esquemas, varios métodos de preparación de los compuestos de la presente invención son ilustrativos. Una persona con capacitación en la técnica sabrá apreciar que estos métodos son representativos y de ninguna manera representan la totalidad de los métodos para la preparación de los compuestos de la presente invención. Los radicales de los esquemas están descriptos en la Fórmula I.

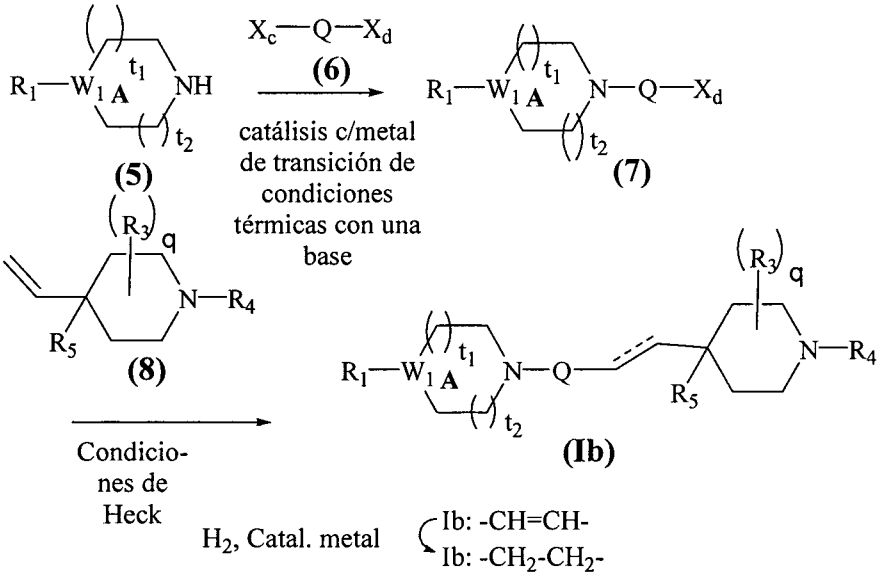
Esquema de reacciones I



Un compuesto de la Fórmula Ia, en el cual W_2 es nitrógeno, puede ser preparado de acuerdo con el esquema de reacciones I mediante la reacción de un compuesto de la Fórmula 3 (en la cual X_a se refiere a un cloruro, bromuro, yoduro, triflato, nonaflato o similar) con un compuesto de la Fórmula 2 (en la cual X_b se refiere a un grupo saliente tal como un éster de arilo o alquilsulfonato, haluro, epóxido donde R_5 es el oxígeno del epóxido u otro grupo apropiado de conocimiento de las personas con capacitación normal en la técnica) en un solvente adecuado tal como N,N–dimetilformamida, tetrahidrofurano y demás, en presencia de una base adecuada tal como Cs_2CO_3, NaH o similar a una temperatura elevada de hasta aproximadamente 80°C para generar un intermediario de la Fórmula 4. Se puede acoplar un compuesto de la Fórmula 5 (en la cual C=X puede ser un C=O o CH_2) con un compuesto de la Fórmula 4 empleando la metodología de Pd o Cu conocida en la técnica (por ejemplo, Shafir, A, Buchwald, S. F.; *J. Am Chem. Soc.* **2006**, 128, 8742 y las referencias citadas en ese trabajo y

Hartwig, J. F. *Handbook of Organopalladium Chemistry for Organic Synthesis*, Negishi, E., Ed., Wiley–Interscience: Weinheim, 2002). En este esquema, se entiende que los grupos designados pueden ser versiones protegidas de los radicales definidos en la Síntesis de la Invención que pueden ser desprotegidos y manipulados hasta obtener un compuesto final de acuerdo con la presente invención una vez completado este esquema o en el durante la ejecución del esquema.

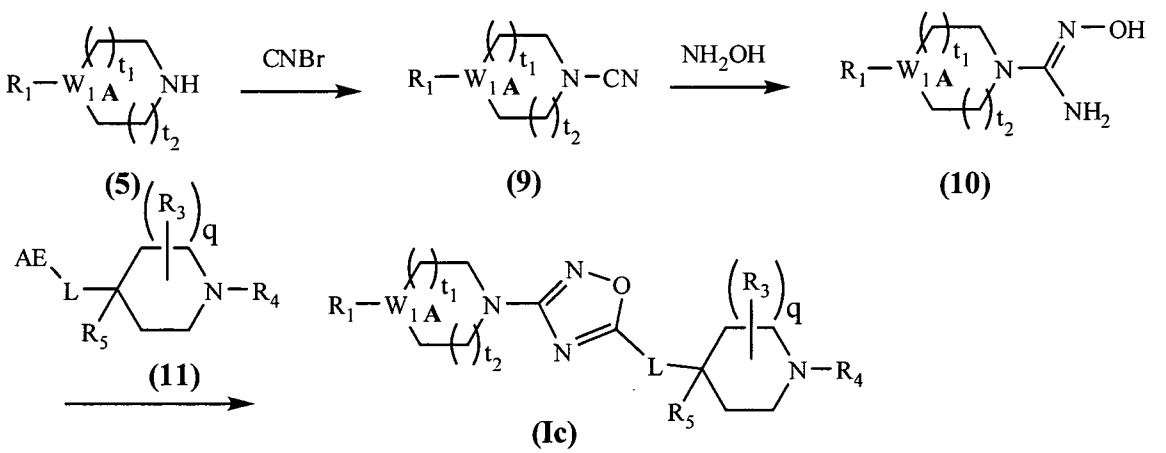
Esquema de reacciones II



Un compuesto de la Fórmula Ib, en el cual W_2 es N y L puede ser –CH=CH– o –CH_2–CH_2–, puede ser preparado de acuerdo con el esquema de reacciones II. Se puede hacer reaccionar un compuesto de la Fórmula 5 con un compuesto de la Fórmula 6 (en la cual tanto X_c como X_d representan independientemente grupos salientes tales como F, Cl, Br, OTf, etc. donde X_c es el grupo más reactivo) empleando la catálisis por metal de transición mencionada en el esquema 1 o utilizando una base estequiométrica tal como K_2CO_3, trietilamina y demás en un solvente adecuado tal como N,N–dimetilformamida y demás a una temperatura elevada para generar un intermediario de la Fórmula 7. A continuación se puede hacer reaccionar el intermediario 7 con una

olefina de la Fórmula 8 utilizando condiciones de reacción de heck (por ejemplo, Littke, A. F.; Fu, G. C, *J. Am. Chem. Soc.* **2001**, 123, 6989) para generar compuestos en los cuales L es –(CH=CH)–, a los que seguidamente se puede reducir empleando hidrógeno y una cantidad catalítica de un metal de transición tal como Pd/C y demás a compuestos en los cuales L es $-(CH_2)_2-$. En este esquema, se entiende que los grupos designados pueden ser versiones protegidas de los radicales definidos en la Síntesis de la Invención que pueden ser desprotegidos y manipulados hasta obtener un compuesto final de acuerdo con la presente invención una vez completado este esquema o en el durante la ejecución del esquema.

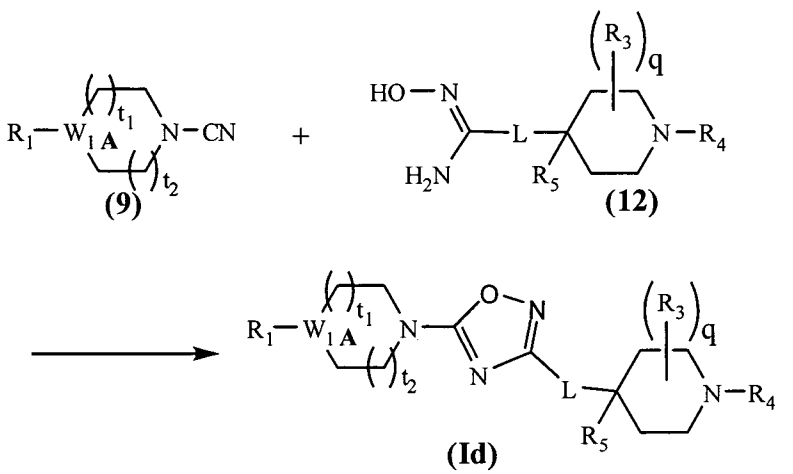
Esquema de reacciones III



Un compuesto de la Fórmula Ic, en la cual Q es un grupo heteroarilo tal como 1,2,4–oxadiazolilo (ilustrado) y W_2 es N, puede ser preparado de acuerdo con el esquema de reacciones III mediante la reacción de un compuesto de la Fórmula 5 con bromuro de cianógeno en un sistema solvente adecuado tal como Na_2CO_3 acuoso y diclorometano y demás para generar un compuesto de la Fórmula 9. A continuación se puede hacer reaccionar este intermediario con hidroxilamina en un solvente apropiado tal como etanol y demás a temperatura elevada tal como 60 °C para producir un compuesto de la Fórmula 10. Seguidamente se puede hacer reaccionar el intermediario 10 con un

compuesto de la Fórmula 11 (en la cual AE representa un equivalente ácido tal como un ácido carboxílico, alquil éster o éster activado tal como un éster de NHS y demás) empleando cualquiera de los protocolos dados a conocer en la literatura (como *Science of Synthesis* **2004**, *13*, 127, *Tetrahedron Lett.* **2006**, *47*, 3629 y *J. Med. Chem.* **2004**, *47*, 5821) para dar origen a los compuestos buscados de la Fórmula Ic. En este esquema, se entiende que los grupos designados pueden ser versiones protegidas de los radicales definidos en la Síntesis de la Invención que pueden ser desprotegidos y manipulados hasta obtener un compuesto final de acuerdo con la presente invención una vez completado este esquema o en el durante la ejecución del esquema.

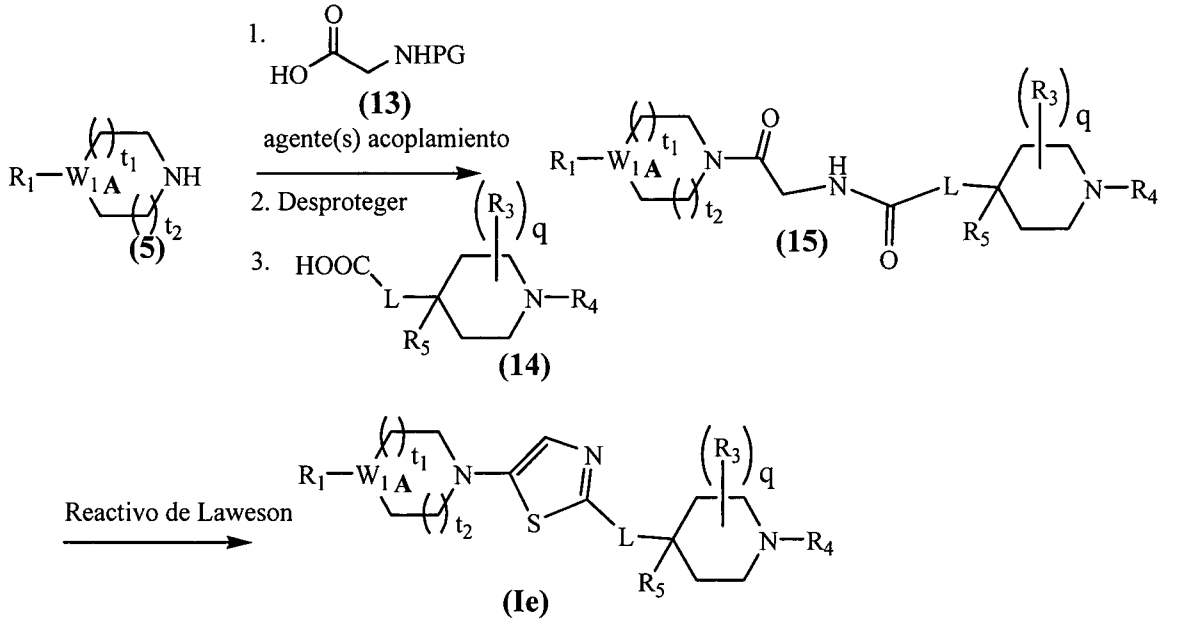
Esquema de reacciones IV



Un compuesto de la Fórmula Id puede ser preparado de acuerdo con el esquema de reacciones IV mediante la reacción de un compuesto de la Fórmula 9 con un compuesto de la Fórmula 12 en un solvente tal como tetrahidrofurano o similar en presencia de un ácido de Lewis tal como $ZnCl_2$ y demás a temperatura elevada. En este esquema, se entiende que los grupos designados pueden ser versiones protegidas de los radicales definidos en la Síntesis de la Invención que pueden ser desprotegidos y manipulados hasta obtener un compuesto final de acuerdo con la

presente invención una vez completado este esquema o en el durante la ejecución del esquema.

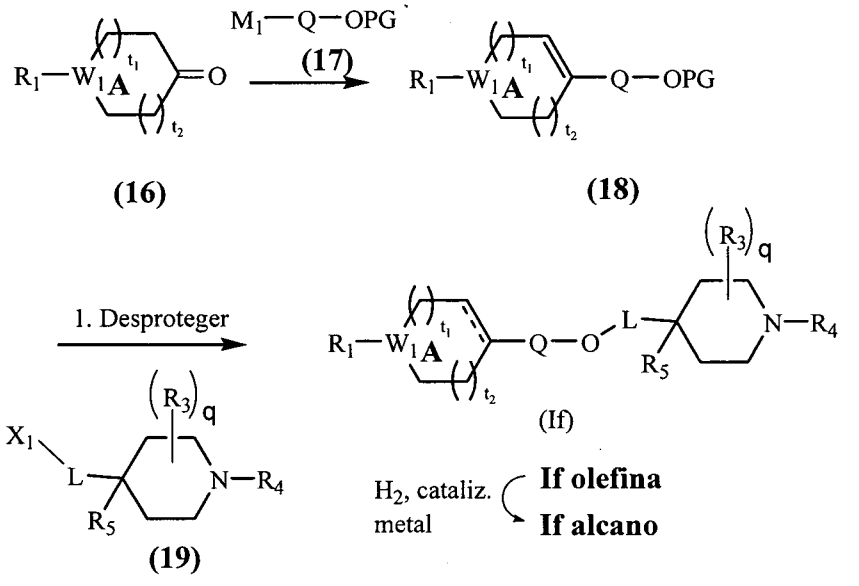
Esquema de reacciones V



Un compuesto de la Fórmula Ie, en la cual Q es tiazolilo (expuesto anteriormente) y W_2 es N, puede ser preparado de acuerdo con el esquema de reacciones V mediante la reacción de un compuesto de la Fórmula 5 con un derivado de glicina protegido de la Fórmula 13 utilizando reactivos de acoplamiento apropiados seguida por la desprotección y acoplamiento con un carboxilato de la Fórmula 14 para generar un intermediario de la Fórmula 15. A continuación se puede ciclar este intermediario empleando un reactivo de Lawesson u otro agente de tiotransferencia/deshidratación en un solvente apropiado tal como xileno a una temperatura elevada tal como 130 °C para generar el compuesto deseado de la Fórmula Ie. En este esquema, se entiende que los grupos designados pueden ser versiones protegidas de los radicales definidos en la Síntesis de la Invención que pueden ser desprotegidos y manipulados hasta

obtener el compuesto final de acuerdo con la presente invención una vez completado este esquema o en el durante la ejecución del esquema.

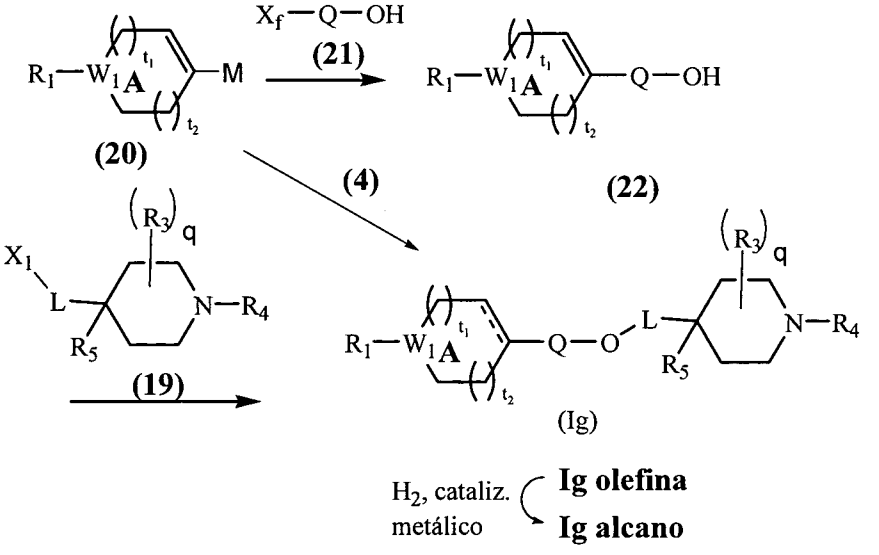
Esquema de reacciones VI



Un compuesto de la Fórmula If, puede ser preparado de acuerdo con el esquema de reacciones VI. Se puede hacer reaccionar un derivado cetona de la Fórmula 16 con un reactivo organometálico de la Fórmula 17 tal como un reactivo de Grignard o similar para producir, después de la deshidratación con un ácido tal como TFA o similar, una olefina de la Fórmula 18. Se puede desproteger este material con los reactivos apropiados, para luego proceder a la reacción con un electrófilo de la Fórmula 19 donde X_1 puede ser un grupo saliente tal como mesilato, haluro o similar en un solvente apropiado tal como N,N–dimetilformamida o similar utilizando una base tal como Cs_2CO_3 o similar para dar If como olefina. Seguidamente se puede reducir la olefina con un catalizador de metal tal como Pd/C o similar con gas hidrógeno o el reactivo de transferencia de hidrógeno adecuado para dar If en forma de alcano. En este esquema, se entiende que los grupos designados pueden ser versiones protegidas de los

radicales definidos en la Síntesis de la Invención que pueden ser desprotegidos y manipulados hasta obtener el compuesto final de acuerdo con la presente invención una vez completado este esquema o en el durante la ejecución del esquema.

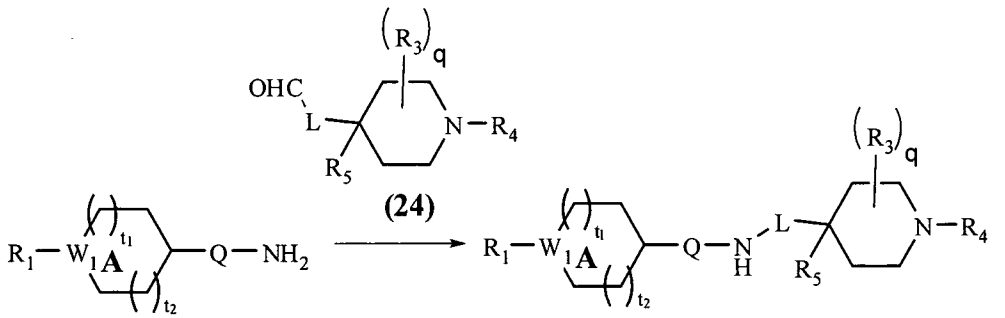
Esquema de reacciones VII



Un compuesto de la Fórmula Ig, puede ser preparado de acuerdo con el esquema de reacciones VII. Se puede hacer reaccionar un derivado de metal vinílico de la Fórmula 19 (donde M es B, Sn, Si, Mg, Zn u otros metales conocidos por participar en reacciones de acoplamiento catalizadas por metal) con un haluro de la Fórmula 21 (en la cual X_f se refiere a un cloruro, bromuro, yoduro, triflato, nonaflato y demás) empleando un catalizador de metal apropiado tal como Pd con un sistema ligando apropiado conocido por las personas con capacitación normal en la técnica para generar un intermediario de la Fórmula 22. A continuación se puede alquilar este intermediario con un intermediario de la Fórmula 18 de acuerdo con lo esbozado en el Esquema VI para dar Ig en forma de olefina. Seguidamente se puede reducir la olefina con un catalizador de metal tal como Pd/C o similar con gas hidrógeno o el reactivo de transferencia de hidrógeno apropiado para dar Ig en forma de alcano. Por otro lado, se puede preparar Ig llevando a cabo un acoplamiento mediado por metal de un

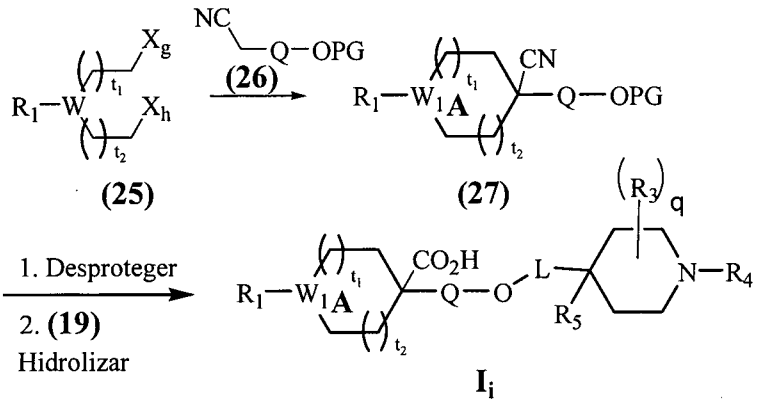
compuesto de la Fórmula 20 con un compuesto de la Fórmula 4 y manipulándolo de la manera antes descripta para obtener el alcano. En este esquema, se entiende que los grupos designados pueden ser versiones protegidas de los radicales definidos en la Síntesis de la Invención que pueden ser desprotegidos y manipulados hasta obtener el compuesto final de acuerdo con la presente invención una vez completado este esquema o en el durante la ejecución del esquema.

Esquema de reacciones VIII



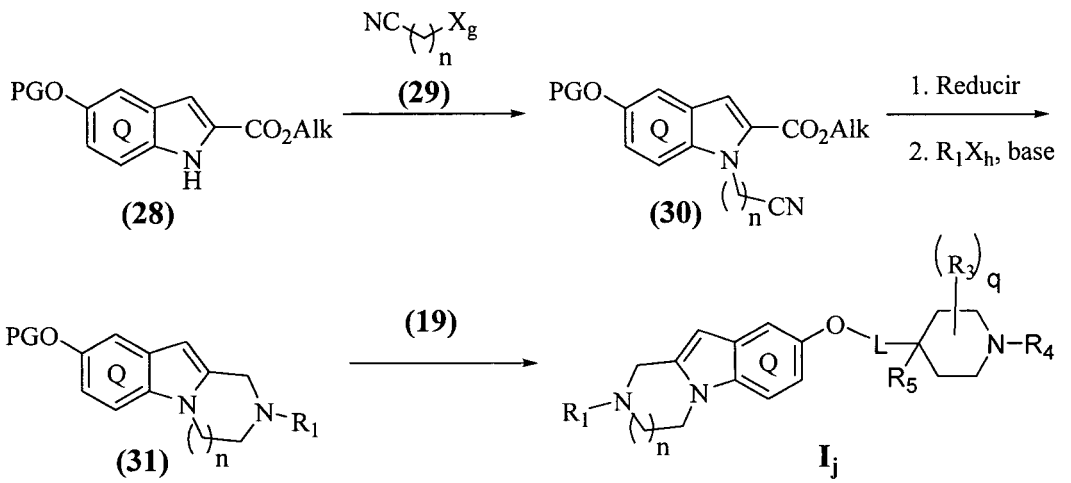
Un compuesto de la Fórmula Ih, puede ser preparado de acuerdo con el esquema de reacciones VIII. Se puede aminar reductivamente un compuesto de la Fórmula 23 con un compuesto de la Fórmula 24 empleando el reductor apropiado tal como $NaHB(OAc)_3$, $NaCNBH_3$ y demás en un solvente apropiado tal como diclorometano, metanol, etanol y demás para dar I_h. A continuación se puede manipular adicionalmente la amina de I_h. En este esquema, se entiende que los grupos designados pueden ser versiones protegidas de los radicales definidos en la Síntesis de la Invención que pueden ser desprotegidos y manipulados hasta obtener el compuesto final de acuerdo con la presente invención una vez completado este esquema o en el durante la ejecución del esquema.

Esquema de reacciones IX



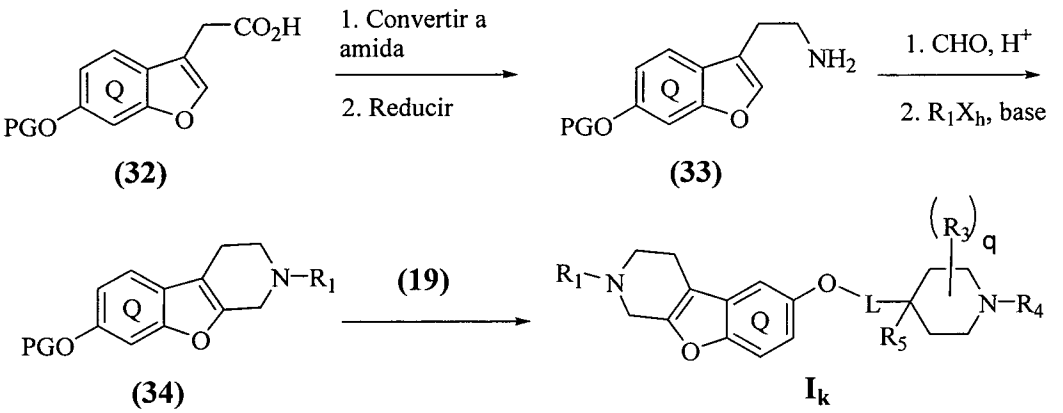
Un compuesto de la Fórmula Ii, puede ser preparado de acuerdo con el esquema de reacciones IX. Se puede hacer reaccionar un compuesto de la Fórmula 25 (en la cual X_g y X_h pueden ser elegidos entre cloro, bromo, yodo, mesilato, tosilato y demás), con un compuesto de la Fórmula 26 empleando una base apropiada tal como hidruro de sodio, LDA y demás en un solvente apropiado tal como N,N–dimetilformamida, N–metilpirrolidinona, DMSO, tetrahidrofurano y demás a temperatura elevada tal como 75 °C o similar para dar un intermediario de la Fórmula 27. A continuación se puede manipular este material de manera similar para que el intermediario 18 del esquema VI llegue a I_i. En este esquema, se entiende que los grupos designados pueden ser versiones protegidas de los radicales definidos en la Síntesis de la Invención que pueden ser desprotegidos y manipulados hasta obtener el compuesto final de acuerdo con la presente invención una vez completado este esquema o en el durante la ejecución del esquema.

Esquema de reacciones X



Un compuesto de la Fórmula Ij, puede ser preparado de acuerdo con el esquema de reacciones X. Se puede hacer reaccionar un compuesto de la Fórmula 28 con un compuesto de la Fórmula 29 (donde X_g puede ser elegido entre cloro, bromo, yodo, mesilato, tosilato y demás) empleando una base apropiada tal como carbonato de cesio, hidruro de sodio, LDA y demás en un solvente apropiado tal como N,N–dimetilformamida, N–metilpirrolidinona, DMSO, tetrahidrofurano y demás para dar un intermediario de la Fórmula 30. A continuación se puede reducir este material utilizando un hidruro de metal apropiado tal como LAH o BH_3 y luego funcionalizarlo con el electrófilo apropiado R_1X_h (donde X_h puede ser elegido entre cloro, bromo, succinato, p–nitrofenilo y demás) para dar un intermediario de la Fórmula 31. Seguidamente se puede manipular este material de manera similar al intermediario 18 del esquema VI para llegar a I_j. En este esquema, se entiende que los grupos designados pueden ser versiones protegidas de los radicales definidos en la Síntesis de la Invención que pueden ser desprotegidos y manipulados hasta obtener el compuesto final de acuerdo con la presente invención una vez completado este esquema o en el durante la ejecución del esquema.

Esquema de reacciones XI



Un compuesto de la Fórmula Ik, puede ser preparado de acuerdo con el esquema de reacciones XI. Se puede convertir un compuesto de la Fórmula 32 a una amida mediante la reacción con un agente activador tal como cloruro de oxalilo o similar en un solvente apropiado tal como diclorometano o similar, seguida por la reacción con amoniaco o un equivalente, seguida por la reducción con un reactivo apropiado tal como LAH o BH_3 para dar el intermediario de la Fórmula 33. A continuación se puede ciclar este material con formaldehído y un ácido tal como ácido acético o similar, para luego funcionalizar con un R_1X_h apropiado (donde X_h puede ser elegido entre cloro, bromo, succinato, p–nitrofenilo y demás) para dar un intermediario de la Fórmula 34. Seguidamente se puede manipular este material de manera similar al intermediario 18 del esquema VI para llegar a I_k. En este esquema, se entiende que los grupos designados pueden ser versiones protegidas de los radicales definidos en la Síntesis de la Invención que pueden ser desprotegidos y manipulados hasta obtener el compuesto final de acuerdo con la presente invención una vez completado este esquema o en el durante la ejecución del esquema.

En los siguientes Ejemplos se dan descripciones de la síntesis de los compuestos de la presente invención.

Otros Procesos para la Preparación de los Compuestos de la Invención

Se puede preparar un compuesto de la presente invención en forma de sal de adición de ácido aceptable para uso farmacéutico mediante la reacción de la forma de base libre del compuesto con un ácido inorgánico u orgánico aceptable para uso farmacéutico. Por otro lado, se puede preparar una sal de adición básica aceptable para uso farmacéutico mediante la reacción de la forma de ácido libre del compuesto con una base inorgánica u orgánica aceptable para uso farmacéutico. Por otro lado, se pueden preparar las formas de sal de los compuestos empleando sales de los materiales de partida o intermediarios.

Las formas de ácido o base libre de los compuestos de la presente invención se pueden preparar a partir de la forma de sal de adición ácida o básica correspondiente, respectivamente. Por ejemplo, se puede convertir un compuesto de la presente invención en forma de adición de sal de ácido a la base libre correspondiente mediante tratamiento con una base adecuada (por ejemplo, una solución de hidróxido de amonio, hidróxido de sodio y demás). Se puede convertir un compuesto de la presente invención, en forma de sal de adición básica, al ácido libre correspondiente mediante tratamiento con un ácido adecuado (por ejemplo, ácido clorhídrico, etc.).

Los compuestos de la presente invención en forma no oxidada se pueden preparar a partir de los N–óxidos de los compuestos de la presente invención mediante tratamiento con un agente reductor (por ejemplo azufre, dióxido de azufre, trifenil fosfaina, borohidruro de litio, borohidruro de sodio o similar) en un solvente orgánico inerte adecuado (por ejemplo, acetonitrilo, etanol, dioxano acuoso o similar) a una temperatura de 0 a 80 °C.

Los derivados profármacos de los compuestos de la invención se pueden preparar por métodos conocidos por las personas con capacitación normal en la técnica (por ejemplo, por más detalles ver Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). Por ejemplo, se pueden preparar los profármacos adecuados mediante la reacción de un compuesto no derivado de la presente invención con un agente de carbamilación adecuado (por ejemplo, 1,1–aciloxialquilcarbanocloridato, para–nitrofenil carbonato, o similar).

Se pueden preparar derivados protegidos de los compuestos de la presente invención por medios conocidos por las personas con capacitación normal en la técnica. Se puede encontrar una descripción detallada de las técnicas aplicables a la creación de grupos protectores y su remoción en T. W. Greene, "Protecting Groups in Organic Chemistry", 3ª edición, John Wiley and Sons, Inc., 1999.

Los compuestos de la presente invención se pueden preparar o formar convenientemente durante el proceso de la presente invención, en forma de solvatos (por ejemplo, hidratos). Los hidratos de los compuestos de la presente invención se pueden preparar de manera conveniente mediante recristalización de una mezcla de solventes acuoso/orgánico, utilizando solventes orgánicos tales como dioxina, tetrahidrofurano o metanol.

Los compuestos de la presente invención se pueden preparar en forma de sus estereoisómeros individuales mediante la reacción de una mezcla racémica del compuesto con un agente de resolución con actividad óptica para formar un par de compuestos diastereoisoméricos, separando los diasterómeros y recuperando los enantiómeros con pureza óptica. Si bien la resolución de los enantiómeros se puede llevar a cabo empleando derivados diastereoméricos covalentes de los compuestos de la invención, son preferibles los complejos disociables (por ejemplo, sales diastereoméricas cristalinas). Los diastereómeros tienen propiedades físicas (por ejemplo, puntos de fusión, puntos de ebullición, solubilidades, reactividad, etc.) diferenciables y se los puede separar fácilmente aprovechando estas disimilitudes. Los diastereómeros se pueden separar por cromatografía o, preferentemente, mediante técnicas de separación/resolución basándose en las diferencias de solubilidad. A continuación se recupera el enantiómero ópticamente puro, junto con el agente de resolución, por cualquier medio práctico que no dé lugar a la racemización. Se puede encontrar una descripción más detallada de las técnicas aplicables a la resolución de los estereoisómeros de los compuestos de sus mezclas racémicas en el trabajo de Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley and Sons, Inc., 1981.

En síntesis, los compuestos de la Fórmula I se pueden preparar mediante un proceso que incluye:

(a) el de los esquemas de reacciones I a XI; y

(b) optativamente, la conversión de un compuesto de la invención a una sal aceptable para uso farmacéutico;

(c) optativamente, la conversión de una forma de sal de un compuesto de la invención a una forma que no es una sal;

(d) optativamente, la conversión de una forma no oxidada de un compuesto de la invención a un N–óxido aceptable para uso farmacéutico;

(e) optativamente, la conversión de una forma de N–óxido de un compuesto de la invención a su forma no oxidada;

(f) optativamente, la resolución de un isómero individual de un compuesto de la invención de una mezcla de isómeros;

(g) optativamente, la conversión de un compuesto no derivado de la presente invención a un derivado profármaco aceptable para uso farmacéutico y

(h) optativamente, la conversión de un derivado profármaco de un compuesto de la invención a su forma no derivada.

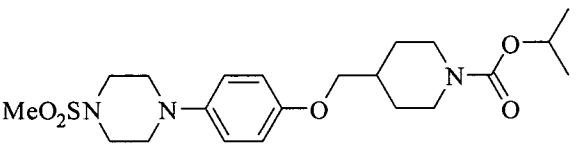
En la medida en que no se describen específicamente los materiales de partida, los compuestos son conocidos y se los puede preparar de manera análoga a los métodos conocidos en la técnica o de acuerdo con lo descripto a continuación en los Ejemplos.

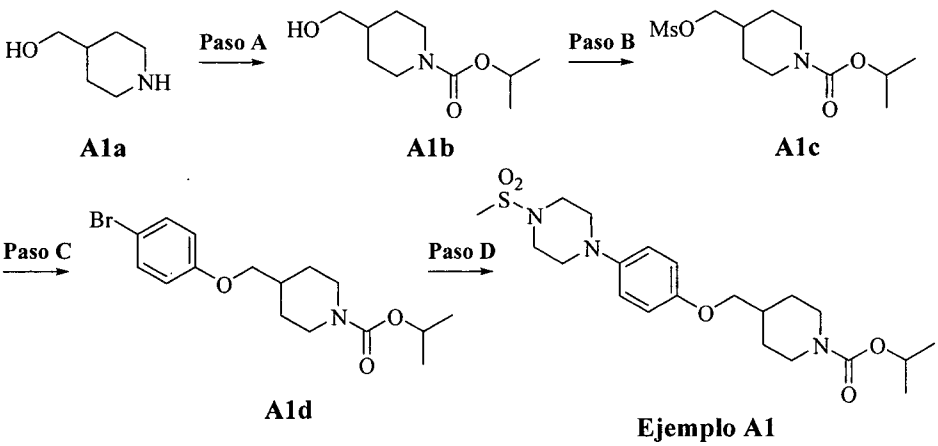
Una persona con capacitación en la técnica sabrá apreciar que las transformaciones detalladas anteriormente sólo son representativas de los métodos de preparación de los compuestos de la presente invención y que se pueden utilizar de igual modo otros métodos muy conocidos.

Ejemplos

Se ilustra más detalladamente la presente invención, aunque no a modo de limitación, mediante los siguientes Ejemplos que explican la preparación de los compuestos de la presente invención.

Ejemplo A1: Isopropil 4–((4–((4–metansulfonilpiperazin)–1–il)fenoxi)metil)piperidin–1–carboxilato.





Paso A: A una solución de **A1a** (5,26 g, 45,7 mmol) en dimetoxietano seco (30 ml) se agrega trietilamina (8,0 g, 56,9 mmol). A la mezcla obtenida, se agrega gota a gota una solución 1,0 M de isopropil cloroformiato en tolueno (50 ml), con agitación vigorosa, en un lapso de 10 min. Se forma un precipitado blanco. Se agita la suspensión a temperatura ambiente por espacio de 4 horas; se separa el precipitado por filtración, se lo lava con más dimetoxietano, y se lo descarta. Se concentra la solución obtenida a sequedad para dar **A1b**; ^{1}H NMR (DMSO–d_6, 400.13 MHz): δ 4,75 (septete, J = 6,2 Hz, 1H), 4,49 (t, J = 5,3 Hz, 1H), 3,95 (dd, J = 5,6, 5,6 Hz, 2H), 3,24 (br, 2H), 1,63 (dd, J =

2,0, 12,9 Hz, 2H), 1,51 (m, 1H), 1,17 (d, J = 6,2 Hz, 6H), 0,98 (m, 2H); no se pudo obtener el espectro de masa.

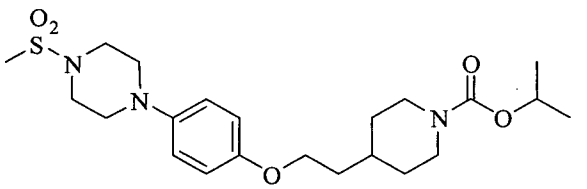
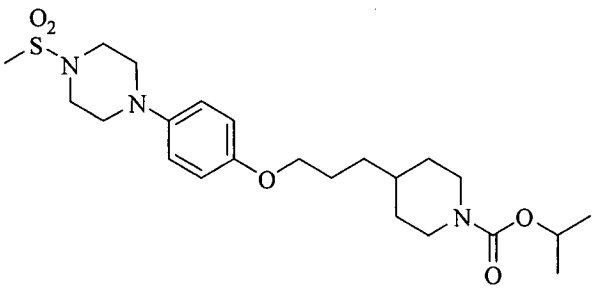
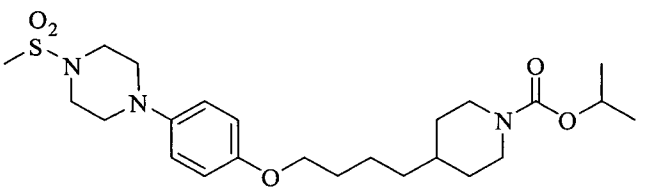
Paso B: A una solución de **A1b** (4.25 g, 21.1 mmol) en diclorometano (30ml) se agrega trietilamina (4,5 g, 32,0 mmol) en una porción. Se enfría la mezcla así obtenida en un baño de agua helada y se agrega gota a gota cloruro de metansulfonilo (1,8 ml, 23,2 mmol), con agitación, en un lapso de 5 min. Se retira el baño y se agita la solución obtenida a temperatura ambiente por espacio de 30 min. Se agrega la mezcla de reacción al agua (40 ml) y se la extrae con diclorometano (2 x 40 ml). Se lavan los extractos orgánicos combinados con una solución acuosa saturada de cloruro de amonio, se la seca sobre $MgSO_4$ y concentra para dar **A1c**; ^1H NMR ($CDCl_3$, 400.13 MHz): δ 4,74 (septete, *J* = 6,2 Hz, 1H), 4,07 (d, *J* = 6,4 Hz, 2H), 3,99 (d, *J* = 11,0 Hz, 2H), 3,17 (s, 3H), 2,51 (br, 2H), 1,88 (dd, *J* = 1,6, 14,6 Hz, 2H), 1,68 (m, 1H), 1,18 (d, *J* = 6,2 Hz, 6H), 1,17 (m, 2H); ESIMS calc, para $C_{11}H_{22}NO_5S$ ($M+H^+$) 280,11, resultó 280,2.

Paso C: Se trata una solución de **A1c** (0,42 g, 1,50 mmol) y 4–bromofenol (0,26 g, 1,50 mmol) en acetonitrilo (5,0 ml) con carbonato de cesio en polvo (0,60 g, 1,84 mmol) y se agita la mezcla a 65 °C por espacio de 16 horas. El enfriamiento a temperatura ambiente, la filtración y concentración da **A1d**; ^1H NMR ($CDCl_3$, 400,13 MHz): δ 7,36 (d, *J* = 9,0 Hz, 2H), 6,76 (d, *J* = 9,0 Hz, 2H), 4,91 (septet, *J* = 6,2 Hz, 1H), 4,19 (br, 2H), 3,76 (d, *J* = 6,4 Hz, 2H), 3,26 (br, 2H), 2,78 (m, 2H), 1,96 (m, 1H), 1,82 (dd, *J* = 1,6, 14,6 Hz, 2H), 1,30 (m, 2H), 1,28 (d, *J* = 6,2 Hz, 6H); ESIMS calc, para $C_{16}H_{23}BrNO_3$ ($M+H^+$) 356,1, resultó 356,0.

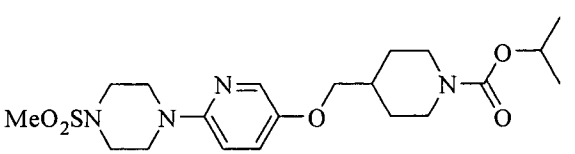
Paso D: Se trata una solución de **A1d** (0,55 g, 1,50 mmol), 4–metansulfonil–piperazina (0,25 g, 1,52 mmol), y tetrafluoroborato de tri–builfosfonio (92,2 mg, 0,32 mmol) en dioxano seco (6 ml) con carbonato de cesio en polvo (1,03 g, 3,16 mmol) y se desgasifica la mezcla empleando argón. Se agrega tris(dibencilideno acetona)dipaladio(0) (0,15 g, 0,16 mmol) y se desgasifica la mezcla una vez más con argón. Se agita vigorosamente la suspensión bajo argón a 110 °C por espacio de 18 horas. El enfriamiento, filtración y purificación empleando HPLC de fase inversa promovida por la masa da **A1**; ^1H NMR ($CDCl_3$, 400,13 MHz): δ 6,90 (d, *J* = 8,9 Hz,

2H), 6,84 (d, *J* = 8,9 Hz, 2H), 4,92 (septet, *J* = 6,2 Hz, 1H), 4,19 (br, 2H), 3,76 (d, *J* = 6,4 Hz, 2H), 3,39 (t, *J* = 3,9 Hz, 4H), 3,17 (t, *J* = 3,9 Hz, 4H), 2,83 (s, 1H), 2,77 (t, *J* = 11,2 Hz, 2H), 1,96 (m, 1H), 1,83 (dd, *J* = 1,4, 14,2 Hz, 2H), 1,27 (m, 2H), 1,24 (d, *J* = 6,2 Hz, 6H); ESIMS calc, para $C_{21}H_{34}N_3O_5S$ ($M+H^+$) 440,2, resultó 440,2.

Siguiendo un procedimiento similar al utilizado para la preparación de **A1** a partir de **A1a,** excepto que sustituyendo **A1a** por el alcohol apropiado, se obtienen los siguientes ejemplos:

Ejemplo	Estructura	Datos analíticos
A2		ESIMS calc. para $C_{22}H_{36}N_3O_5S$ ($M+H^+$) 454,2, resultó 454,2.
A3		ESIMS calc. para $C_{23}H_{38}N_3O_5S$ ($M+H^+$) 468,2, resultó 468,2.
A4		ESIMS calc. para $C_{24}H_{40}N_3O_5S$ ($M+H^+$) 482,2, resultó 482,2.

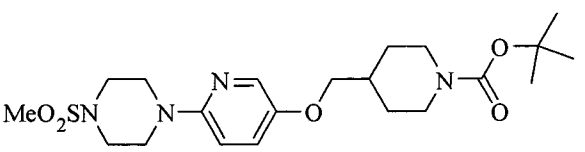
Ejemplo B1: Isopropil 4–((6–(4–(metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato.

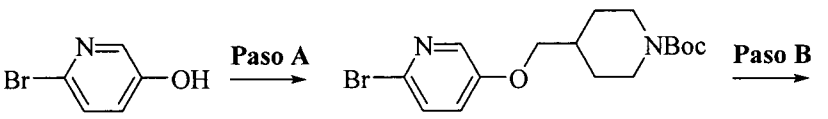


Siguiendo un procedimiento similar al utilizado para la preparación de **A1** a partir de **A1a** excepto que sustituyendo el 4–bromofenol por 2–cloro–5–hidroxipiridina y ejecutando el Paso D de la siguiente manera, se prepara **B1**;

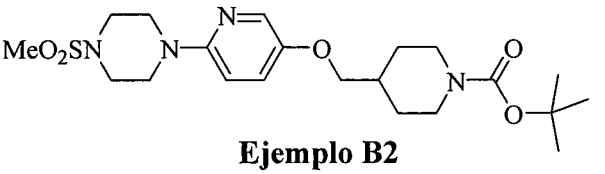
Se carga un matraz con Pd_2dba_3 (6 mg, 0,006 mmol), xantfos (11 mg, 0,019 mmol), 1–(metilsulfonil)piperazina (63 mg, 384 mmol), *terc*–butóxido de sodio (46 mg, 0,48 mmol), y una solución de isopropil 4–((6–cloropiridin–3–iloxi)metil)piperidin–1–carboxilato (100 mg, 0,32 mmol) en tolueno (1ml). Se purga la reacción haciendo burbujear nitrógeno a través de la solución por espacio de 5 minutos y luego sellándola. A continuación se sumerge la reacción en un baño precalentado a 100°C y se la agita a esta temperatura durante 3 horas. Después de enfriar a temperatura ambiente, se trata la reacción con acetato de etilo y se aísla la fase acuosa, se la lava una vez más y se la descarta. Se secan los orgánicos combinados sobre $MgSO_4$ y se separan los solventes. Se purifica el residuo en una columna de gel de sílice empleando un gradiente lineal de acetato de etilo 0–100 % en hexano como eluyente para producir **B1**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7,92 (d, J = 3,0, 1H), 7,18 (dd, J = 3,0, 9,1, 1H), 6,67 (d, J = 9,1, 1H), 4,91 (m, 1H), 4,20 (m, 2H), 3,78 (d, J = 6,4, 2H), 3,56 (m, 4H), 3,34 (m, 4H), 2,81 (s, 3H), 2,76 (m, 2H), 1,94 (m, 1H), 1,81 (m, 2H), 1,29 (m, 2H), 1,24, d, J = 6,2, 6H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{20}H_{33}N_4O_5S$ calc.: 441,2, resultó: 441,3.

Ejemplo B2. *terc*–Butil 4–((6–(4–(metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato.





B2a **B2b**

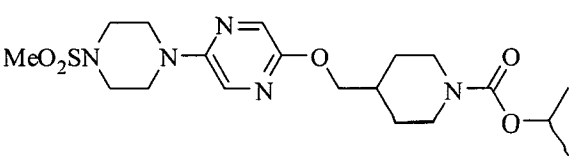


Ejemplo B2

Paso A: Se trata una solución de **B2a** (4.00 g, 23 mmol) y terc–butil 4–((metilsulfoniloxi)metil)piperidin–1–carboxilato (7,08 g, 24 mmol) en N–metilpirrolidinona (50 ml) con Cs_2CO_3 (9,74 g, 30 mmol) y se la calienta a 100 °C de un día para otro. A continuación se diluye la reacción con acetato de etilo, se la extrae 3 veces con agua, se la seca sobre $MgSO_4$, filtra, evapora y cristaliza de tolueno/hexano para dar **B2b**; ESIMS *m/z* correspondiente a $(M–tBu+H)^+$ $C_{12}H_{16}BrN_2O_3$ calc.: 315.0, resultó: 315.0,

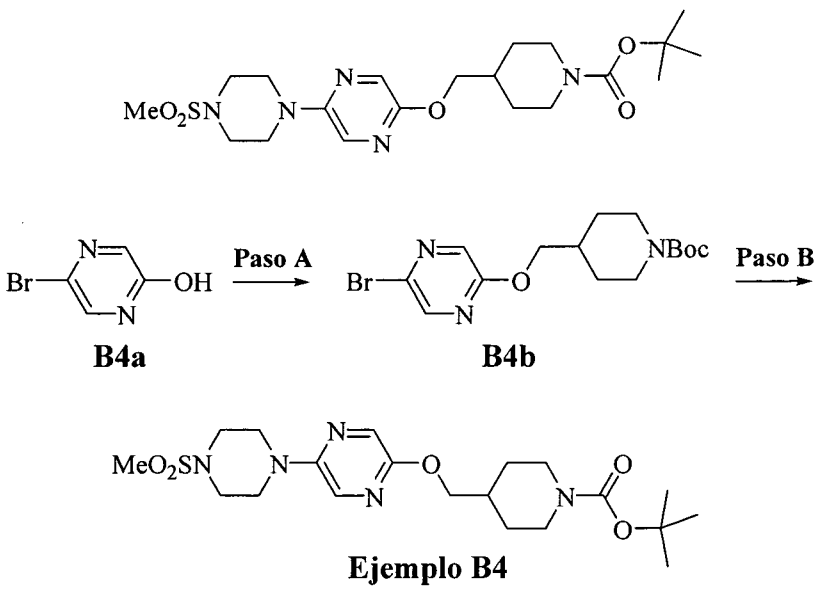
Paso B: Siguiendo el procedimiento descripto con respecto al acoplamiento de paladio delineado anteriormente para **B1** y sustituyendo isopropil 4–((6–cloropiridin–3–iloxi)metil)piperidin–1–carboxilato por **B2b,** se prepara **B2;** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7,91 (d, *J* = 2,9, 1H), 7,15 (dd, *J* = 9,1, 3,1, 1H), 6,65 (d, *J* = 9,0, 1H), 4,15 (m, 2H), 3,78 (d, *J* = 6,4, 2H), 3,54 (m, 4H), 3,33 (m, 4H), 2,81 (s, 3H), 2,72 (m, 2H), 1,93 (m, 1H), 1,80 (m, 2H), 1,46 (s, 9H), 1,25 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{35}N_4O_5S$ calc.: 455,2, resultó: 455,2.

Ejemplo B3: Isopropil 4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



Siguiendo un procedimiento similar al utilizado para la preparación de **B1** excepto que se utiliza 2–bromo–5–hidroxipirazina como heterociclo, se prepara **B3**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7,87 (d, *J* = 1,4, 1H), 7,62 (d, *J* = 1,5, 1H), 4,92 (m, 1H), 4,18 (m, 2H), 4,08 (d, *J* = 6,5, 2H), 3,52 (m, 4H), 3,37 (m, 4H), 2,82 (s, 3H), 2,76 (m, 2H), 1,96 (m, 1H), 1,79 (m, 2H), 1,29 (m, 2H), 1,24, (d, *J* = 6,2, 6H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{19}H_{32}N_5O_5S$ calc.: 442,2, resultó: 442,3.

Ejemplo B4: *terc*–Butil 4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.

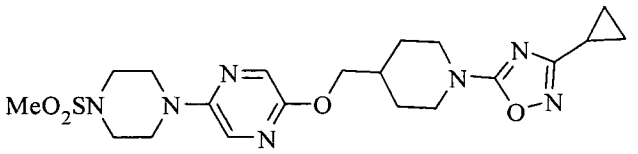


Ejemplo B4

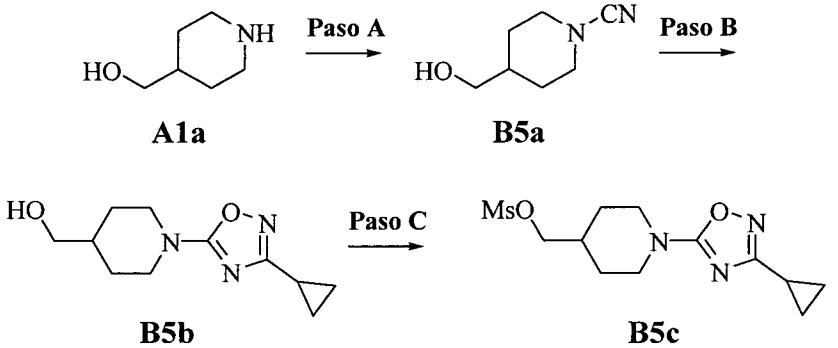
Paso A: Siguiendo un procedimiento similar al utilizado para la preparación de **B2b** a partir de **B2a** excepto que se sustituye **B2a** por **B4a,** se prepara **B4b**; ESIMS *m/z* correspondiente a $(M–t\text{Bu}+H^+)$ $C_{11}H_{15}BrN_3O_3$ calc.: 316.0, resultó: 316.0,

Paso B: Siguiendo el procedimiento respectivo al paladio delineado con respecto a la preparación **B1** excepto que sustituyendo isopropil 4–((6–cloropiridin–3–iloxi)metil)piperidin–1–carboxilato por **B4b**, se prepara **B4**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7,87 (d, *J* = 1,2, 1H), 7,62 (d, *J* = 1,2, 1H), 4,13 (m, 2H), 4,08 (d, *J* = 6,8, 2H), 3,52 (m, 4H), 3,37 (m, 4H), 2,82 (s, 3H), 2,72 (m, 2H), 1,93 (m, 1H), 1,46 (s, 9H), 1,26 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{20}H_{34}N_5O_5S$ calc.: 456,2, resultó: 456,2.

Ejemplo B5: 3–Ciclopropil–5–(4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–il)–1,2,4–oxadiazol.



Siguiendo un procedimiento similar al utilizado para la preparación de **B3** a partir de **B2a** excepto que se sustituye **B2a** por **B5c** (ver el siguiente esquema) se prepara **B5**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7,88 (d, *J* = 1,3, 1H), 7,62 (d, *J* = 1,4, 1H), 4,16 (m, 2H), 4,10 (d, *J* = 6,8, 2H), 3,53 (m, 4H), 3,37 (m, 4H), 3,05 (ddd, *J* = 12,9, 12,9, 2,8, 2H), 2,82 (s, 3H), 2,02 (m, 1H), 1,88 (m, 4H), 1,41 (m, 2H), 0,94 (m, 4H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{20}H_{30}N_7O_4S$ calc.: 464,2, resultó: 464,3,

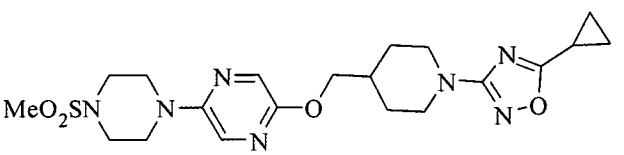


Paso A: Se trata una muestra de **A1a** (10,19 g, 84,9 mmol) con una solución de K_2CO_3 (24,5 g, 177 mmol) en agua (100 ml). Se enfría la reacción en un baño de agua/hielo y se la trata con una solución de bromuro de cianógeno (10,31 g, 97,3 mmol) en diclorometano (100 ml) por goteo. Después de agitar durante una hora, se aísla la capa orgánica y se extrae la capa acuosa una vez más con diclorometano. Se secan los extractos orgánicos combinados sobre $MgSO_4$, se los filtra y evapora para dar **B5a**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_7H_{13}N_2O$ calc.: 141.1, resultó: 141.1.

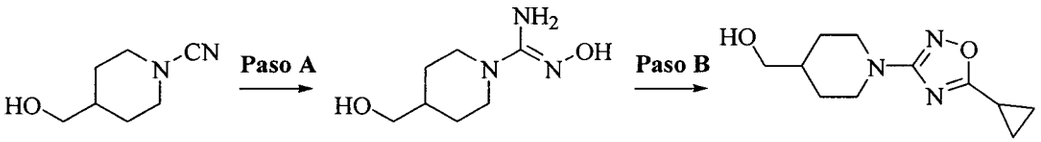
Paso B: Se calienta una solución de **B5a** (993 mg, 7,1 mmol), N'–hidroxiciclopropan carboximidamida (1.064 g, 10,6 mmol) y $ZnCl_2$ (1,448 g, 10,6 mmol) en dioxano (25 ml) a 100 °C de un día para otro. A continuación se evapora la reacción a sequedad y se la reparte entre acetato de etilo y HCl 1 M. Se aísla la fase orgánica, se la extrae con HCl 1 M una vez más, se la seca sobre $MgSO_4$, filtra, evapora y purifica por gel de sílice para dar **B5b**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{11}H_{18}N_3O_2$ calc.: 224,1, resultó: 224.1.

Paso C: Se enfría una solución de **B5b** (278,4 mg, 1,25 mmol) y trietilamina (131 mg, 130 mmol) en diclorometano (1 ml) en un baño de agua y hielo, se la trata con cloruro de metansulfonilo (149 mg, 1,3 mmol) y se la agita de un día para otro. Se diluye la reacción con agua y se la extrae con diclorometano. Se diluye la reacción con agua y se la extrae con diclorometano. Se secan los extractos orgánicos sobre $MgSO_4$, se los filtra y purifica en gel de sílice utilizando un gradiente lineal de 0 a 100 % de acetato de etilo en hexano para producir **E5c**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{12}H_{20}N_3O_4S$ calc.: 302.1, resultó: 302.1.

Ejemplo B6: 5–Ciclopropil–3–(4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–il)–1,2,4–oxadiazol.



Siguiendo un procedimiento similar al empleado para **B5** excepto que se sustituye **B5b** por **B6b** (ver el siguiente esquema), se obtiene **B6**; ^1H NMR ($CDCl_3$, 400 MHz): δ 7,87 (d, *J* = 1,5, 1H), 7,63 (d, *J* = 1,5, 1H), 4,10 (d, *J* = 6,8, 2H), 4,00 (m, 2H), 3,53 (m, 4H), 3,37 (m, 4H), 2,89 (ddd, *J* = 12,7, 12,7, 2,7, 2H), 2,82 (s, 3H), 2,00 (m, 1H), 1,86 (m, 4H), 1,40 (ddd, *J* = 25,0, 12,4, 4,3, 2H), 1,14 (m, 4H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{20}H_{29}N_7O_4S$ calc.: 464,2, resultó: 464,3.

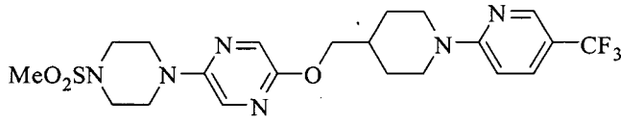


B5a **B6a** **B6b**

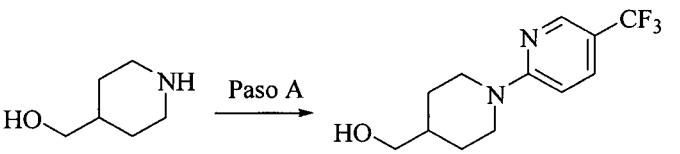
Paso A: Se tapa herméticamente una solución de **B5a** (4,01 g, 28,6 mmol) e hidroxilamina (3,51 ml de una solución acuosa al 50 % en peso, 57,2 mmol) en etanol (50 ml) y se la calienta a 60 °C de un día para otro. A continuación se separa el solvente y se obtiene **B6a**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_7H_{16}N_3O_2$ calc.: 174.1, resultó: 174.1.

Paso B: Se calienta una solución de **B6a** (905 mg, 5,2 mmol) y 2,5–dioxopirrolidin–1–il ciclopropancarboxilato (957 mg, 5,2 mmol) en dioxano (50 ml) a 80 °C por espacio de 3 horas y luego a 70 °C de un día para otro. A continuación se enfría la reacción a temperatura ambiente, se la concentra y purifica en gel de sílice utilizando un gradiente lineal de 0–80% de acetato de etilo en hexano para producir **B6b**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{11}H_{18}N_3O_2$ calc.: 224.1, resultó: 224.1.

Ejemplo B7: 2–(4–(Metilsulfonil)piperazin–1–il)–5–((1–(5–(trifluorometil)piridin–2–il)piperidin–4–il)metoxi)pirazina.



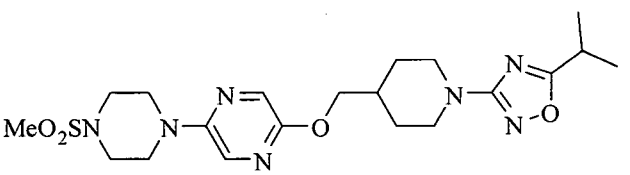
Siguiendo un procedimiento similar al utilizado para la preparación de **B3** a partir de **B2a** excepto que sustituyendo **A1b** por **B7a** (ver el siguiente esquema), se prepara **B7**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8,37 (m, 1H), 7,88 (d, *J* = 1,4, 1H), 7,63 (d, *J* = 1,4, 1H), 7,60 (dd, *J* = 9,1, 2,5, 1H), 6,65 (d, *J* = 9,1, 1H), 4,45 (m, 2H), 4,11 (d, *J* = 6,5, 1H), 3,53 (m, 4H), 3,37 (m, 4H), 2,95 (m, 2H), 2,82 (s, 3H), 2,11 (m, 1H), 1,93 (m, 2H), 1,37 (ddd, *J* = 24,9, 12,5, 4,1, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{28}F_3N_6O_3S$ calc.: 501,2, resultó: 501,3.



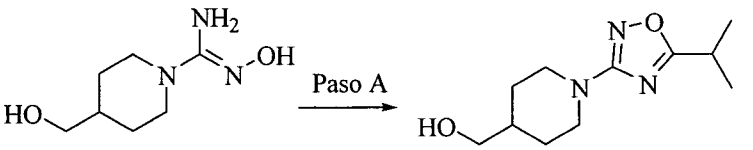
A1a **B7a**

Paso A: Se calienta una mezcla de **A1a** (522,5 mg, 4,5 mmol), 2–cloro–5–trifluorometilpiridina (1,19 g, 6,5 mmol) y K_2CO_3 (941 mg, 6,8 mmol) en N,N–dimetilformamida (8 ml) a 160 °C por espacio de 10 minutos, se la enfría a temperatura ambiente y se la diluye con acetato de etilo y agua. Se extraen los orgánicos con agua, se los seca sobre $MgSO_4$, filtra y evapora y se los purifica en gel de sílice utilizando un gradiente lineal de 0 a 100% de acetato de etilo en hexano para dar **B1a**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{12}H_{16}F_3N_2O$ calc.: 261.1, resultó: 261.1.

Ejemplo B8: 5–Isopropil–3–(4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–il)–1,2,4–oxadiazol.



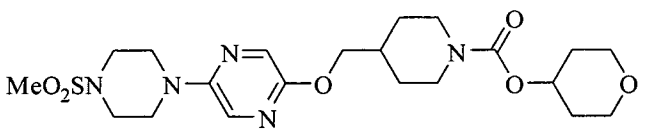
Siguiendo un procedimiento similar al utilizado para la preparación de **B6** a partir **B6b** excepto que se sustituye **B6b** por **B8a** (ver el esquema siguiente), se prepara **B8**; ^1H NMR ($CDCl_3$, 400 MHz): δ 7,88 (d, *J* = 1,5, 1H), 7,63 (d, *J* = 1,5, 1H), 7,60 (dd, *J* = 9,1, 2,5, 1H), 4,11 (d, *J* = 6,6, 1H), 3,53 (m, 4H), 3,37 (m, 4H), 3,07 (m, 1H), 2,92 (ddd, *J* = 12,7, 12,7, 2,7, 2H), 2,82 (s, 3H), 2,01 (m, 1H), 1,88 (m, 2H), 1,42 (m, 2H), 1,35 (d, *J* = 7,0, 6H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{20}H_{32}N_7O_4S$ calc.: 466,2, resultó: 466,2.



B6a **B8a**

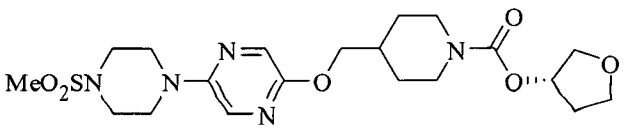
Paso A: Se calienta una solución de **B6a** (460,3 mg, 2,7 mmol) y anhídrido isobutírico (420 mg, 2,7 mmol) en dioxano (3 ml) a 150 °C durante 5 minutos. Se enfría la reacción a temperatura ambiente y se la diluye con acetato de etilo y agua. Se aíslan los extractos orgánicos y se los lava una vez con agua, se los seca sobre $MgSO_4$, filtra y evapora y se los purifica en gel de sílice utilizando un gradiente lineal de acetato de etilo en hexano para producir **B8a**. No se pudo obtener un análisis satisfactorio de espectros de masas.

Ejemplo B9: Tetrahidro–2H–piran–4–il 4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



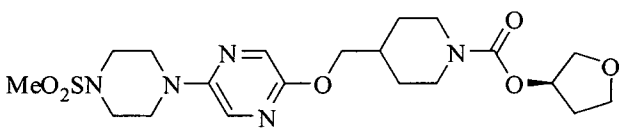
Siguiendo un procedimiento similar al utilizado para la preparación de **B3** a partir de **A1a** excepto que en el primer paso se sustituye el isopropil cloroformiato por 4–nitrofenil tetrahidro–2H–piran–4–il carbonato, se prepara **B9**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7,87 (d, *J* = 1,5, 1H), 7,62 (d, *J* = 1,5, 1H), 4,87 (m, 1H), 4,20 (m, 2H), 4,09 (d, *J* = 6,5, 1H), 3,89 (m, 2H), 3,57 (m, 2H), 3,54 (m, 4H), 3,46 (m, 4H), 2,82 (s, 3H), 2,80 (m, 2H), 1,95 (m, 3H), 1,82 (m, 2H), 1,67 (m, 3H), 1,28 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{34}N_5O_6S$ calc.: 484,2, resultó: 484,2.

Ejemplo B10: (S)–Tetrahidrofuran–3–il 4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



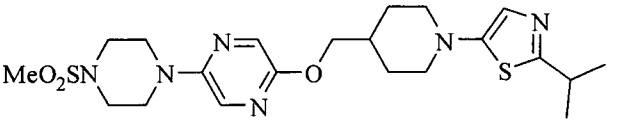
Siguiendo un procedimiento similar al utilizado para la preparación de **B3** a partir de **A1a** excepto que en el primer paso se sustituye el isopropil cloroformiato por (S)–4–nitrofenil tetrahidrofuran–3–il carbonato, se prepara **B10**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7,87 (d, J = 1,5, 1H), 7,62 (d, J = 1,5, 1H), 5,26 (m, 1H), 4,18 (m, 2H), 4,08 (d, J = 6,5, 1H), 3,89 (m, 4H), 3,53 (m, 4H), 3,47 (m, 4H), 2,82 (s, 3H), 2,80 (m, 2H), 2,17 (m, 1H), 2,00 (m, 2H), 1,82 (m, 2H), 1,27 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{20}H_{31}N_5O_6S$ calc.: 470,2, resultó: 470,2.

Ejemplo B11: (R)–Tetrahidrofuran–3–il 4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.

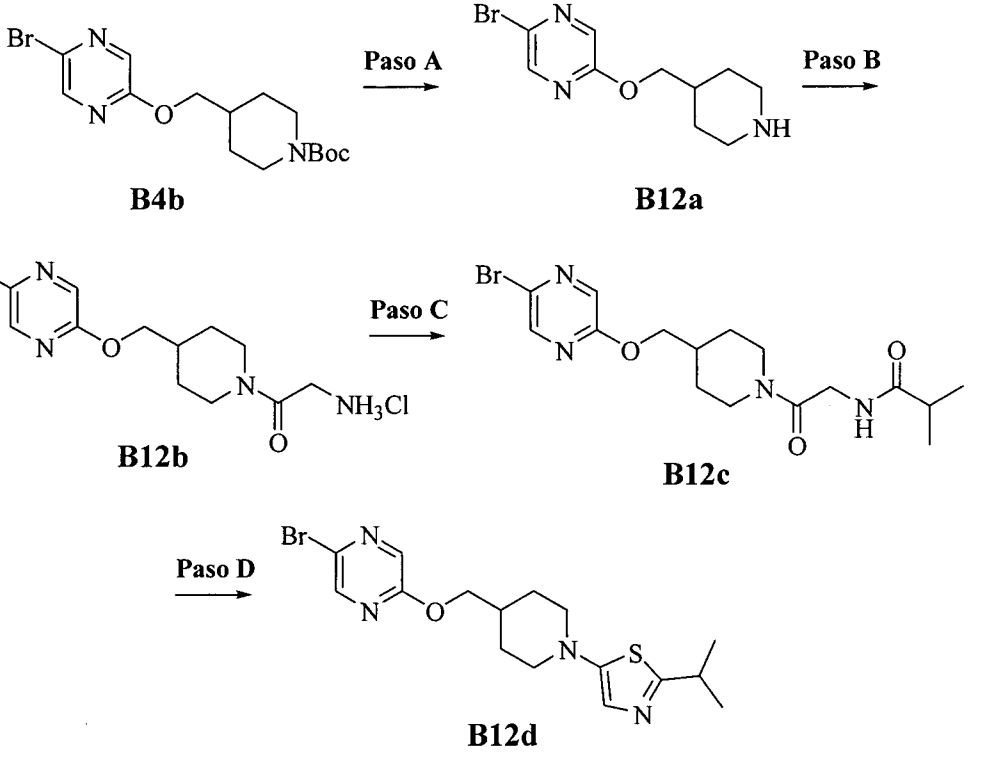


Siguiendo un procedimiento similar al utilizado para la preparación de **B3** a partir de **A1a** excepto que en el primer paso se sustituye el isopropil cloroformiato por (R)–4–nitrofenil tetrahidrofuran–3–il carbonato, se prepara **B11** con datos idénticos a los de **B10,**

Ejemplo B12: 2–Isopropil–5–(4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–il)tiazol.



Siguiendo un procedimiento similar al utilizado para la preparación de **B3** a partir de **A1d** excepto que se sustituye **A1d** por **B12d** (ver el esquema siguiente), se prepara **B12**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7,88 (d, J = 1,5, 1H), 7,63 (d, J = 1,5, 1H), 7,60 (dd, J = 9,1, 2,5, 1H), 6,79 (s, 1H), 4,13 (d, J = 6,2, 1H), 3,53 (m, 4H), 3,46 (m, 2H), 3,37 (m, 4H), 3,14 (m, 1H), 2,82 (s, 3H), 2,79 (m, 2H), 1,91 (m, 3H), 1,53 (m, 2H), 1,34 (d, J = 6,9, 6H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{33}N_6O_3S_2$ calc.: 481,2, resultó: 481,2.



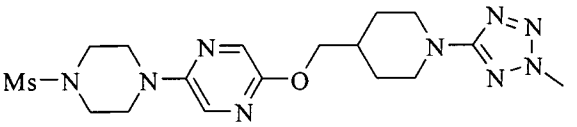
Paso A: Se trata una muestra de **B4b** (5,55 g, 14,9 mmol) con HCl 4 M en dioxano (20 ml) y se lo hace madurar por espacio de 1 hora. Se trata la reacción con agua y se retira el solvente al vacío. Se reparte el residuo entre acetato de etilo y NaOHOURS1 M. S aísla la fase acuosa, se la extrae una vez más con acetato de etilo y se la descarta. Se secan los extractos orgánicos combinados sobre $MgSO_4$, se los filtra y evapora para dar **B12a** que es utilizado sin más purificación; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{10}H_{15}BrN_3O$ calc.: 272.0, resultó: 272.0,

Paso B: Se trata una solución de **B12a** (1 g, 3,7 mmol), Boc–gly (966 mg, 5,5 mmol) y HOBt (596 mg, 4,4 mmol) en N–metilpirrolidinona (5 ml) con EDC (845 mg, 845 mg, 4,4 mmol) y se la agita por espacio de 1 hora. A continuación se diluye la reacción con acetato de etilo y se la extrae con agua e hidrogenocarbonato de sodio acuoso saturado dos veces. SE secan los extractos orgánicos sobre $MgSO_4$, se los filtra y evapora. Se trata el residuo con HCl 4 M en dioxano y se lo hace madurar durante 1 hora. Se suspende la mezcla con éter y se recoge el sólido para dar **B12b**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{12}H_{18}BrN_4O_2$ calc.: 329.1, resultó: 329.1.

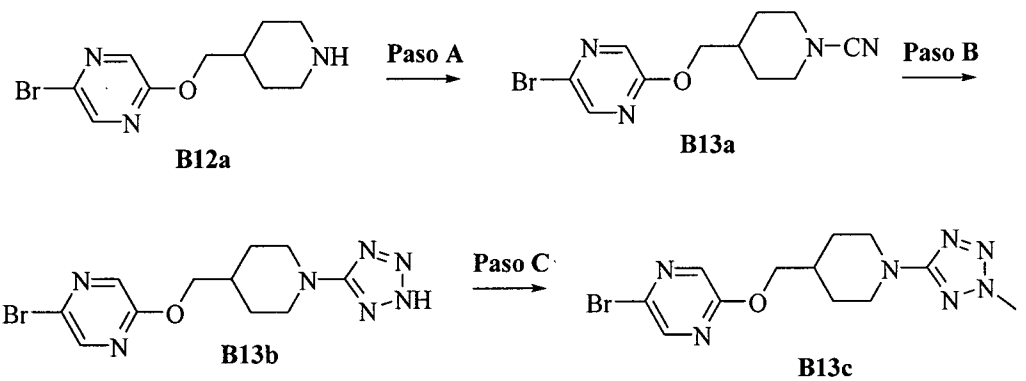
Paso C: Se trata una suspensión de **B12b** (400 mg, 1,1 mmol) en acetonitrilo (8 ml) con anhídrido isobutírico (208 mg, 1,3 mmol) seguido por trietilamina (360 mg, 3,6 mmol) y se la agita durante 1 hora. Se separa el solvente y se reparte el residuo entre acetato de etilo e hidrogenocarbonato de sodio acuoso saturado. Se aísla la fase acuosa, se la extrae una vez más con acetato de etilo y se la descarta. Se secan los extractos orgánicos sobre $MgSO_4$, se los filtra y evapora para producir **B12c** que es utilizado sin más purificación; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{16}H_{24}BrN_4O_3$ calc.: 399,1, resultó: 399.1.

Paso D: Se trata una solución de **B12c** (440 mg, 1,1 mmol) en *m*–xileno (2 ml) con reactivo de Laewesson (446 mmol, 1,1 mmol) y se lo calienta a 140 °C durante 5 minutos y luego se lo purifica en gel de sílice utilizando un gradiente lineal de 0–100 % de acetato de etilo en hexano. Se purifica a su vez el material producido en HPLC de preparación para dar **B12d**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{16}H_{22}BrN_4OS$ calc.: 397,1, resultó: 397,1.

Ejemplo B13: 2-((1-(2-metil-2H-tetrazol-5-il)piperidin-4-il)metoxi)-5-(4-(metilsulfonil)piperazin-1-il)pirazina.



Siguiendo un procedimiento similar al utilizado para la preparación de **B3** a partir de **A1d** excepto que se sustituye **A1d** por **B13c** (ver el esquema siguiente), se prepara **B13**; ^{1}H NMR (400 MHz, CD_3CN) δ 7,84 (d, *J* = 0,9 Hz, 1H), 7,72 (d, *J* = 1,2 Hz, 1H), 4,10 (s, 3H), 4,10 (d, *J* = 4,8 Hz, 2H), 4,02 (m, 2H), 3,51 (t, *J* = 3,9 Hz, 4H), 3,27 (t, *J* = 3,9 Hz, 4H), 2,91 (dt, *J* = 2,1, 9,6 Hz, 2H), 2,79 (s, 3H), 1,39 (ddd, *J* = 3,3, 9,3, 16,8 Hz, 4H), 2,20 (t, *J* = 5,4 Hz, 2H), 0,88 (m, 2H); ESIMS $(M+H)^+$ $C_{17}H_{28}N_9O_3S$ calc,: 438,2, resultó 438,2 (M+1).

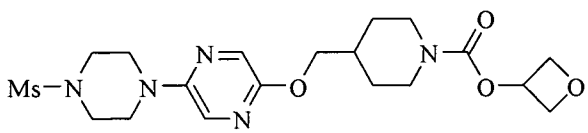


Paso A: A una suspensión agitada de **B12a** (200 mg, 0,74 mmol) e hidrogenocarbonato de sodio (0,15 g, 1,78 mmol) en un solvente mixto de agua (0,1 ml) y diclorometano (1 ml) a 0 °C se agrega bromuro de cianógeno (93 mg, 0,89 mmol) en una porción. A continuación se agita la reacción a temperatura ambiente por espacio de 4 h y se agrega más bromuro de cianógeno (93 mg, 0,89 mmol). Después de agitar de un día para otro, se diluye la reacción con diclorometano (30 ml), se la seca sobre $MgSO_4$ y evapora para dar **B13a**; ESIMS $(M+H)^+$ $C_{11}H_{14}BrN_4O$ calc.: 297.0, resultó 297.0,

Paso B: Se agita el **B13a** crudo obtenido con azida sódica (143 mg, 2,2 mmol) y cloruro de amonio (117 mg, 0,22 mmol) N,N–dimetilformamida anhidra (2 ml) a 110 °C por espacio de 2 horas. Se agrega más azida sódica (143 mg, 2,2 mmol) y cloruro de amonio (117 mg, 0,22). Después de agitar de un día para otro, se agrega agua lentamente para que el producto precipite. Se recoge el sólido blancuzco por filtración, se lo lava con agua (10 ml) y se lo seca al vacío para dar **B13b**; ^{1}H NMR (400 MHz, DMSO–d_6) δ 8,41 (d, *J* = 1,2 Hz, 1H), 8,20 (d, *J* = 0,9 Hz, 1H), 4,18 (d, *J* = 5,1 Hz, 2H), 3,86 (m, 2H), 3,02 (dt, *J* = 2,1, 9,6 Hz, 2H), 2,03 (m, 1H), 1,81 (m, 2H), 1,34 (ddd, *J* = 3,3, 9,6, 18,9 Hz, 2H); ESIMS $(M+H)^+$ $C_{11}H_{15}BrN_7O$ calc.: 340,0, resultó: 340,0,

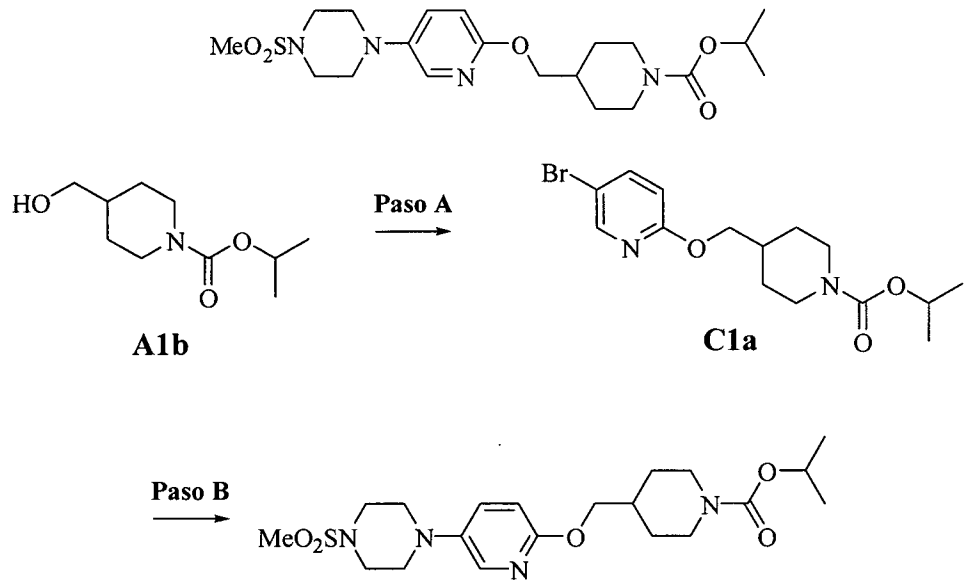
Paso C: Se agita una mezcla de **B13b** (50 mg, 0,15 mmol), yodometano (14 ul, 0,22 mmol) y K_2CO_3 (28 mg, 0,25 mmol) en N,N–dimetilformamida anhidra (1 ml) a temperatura ambiente por espacio de 3 horas. Se evapora el solvente al vacío y se utiliza el **B13c** crudo sin purificación: ESIMS $(M+H)^+$ $C_{12}H_{17}BrN_7O$ calc.: 354.1, resultó 354.0 (M+1).

Ejemplo B14. Oxetan–3–il 4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato



Siguiendo un procedimiento similar al utilizado para la preparación de **B3** a partir de **A1a** excepto que en el primer paso se sustituye isopropil cloroformiato por 4–nitrofenil oxetan–3–il carbonato, se prepara **B14**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{19}H_{30}N_5O_6S$ calc: 456.2, resultó: 456.0,

Ejemplo C1: Isopropil 4–((5–(4–(metilsulfonil)piperazin–1–il)piridin–2–iloxi)metil)piperidin–1–carboxilato.



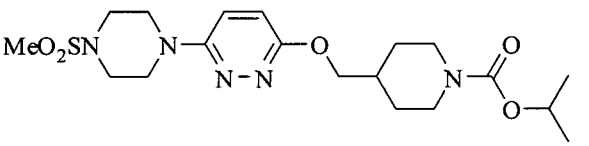
Ejemplo C1

Paso A: Se trata una solución de 2–cloro–5–bromopiridina (344 mg, 1,8 mmol) y **A1b** (300 mg, 1,5 mmol) en dimetilformamida (3 ml) con NaH (43 mg, 1,8 mmol) y se deja agitar la reacción de un día para otro. Después de inactivarla mediante la adición de agua, se diluye la reacción con acetato de etilo. Se aíslan los extractos orgánicos y se los extrae con agua una vez más, se los seca sobre $MgSO_4$, filtra y evapora. Se purifica el residuo en una columna de gel de sílice empleando un gradiente lineal de 0–50% de acetato de etilo en hexano para dar **C1b**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{15}H_{22}ClN_2O_3$ calc.: 313.1, resultó: 313.1.

Paso B: Siguiendo un procedimiento de acoplamiento con Pd similar al descripto para la preparación de **B1** excepto que se sustituye **C1a** como asociado par el acoplamiento de bromuro, se prepara **B14**; ^1H NMR ($CDCl_3$, 400 MHz): δ 7,78 (d, *J* = 2,9, 1H), 7,18 (dd, *J* = 3,0, 8,9, 1H), 6,69 (d, *J* = 8,9, 1H), 4,91 (m, 1H), 4,18 (m, 2H), 4,09 (d, *J* = 6,4, 2H), 3,38 (m, 4H), 3,17 (m, 4H), 2,84 (s, 3H), 2,77 (m, 2H), 1,96 (m, 1H), 1,81 (m, 2H),

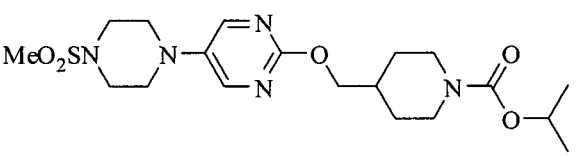
1,29 (m, 2H), 1,24, d, *J* = 6,3, 6H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{20}H_{33}N_4O_5S$ calc.: 441,2, resultó: 441,2.

Ejemplo C2: Isopropil 4–((6–(4–(metilsulfonil)piperazin–1–il)piridazin–3–iloxi)metil)piperidin–1–carboxilato.



Siguiendo un procedimiento similar al utilizado para la preparación de **C1** a partir de **A1b** excepto que en el primer paso se sustituye for 2–cloro–5–bromopiridina por 2,5–dicloropiridazina, se prepara **C2**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7,04 (d, *J* = 9,6, 1H), 6,88 (d, *J* = 9,6, 1H), 4,91 (m, 1H), 4,29 (m, 2H), 4,18 (m, 2H), 3,64 (m, 4H), 3,35 (m, 4H), 2,81 (s, 3H), 2,77 (m, 2H), 2,03 (m, 1H), 1,80 (m, 2H), 1,29 (m, 2H), 1,24, d, *J* = 6,4, 6H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{19}H_{32}N_5O_5S$ calc.: 442,2, resultó: 442,3.

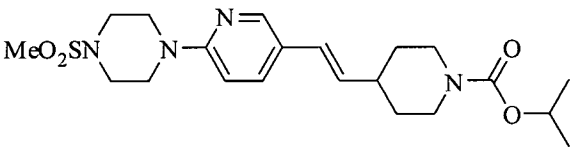
Ejemplo C3: Isopropil 4–((5–(4–(metilsulfonil)piperazin–1–il)pirimidin–2–iloxi)metil)piperidin–1–carboxilato.

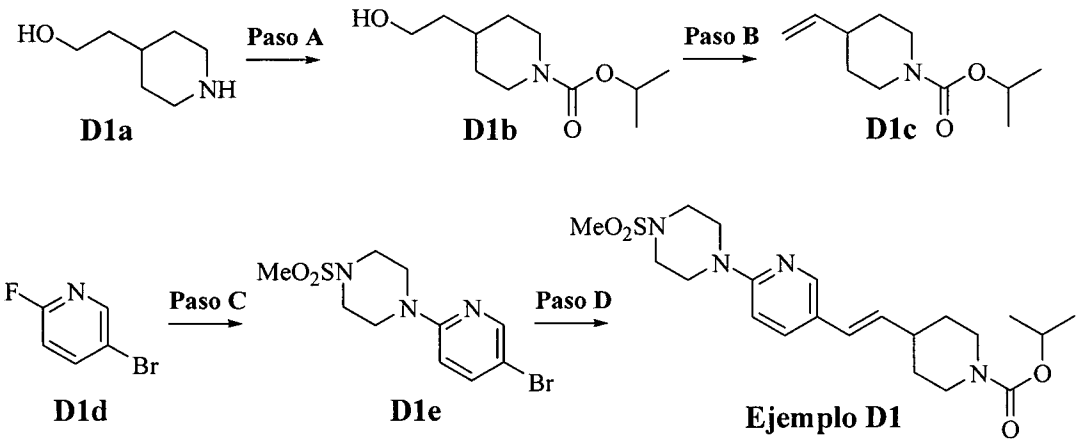


Siguiendo un procedimiento similar al utilizado para la preparación de **C1** a partir de **A1b** excepto que se sustituye 2–cloro–5–bromopirimidine for 2–cloro–5–bromopiridina en el primer Paso, se prepara **C3**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8,38 (s, 2H), 4,91 (sept,, J = 6,3 Hz, 1H), 4,23 (m, 5H), 3,50 (m, 4H), 3,29 (m, 4H), 2,87 (s, 3H), 2,76 (m,

2H), 2,04 (m, 1H), 1,84 (m, 2H), 1,27 (m, 1H), 1,24 (d, J = 6,3 Hz, 6H),; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{19}H_{32}N_5O_5S$ calc.: 442,2, resultó: 442,3.

Ejemplo D1: (E)–isopropil 4–(2–(6–(4–(metilsulfonil)piperazin–1–il)piridin–3–il)vinil)piperidin–1–carboxilato.





Paso A: Se trata una solución de **D1a** (10 g, 0,077 mol) en diclorometano (100 ml) con una solución de isopropil cloroformiato en tolueno (93 ml de una solución 1M) por goteo. Seguidamente se agita la reacción a temperatura ambiente por espacio de 2,5 horas y se la inactiva con una solución acuosa saturada de cloruro de amonio. Se separan las fases y se extrae la fase acuosa una vez más con diclorometano y se la descarta. Se extraen los extractos orgánicos combinados una vez con HCl 1 M, una vez con hidrogenocarbonato de sodio acuoso saturado, se los seca sobre $MgSO_4$, se los filtra y evapora para dar **D1b**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_7H_{16}NO$ calc.: 130,1, resultó: 130,1.

Paso B: Se trata una solución fría (baño de hielo/agua) de **D1b** (9,9 g, 0,046 mol) y trietilamina (6,7 ml, 0,048 mol) en diclorometano con la adición gota a gota de cloruro

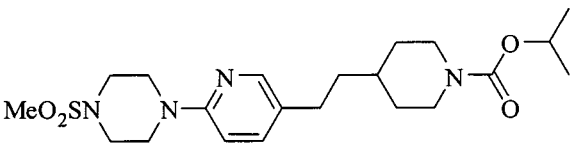
de metansulfonilo (3,7 ml, 0,048 mol) y se la agita por espacio de 2 horas. Se trata la mezcla con agua y se la extrae con diclorometano. Se agrupan las sustancias orgánicas, se las seca sobre $MgSO_4$, se las filtra y concentra. Se diluye el material crudo en acetona (10 ml) y se la agrega por goteo a una suspensión de bromuro de litio (12 g, 0,138 mol) en acetona (50 ml). Se calienta la reacción a 35°C y se la mantiene de un día para otro. Después de enfriar a temperatura ambiente, se concentra la reacción, se la diluye con acetato de etilo y se la lava con agua. Se recoge la fase orgánica, se la seca sobre $MgSO_4$ y concentra. Se diluye este residuo en tetrahidrofurano (150 ml) y se lo trata mediante la adición en porciones de terc–butóxido de potasio (23.05 g, 0,2054 mol) cada 30 min durante 3 horas. Seguidamente se calienta la reacción a 40 °C y se la mantiene de un día para otro. Una vez enfriada la reacción a temperatura ambiente, se introduce cloruro de amonio acuoso saturado y se extrae la reacción con Et_2O. Se recogen los extractos orgánicos, se los seca sobre $MgSO_4$, concentra y purifica por destilación (68°–70 °C, 180 mTorr) para dar **D1c**. ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{11}H_{20}NO_2$ calc.: 198.3 resultó: 198,1.

Paso C: Se trata una solución de **D1d** (321 mg, 1,8 mmol) y metansulfonilpiperazina (300 mg, 1,8 mmol) en N–metilpirrolidinona (2ml) con K_2CO_3 (380 mg, 2,7 mmol) y se la calienta a 160 °C durante 5 minutos. A continuación se reparte la reacción entre acetato de etilo y agua y se extrae la fase orgánica con agua una vez más, se la seca sobre $MgSO_4$, evapora y purifica en gel de sílice empleando 0–100% de acetato de etilo en hexano para dar **D1e**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{10}H_{15}BrN_3O_2S$ calc.: 320,0, resultó: 320,1.

Paso D: Se calienta una solución de **D1e** (50 mg, 0,18 mmol), **D1c** (44 mg, 0,22 mmol) Pd_2dba_3 (5 mg, 0,006 mmol) y tetrafluoroborato de tri–*terc*–butilfosfonio (3.2 mg, 0,011 mmol) y diciclohexilmetilamina (72 mg, 0,37 mmol) en dioxano (1ml) a 120 °C por espacio de 1 hora. A continuación se reparte la reacción entre acetato de etilo y agua y se extraen los orgánicos con agua una vez más, se los seca sobre $MgSO_4$, filtra y evapora y se los purifica en gel de sílice utilizando un gradiente de 0–100 % de acetato de etilo en hexano para dar **D1**; ^1H NMR ($CDCl_3$, 400 MHz): δ 8,11 (d, J = 2,3, 1H), 7,57 (dd, J = 8,8, 2,4, 1H), 6,63 (d, J = 8,8, 1H), 6,27 (d, J = 15,9, 1H), 5,99 (dd, J = 16,0,

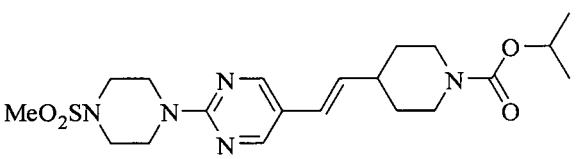
6,9, 1H), 4,91 (m, 1H), 4,17 (m, 2H), 3,67 (m, 4H), 3,32 (m, 4H), 2,80 (m, 2H), 2,80 (s, 3H), 2,23 (m, 1H), 1,77 (m, 2H), 1,38 (m, 2H), 1,24, d, *J* = 6,2, 6H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{33}N_4O_4S$ calc.: 437,2, resultó: 437,2.

Ejemplo D2. Isopropil 4–(2–(6–(4–(metilsulfonil)piperazin–1–il)piridin–3–il)etil)piperidin–1–carboxilato.



Se trata una solución de **D2** (25 mg, 0,057 mmol) en metanol (2 ml) con Pd/C al 10% (5 mg) y se la hidrogena durante 1 hora. Se intercambia la atmósfera por nitrógeno y se filtra la reacción a través de una plancha de Celite® y se separa el solvente para dar **D2**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8,02 (d, *J* = 2,2, 1H), 7,35 (dd, *J* = 8,6, 2,4, 1H), 6,63 (d, *J* = 8,6, 1H), 4,90 (m, 1H), 4,12 (m, 2H), 3,62 (m, 4H), 3,32 (m, 4H), 2,80 (s, 3H), 2,68 (m, 2H), 2,52 (m, 2H), 1,70 (m, 2H), 1,52 (m, 2H), 1,42 (m, 1H), 1,23 (d, *J* = 6,2, 6H), 1,12 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{35}N_4O_4S$ calc.: 439,2, resultó: 439,3.

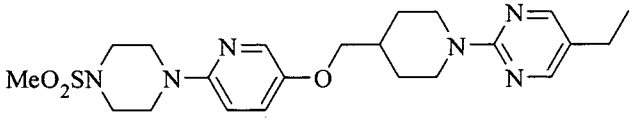
Ejemplo D3. (E)–Isopropil 4–(2–(2–(4–(metilsulfonil)piperazin–1–il)pirimidin–5–il)vinil)piperidin–1–carboxilato.

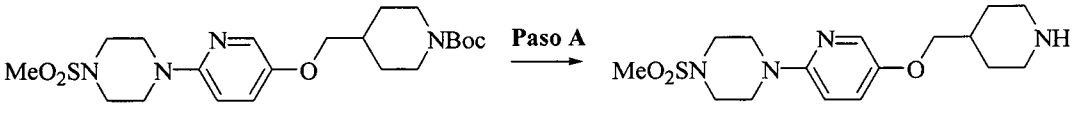


Siguiendo un procedimiento similar al utilizado para la preparación de **D1** a partir de **D1a** excepto que se sustituye **D1d** por 2–cloro–5–bromopirimidina, se prepara **D3**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8,38 (s, 2H), 6,18 (d, J = 16,2 Hz, 1H), 6,05 (dd, J = 16,1, 6,6 Hz, 1H), 4,92 (m, 1H), 4,18 (m, 2H), 3,98 (m, 4H), 3,30 (m, 4H), 2,80 (s, 3H), 2,80 (m,

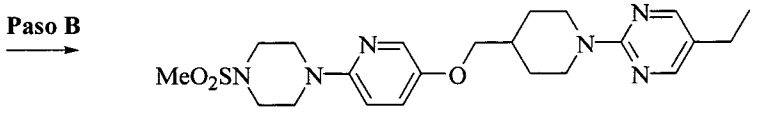
2H), 2,29 (m, 1H), 1,76 (m, 2H), 1,38 (m, 2H), 1,24 (d, J = 6,2 Hz, 6H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{20}H_{32}N_5O_4S$ calc.: 438,2, resultó: 438,3.

Ejemplo E1. 5–Etil–2–(4–((6–(4–(metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–il)pirimidina.





B2 **E1a**



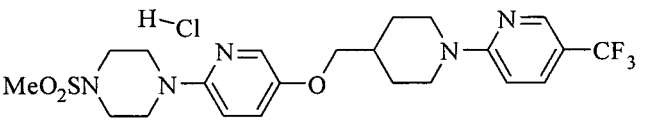
Ejemplo E1

Paso A: Se trata una muestra de **B2** (202 mg, 0,445 mmol) con HCl 4 M en dioxano (3 ml) y se lo hace madurar durante 1 hora. A continuación se separa el solvente y se reparte el residuo entre acetato de etilo y NaOH 1 M. Se aísla la fase acuosa, se la extrae una vez más con acetato de etilo y se la descarta. Se secan los extractos orgánicos sobre $MgSO_4$, se los filtra y evapora para dar **E1a**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{16}H_{27}N_4O_3S$ calc.: 355.2, resultó: 355.2.

Paso B: Se trata el material obtenido con 2–cloro–5–etilpirimidina (121 mg, 0,85 mmol), CuI (12 mg, 0,063 mmol), diisopropiletilamina (176 mg, 1,4 mmol) y N–metilpirrolidinona (2 ml). Se sella la solución obtenida en un vial de reacción y se la calienta a 160 °C durante 10 minutos utilizando un reactor de microondas. A continuación se diluye la reacción con acetato de etilo y se la extrae con agua una vez, una vez con HCl 1 M y una vez con hidrogenocarbonato de sodio acuoso saturado, se

la seca sobre $MgSO_4$, filtra y evapora y purifica en gel de sílice utilizando un gradiente lineal de 0–100% de acetato de etilo en hexano seguido por liofilización de HCl 1 M para dar **E1** en forma de sal de HCl; ^{1}H NMR (DMSO–d6, 400 MHz): δ 8,27 (s, 2H), 7,82 (d, *J* = 2,9, 1H), 7,50 (m, 1H), 7,05 (m, 1H), 4,63 (m, 2H), 3,86 (d, *J* = 6,4, 2H), 3,57 (m, 4H), 3,22 (m, 4H), 2,91 (s, 3H), 2,91 (m, 2H), 2,43 (dd, *J* = 15,1, 7,6, 2H), 2,03 (s, 1H), 1,82 (m, 2H), 1,22 (m, 2H), 1,13 (dd, *J* = 7,6, 7,6, 36H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{22}H_{33}N_6O_3S$ calc.: 461,2, resultó: 461,2.

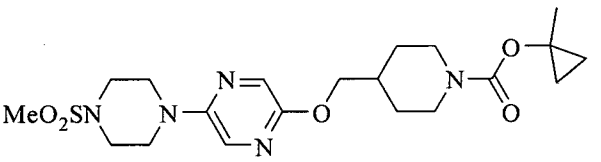
Ejemplo E2. 1–(Metilsulfonil)–4–(5–((1–(5–(trifluorometil)piridin–2–il)piperidin–4–il)metoxi)piridin–2–il)piperazina.

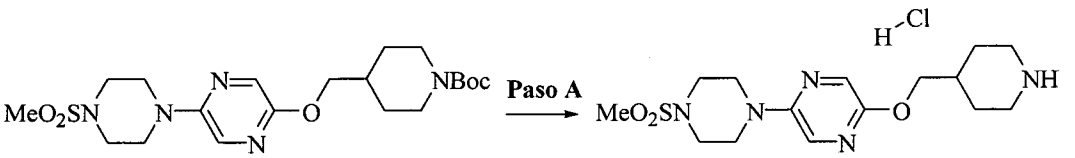


Siguiendo un procedimiento similar al utilizado para la preparación de **E1** a partir de **B2** excepto que se sustituye el **Paso B** por el siguiente procedimiento, se prepara **E2**;

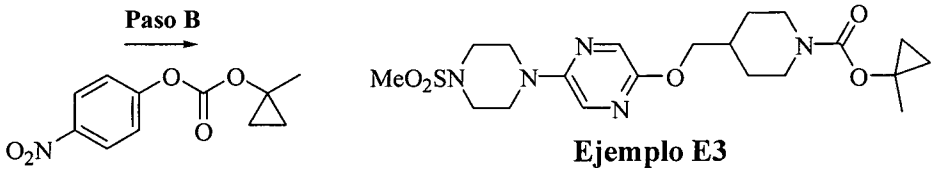
Se trata una muestra de clorhidrato de **E1a** (900 mg, 2,3 mmol) con 2–cloro–3–trifluorometilpiridina (501 mg, 2,76 mmol), K_2CO_3 (795 mg, 5,8 mmol), N–metilpirrolidinona (10 ml) y agua (8 ml) y se la calienta en un recipiente herméticamente cerrado en un reactor de microondas a 160 °C por espacio de 10 minutos. Se trata la suspensión obtenida con acetato de etilo y agua y se la filtra. Se lava el sólido obtenido con agua y acetato de etilo, se lo disuelve en HCl 1 M y se la liofiliza para dar **E2** ; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8,22 (m, 1H), 8,10 (dd, *J* = 9,8, 2,3, 1H), 7,86 (dd, *J* = 9,9, 2,9, 1H), 7,60 (d, *J* = 2,9, 1H), 7,53 (d, *J* = 9,8, 1H), 7,42 (d, *J* = 9,1, 1H), 4,30 (m, 2H), 3,94 (d, *J* = 6,2, 1H), 3,71 (m, 4H), 3,37 (m, 4H), 2,86 (s, 3H), 2,28 (m, 1H), 2,06 (m, 2H), 1,57 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{22}H_{29}F_3N_5O_3S$ calc.: 500,2, resultó: 500,2.

Ejemplo E3. 1–Metilciclopropil 4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.





B4 **E3a**



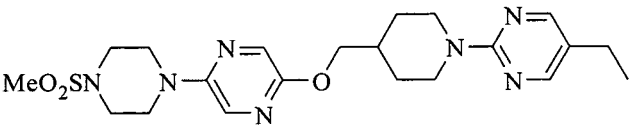
E3b **Ejemplo E3**

Paso A: Se trata una muestra de **B4** (745 mg, 0,16 mmol) con HCl 4 M HCl en dioxano y de la agita por espacio de 3 horas. Se decanta el solvente y se liofiliza el residuo del agua para dar **E3a**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{15}H_{26}N_5O_3S$ calc.: 356.2, resultó: 356.2.

Paso B: Se trata una muestra de **E3a** (181,8 mg, 0,46 mmol) con N, N–dimetilformamida (1,5 ml), **E3b** (110 mg, 0,46 mmol) y diisopropiletilamina (242 µl, 1,4 mmol) y se la agita de un día para otro. A continuación se reparte la reacción entre acetato de etilo y agua y se aíslan los extractos orgánicos, se los extrae con NaOH 1 M tres veces, se los seca sobre $MgSO_4$, filtra y evapora y se los purifica en gel de sílice empleando un gradiente lineal de 0–100% de acetato de etilo en hexano para dar **E3**; ^1H NMR ($CDCl_3$, 400 MHz): δ 7,87 (d, J = 1,5, 1H), 7,62 (d, J = 1,4, 1H), 4,18 (m, 2H), 4,08 (d, J = 6,5, 2H), 3,52 (m, 4H), 3,36 (m, 4H), 2,82 (s, 3H), 2,72 (m, 2H), 1,93 (m,

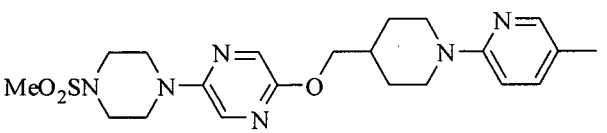
1H), 1,80 (m, 2H), 1,56 (d, *J* = 9,9, 3H), 1,23 (m, 2H), 0,87 (m, 2H), 0,62 (m,2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{20}H_{32}N_5O_5S$ calc.: 454,2, resultó: 454,2.

Ejemplo E4. 5–Etil–2–(4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–il)pirimidina.



Siguiendo un procedimiento similar al utilizado para la preparación de **E1** a partir de **E1a** excepto que se sustituye **E1a** por **E3a**, se prepara **E4**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8,17 (s, 2H), 7,88 (d, *J* = 1,4, 1H), 7,63 (d, *J* = 1,5, 1H), 4,76 (m, 2H), 4,11 (d, *J* = 6,6, 2H), 3,52 (m, 4H), 3,37 (m, 4H), 2,90 (m, 2H), 2,82 (s, 3H), 2,45 (dd, *J* = 15,2, 7,6, 2H), 2,08 (m, 2H), 1,90 (m, 2H), 1,33 (ddd, *J* = 24,9, 12,4, 4,2, 2H), 1,18 (dd, *J* = 7,6, 7,6, 3H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{32}N_7O_3S$ calc.: 462.2, resultó: 462.3.

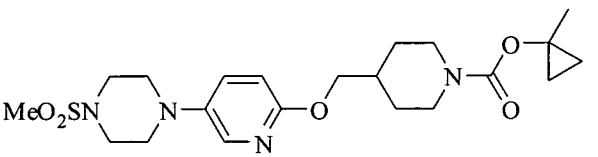
Ejemplo E5. 2–((1–(5–Metilpiridin–2–il)piperidin–4–il)metoxi)–5–(4–(metilsulfonil)piperazin–1–il)pirazina.



Se purga con nitrógeno una mezcla de **E3a** (103 mg, 0,26 mmol), 2–bromo–5–metilpiridina (45.3 mg, 0,26 mmol), Pd_2dba_3 (4.8 mg, 0,005 mmol), xantfos (9,1 mg, 0,016 mmol), *terc*–butóxido de sodio (78 mg, 0,815 mmol) y tolueno (1,5 ml) por espacio de 5 minutos y se la calienta en un baño de aceite a 100 °C de un día para otro. Se enfría la reacción a temperatura ambiente y se la diluye con agua y acetato de etilo. Se secan los extractos orgánicos sobre $MgSO_4$, se los filtra, evapora y purifica por cromatografía en columna sobre gel de sílice utilizando un gradiente lineal de 0–100 % de acetato de etilo en hexano para dar **E5**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8,01 (m, 1H),

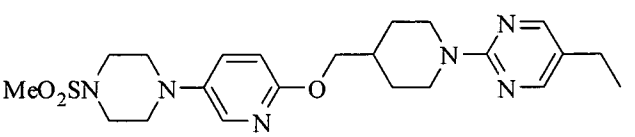
7,88 (d, *J* = 1,4, 1H), 7,30 (m, 1H), 6,62 (d, *J* = 8,6, 1H), 4,27 (m, 2H), 4,11 (d, *J* = 6,6, 1H), 3,53 (m, 4H), 3,37 (m, 4H), 2,82 (m, 2H), 2,82 (s, 3H), 2,19 (s, 3H), 2,02 (m, 1H), 1,91 (m, 2H), 1,42 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{31}N_6O_3S$ calc.: 447,2, resultó: 447,3.

Ejemplo E6. 1–Metilciclopropil 4–((5–(4–(metilsulfonil)piperazin–1–il)piridin–2–iloxi)metil)piperidin–1–carboxilato.



Siguiendo un procedimiento similar al utilizado para la preparación de **E3** a partir **B4** excepto que se sustituye **B4** por *terc*–butil 4–((5–(4–(metilsulfonil) piperazin–1–il)piridin–2–iloxi)metil)piperidin–1–carboxilato, se prepara **E6**; se prepara *terc*–Butil 4–((5–(4–(metilsulfonil) piperazin–1–il)piridin–2–iloxi)metil)piperidin–1–carboxilato de manera análoga a **B4** excepto que se utiliza 2–fluoro–5–bromopiridina en lugar de **A1d**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7,78 (d, *J* = 2,9, 1H), 7,28 (dd, *J* = 8,9, 3,0, 1H), 6,68 (d, *J* = 8,9, 1H), 4,18 (m, 2H), 4,08 (d, *J* = 6,5, 2H), 3,38 (m, 4H), 3,14 (m, 4H), 2,83 (s, 3H), 2,73 (m, 2H), 1,93 (m, 1H), 1,79 (m, 2H), 1,54 (s, 3H), 1,23 (m, 2H), 0,86 (m, 2H), 0,61 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{33}N_4O_5S$ calc: 453,2, resultó: 453,3.

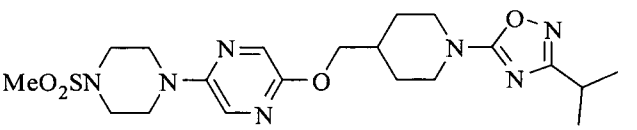
Ejemplo E7. 5–Etil–2–(4–((5–(4–(metilsulfonil)piperazin–1–il)piridin–2–iloxi)metil)piperidin–1–il)pirimidina.

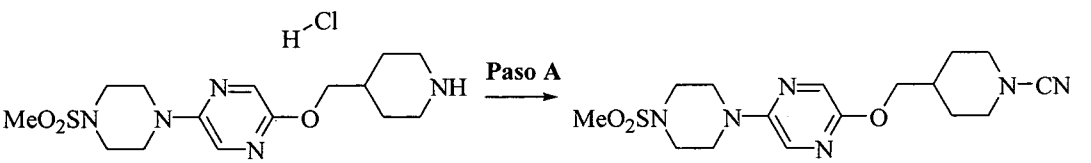


Siguiendo un procedimiento similar al utilizado para la preparación de **E1** a partir de **E1a** excepto que se sustituye **E1a** por *terc*–butil 4–((5–(4–(metilsulfonil) piperazin–1–

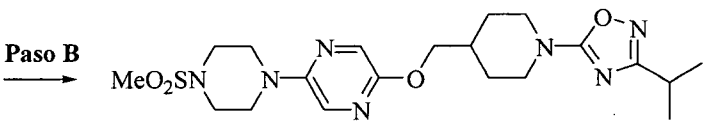
il)piridin–2–iloxi)metil)piperidin–1–carboxilato, se prepara **E7**; se prepara *terc*–Butil 4–((5–(4–(metilsulfonil) piperazin–1–il)piridin–2–iloxi)metil)piperidin–1–carboxilato de manera análoga a **B4** excepto que se utiliza 2–fluoro–5–bromopiridina en lugar de **A1d**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8,16 (s, 2H), 7,78 (d, *J* = 2,9, 1H), 7,28 (dd, *J* = 8,9, 3,0, 1H), 6,69 (d, *J* = 9,0, 1H), 4,73 (m, 2H), 4,11 (d, *J* = 6,6, 1H), 3,38 (m, 4H), 3,14 (m, 4H), 2,89 (m, 2H), 2,83 (s, 3H), 2,44 (dd, *J* = 15,2, 7,6, 2H), 2,08 (m, 1H), 1,90 (m, 2H), 1,34 (ddd, *J* = 24,8, 12,4, 4,1, 2H), 1,73 (dd, *J* = 7,6, 7,6, 3H); ESIMS *m/z* correspondiente a $(M+H)^+$.$C_{22}H_{33}N_6O_3S$ calc.: 461,2, resultó: 461,3.

Ejemplo E8. 3–Isopropil–5–(4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–il)–1,2,4–oxadiazol.





E3a **E8a**



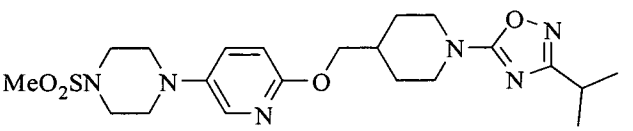
Ejemplo E8

Paso A: Se trata una solución fría (baño de hielo/agua) de **E3a** (256 mg, 0,65 mmol) en diclorometano (5 ml) con una solución de K_2CO_3 (298 mg, 2,2 mmol) en agua (5 ml). Se trata la solución con agitación vigorosa con una solución de bromuro de cianógeno (76.1 mg, 0,72 mmol) en diclorometano (2 ml) y se deja agitar la reacción a frío por espacio de 3 horas. A continuación se separan las fases y se seca la fase orgánica sobre $MgSO_4$, se la filtra y evapora para producir **E8a** que es utilizado sin más

purificación; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{16}H_{25}N_6O_3S$ calc.: 381.2, resultó: 381,1.

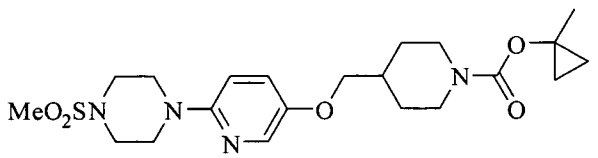
Paso B: Se trata una solución de **E3a** (215.5 mg, 0,57 mmol) en dioxano (2 ml) con N'–hidroxiisobutirimidamida (86,8 mg, 0,85 mmol) y $ZnCl_2$ (115.8 mgl, 0,85 mmol) y se la agita a 100 °C de un día para otro. A continuación se reparte la reacción entre acetato de etilo y NaOH 1 M y se aísla la fase orgánica, se la seca sobre $MgSO_4$, filtra y evapora y se la purifica en gel de sílice utilizando un gradiente lineal de 0–100% de acetato de etilo en hexano para producir **E8**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7,88 (d, *J* = 1,4, 1H), 7,62 (d, *J* = 1,4, 1H), 4,19 (m, 2H), 4,11 (d, *J* = 6,5, 2H), 3,53 (m, 4H), 3,37 (m, 4H), 3,08 (ddd, *J* = 12,9, 12,9, 2,8, 2H), 2,87 (m, 1H), 2,82 (s, 3H), 2,03 (m, 1H), 1,91 (m, 2H), 1,43 (ddd, *J* = 25,2, 12,5, 4,4, 2H), 1,28 (d, *J* = 7,0, 3H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{20}H_{32}N_7O_4S$ calc.: 466,2, resultó: 466,3.

Ejemplo E9. 3–Isopropil–5–(4–((5–(4–(metilsulfonil)piperazin–1–il)piridin–2–iloxi)metil)piperidin–1–il)–1,2,4–oxadiazol.



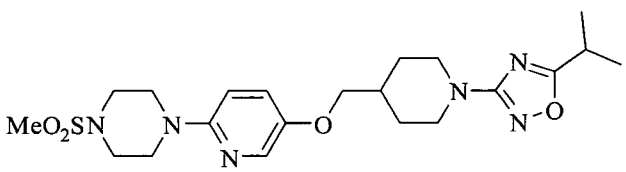
Siguiendo un procedimiento similar al utilizado para la preparación de **E8** a partir de **B4** excepto que se sustituye **B4** por *terc*–butil 4–((5–(4–(metilsulfonil) piperazin–1–il)piridin–2–iloxi)metil)piperidin–1–carboxilato, se prepara **E9**; se prepara *terc*–Butil 4–((5–(4–(metilsulfonil) piperazin–1–il)piridin–2–iloxi)metil)piperidin–1–carboxilato de manera análoga a **B4** excepto que se utiliza 2–fluoro–5–bromopiridina en lugar de **A1d**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7,78 (d, *J* = 2,9, 1H), 7,29 (dd, *J* = 8,9, 3,0, 1H), 6,69 (d, *J* = 8,9, 1H), 4,17 (m, 2H), 4,13 (d, *J* = 6,5, 1H), 3,40 (m, 4H), 3,17 (m, 4H), 3,08 (ddd, *J* = 12,9, 12,9, 2,8, 2H), 2,88 (m, 1H), 2,84 (s, 3H), 2,03 (m, 1H), 1,91 (m, 2H), 1,34 (ddd, *J* = 25,1, 12,5, 4,4, 2H), 1,28 (d, *J* = 7,0, 3H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{33}N_6O_4S$ calc.: 465,2, resultó: 465,3.

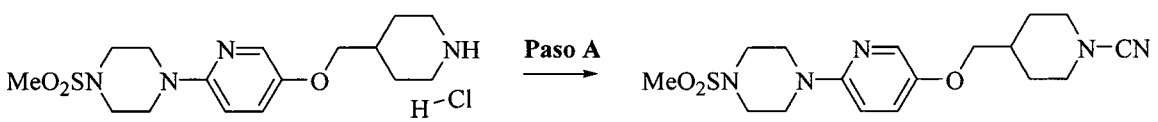
Ejemplo E10, 1–Metilciclopropil 4–((6–(4–(metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato.



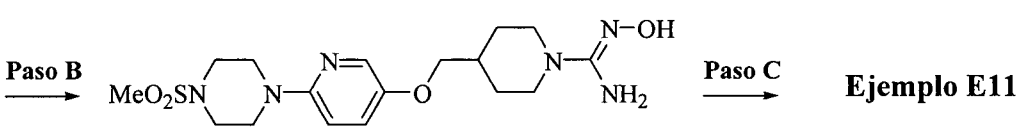
Siguiendo un procedimiento similar al utilizado para la preparación de **E3** a partir de **B4** excepto que se sustituye **B4** por **B2**, **E10** se prepara; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7,90 (d, J = 2,9, 1H), 7,14 (dd, J = 9,1, 3,0, 1H), 6,65 (d, J = 9,0, 1H), 4,12 (m, 2H), 3,77 (d, J = 6,3, 1H), 3,54 (m, 4H), 3,33 (m, 4H), 2,80 (s, 3H), 2,73 (m, 2H), 1,92 (m, 1H), 1,89 (m, 2H), 1,54 (s, 3H), 1,23 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{33}N_4O_5S$ calc.: 453,2, resultó: 453,2.

Ejemplo E11. 5–Isopropil–3–(4–((6–(4–(metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–il)–1,2,4–oxadiazol.





E1a·HCl **E11a**



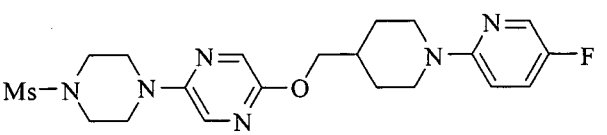
E11b

Paso A: Se enfría una mezcla de **E1a·HCl** (202,3 mg, 0,52 mmol) y K_2CO_3 (143 mg, 1,0 mmol) en agua (3 ml) a la temperatura del baño de hielo/agua y se la trata por goteo con una solución de bromuro de cianógeno (60,3 mg, 0,57 mmol) en diclorometano (3 ml) y se la agita por espacio de 2 horas mientras se enfría. A continuación se diluye la reacción con diclorometano, se la extrae con agua, se la seca sobre $MgSO_4$, filtra y evapora para dar **E11a** que es utilizado sin más purificación; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{17}H_{26}N_5O_3S$ calc.: 380,2, resultó: 380,2.

Paso B: Se calienta una solución de **E11a** (152,4 mg, 0,40 mmol) y hidroxilamina (492 µl de una solución acuosa al 50%, 0,80 mmol) en etanol (2 ml) a 60 °C en un recipiente herméticamente cerrado de un día para otro. Se enfría la reacción a temperatura ambiente y se produce una muestra de **E11b**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{17}H_{29}N_6O_4S$ calc.: 413.2, resultó: 413.2.

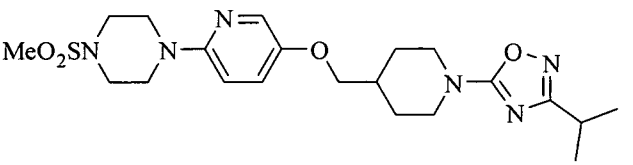
Paso C: Se calienta una solución de **E11b** (134,2 mg, 0,32 mmol) y anhídrido isobutírico (50 mg, 0,32 mmol) en dioxano a 400 W en un reactor de microondas por espacio de 10 minutos (~120 °C). Se enfría la reacción a temperatura ambiente, se la evapora y reparte entre acetato de etilo e hidrogenocarbonato de sodio acuoso saturado. Se aísla la fase orgánica, se la seca sobre $MgSO_4$, filtra y evapora y se la purifica en gel de sílice utilizando un gradiente lineal de 0–100% de acetato de etilo en hexano y se la liofiliza de HCl 1 M para dar **E11** en forma de sal de HCl; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7,92 (d, *J* = 3,0, 1H), 7,16 (dd, *J* = 9,1, 3,0, 1H), 6,65 (d, *J* = 9,1, 1H), 4,06 (m, 2H), 3,80 (d, *J* = 6,4, 1H), 3,54 (m, 4H), 3,33 (m, 4H), 3,07 (m, 1H), 2,92 (ddd, *J* = 12,7, 12,7, 2,7, 1H), 2,80 (s, 3H), 2,73 (m, 2H), 1,99 (m, 1H), 1,88 (m, 2H), 1,42 (m, 2H), 1,34 (d, *J* = 7,0, 6H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{33}N_6O_4S$ calc.: 465,2, resultó: 453,3.

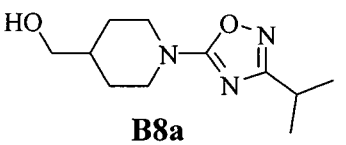
Ejemplo E12. 2–((1–(5–Fluoropiridin–2–il)piperidin–4–il)metoxi)–5–(4–(metilsulfonil)piperazin–1–il)pirazina.



Siguiendo un procedimiento similar al utilizado para la preparación de **E5** a partir de **E3a** excepto que se sustituye 2–bromo–5–metilpiridina por 2–bromo–5–fluoropiridina y xantfos por diciclohexil(2',6'–dimetoxibifenil–4–il)fosfina, se prepara **E12**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{20}H_{28}FN_6O_3S$ calc: 451.2, resultó: 451.2.

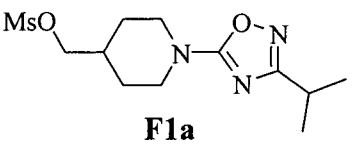
Ejemplo F1. 3–Isopropil–5–(4–((6–(4–(metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–il)–1,2,4–oxadiazol



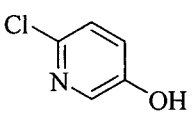


B8a

Paso A

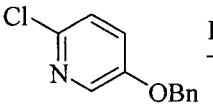


F1a



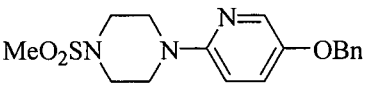
F1b

Paso B



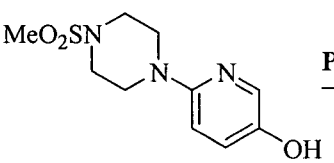
F1c

Paso C



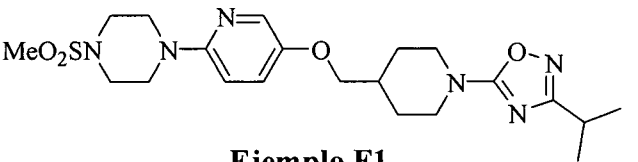
F1d

Paso D



F1e

Paso E



Ejemplo F1

Paso A: Siguiendo un procedimiento similar al utilizado para la preparación de **B5c** a partir de **B5b** excepto que se sustituye **B5b** por **B8a**, se prepara **F1a**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{12}H_{22}N_3O_4S$ calc: 304.1, resultó: 304.1.

Paso B: Se trata una solución de **F1b** (3.00 g, 23,0 mmol) y cloruro de bencilo (2,93 ml, 25,5 mmol) en acetonitrilo (50 ml) con Cs_2CO_3 (15,0 g, 46,0 mmol) y se calienta la mezcla de reacción a 90 °C por espacio de 2 horas, se la enfría y filtra. Se evaporan los solventes y se purifica el compuesto crudo en gel de sílice utilizando un gradiente lineal de 0–100% de acetato de etilo en hexano para producir **F1c**; ^{1}H–NMR (400 MHz, $CDCl_3$) δ 8,15 (dd, *J* = 0,8, 2,8 Hz, 1H), 7,42 (m, 4H), 7,39 (m, 1H), 7,25 (m, 2H), 5,12 (s, 2H); ESIMS calc, para $[M+H]^+$ $C_{12}H_{11}ClNO$: 220,1 resultó: 220,1.

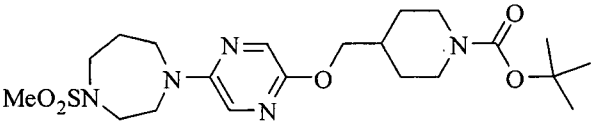
Paso C: Se carga **F1c** (2,67 g, 12,2 mmol), 1–metansulfonil piperazina (3 g, 18,3 mmol), $Pd(OAc)_2$ (548 mg, 2,4 mmol), ((2–diciclohexil)fosfino)bifenilo (1,7 g, 4.8 mmol), NaO*t*Bu (3,5 g, 36,6 mmol) y tolueno (20 ml) en un matraz herméticamente cerrado y se desgasifica con Ar burbujeante por espacio de 30 minutos. Se calienta la mezcla a 120 °C por espacio de 18 h, luego se la filtra en caliente para eliminar las sustancias en partículas. Se lava la torta de filtro con acetato de etilo (10 ml) y agua (20 ml) y se combinan y extraen los filtrados con acetato de etilo (20 ml). Se extrae la capa orgánica con HCl 1 N (3 x 20 ml) y se la descarta. Seguidamente se basifica la capa ácida con NaOH y se la extrae con acetato de etilo (3 x 20 ml). Se combinan las capas orgánicas restantes, se las seca ($MgSO_4$), filtra y concentra. Se hace recristalizar el residuo de acetato de etilo /Hexano para producir **F1d**; ESIMS calc. para $[M+H]^+$ $C_{17}H_{22}N_3O_3S$: 348.1 resultó: 348,1.

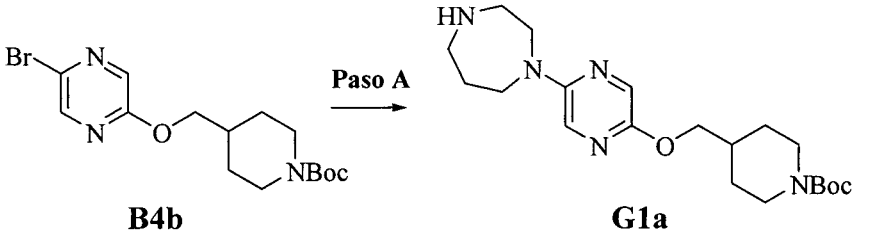
Paso D: Se trata una solución de **F1d** (1,3 g, 3,88 mmol) en EtOH con Pd/C (0,2 g de 10%, húmedo). Se agita la reacción bajo H_2 (1 atmósfera) por espacio de 12 horas. Se filtra la mezcla y se la concentra para producir **F1e** que es utilizado sin más purificación: ESIMS calc. para $[M+H]^+$ $C_{10}H_{16}N_3O_3S$: 258.1 resultó: 258.1.

Paso E: Se trata una solución de **F1e** (97,7 mg, 0,38 mmol) y **F1a** (115,2 mg, 0,38 mmol) en N, N–dimetilformamida (1,5 ml) con Cs_2CO_3 (185,6 mg, 0,57 mmol) y se la calienta a 60 °C de un día para otro. Se enfría la reacción a temperatura ambiente, se la diluye con acetato de etilo, se la extrae con agua, se la seca sobre $MgSO_4$, filtra, evapora y purifica por cromatografía en columna sobre gel de sílice utilizando un gradiente lineal de 0 a 100% de acetato de etilo en hexano y luego se la liofiliza de HCl para dar **F1** en forma de sal de HCl; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8,01 (m, 0,5H), 7,92

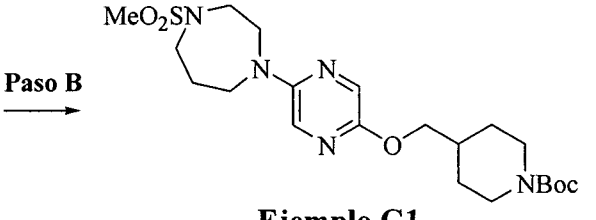
(d, *J* = 2,8, 1H), 7,16 (dd, *J* = 9,1, 3,1, 1H), 6,66 (d, *J* = 9,1, 1H), 4,20 (m, 2H), 3,81 (d, *J* = 6,3, 1H), 3,54 (m, 4H), 3,33 (m, 4H), 3,09 (m, 2H), 2,88 (m, 1H), 2,81 (s, 3H), 2,00 (m, 1H), 1,92 (m, 2H), 1,44 (m, 2H), 1,28 (d, *J* = 7,0, 3H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{33}N_6O_4S$ calc.: 465,2, resultó: 465,3.

Ejemplo G1. *terc*–Butil 4–((5–(4–(metilsulfonil)–1,4–diazepan–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.





B4b **G1a**



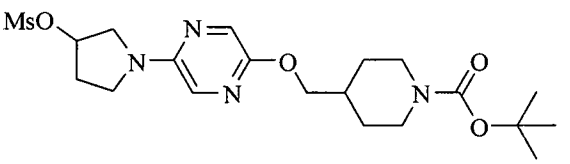
Ejemplo G1

Paso A: Se rocía una mezcla de **B4b** (307,5 mg, 0,83 mmol), homopiperazina (248,2 mg, 2,5 mmol), xantfos (28,7 mg, 0,050 mmol), *terc*–butóxido de sodio 119 mg, 1,2 mmol) y tolueno (5 ml) con nitrógeno por espacio de 5 minutes y se la trata con Pd_2dba_3 (15,1 mg, 0,017 mmol). A continuación se tapa herméticamente la reacción y se la sumerge en un baño de aceite precalentado a 100 °C. Se agita la reacción a esta temperatura por espacio de 4 horas, se la enfría a temperatura ambiente, se la diluye con acetato de etilo y se la extrae con agua dos veces. Se secan los extractos orgánicos sobre $MgSO_4$, se los filtra, evapora y purifica en una columna de gel de sílice

utilizando metanol al 0–10% en diclorometano para dar **G1a**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{35}N_4O_3$ calc.: 391,3, resultó: 391,3.

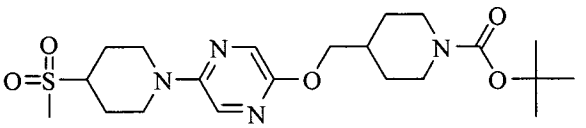
Paso B: Se enfría una solución de **G1a** (139 mg, 3,6 mmol) en diclorometano (0,25 ml) a una temperatura del baño de hielo/agua y se la trata con trietilamina (37,4 mg, 0,37 mmol) seguida por cloruro de metansulfonilo (42,3 mg, 0,37 mmol) y se la agita de un día para otro. A continuación se vierte la reacción en agua y se la extrae con diclorometano dos veces. Se secan los extractos orgánicos combinados sobre $MgSO_4$, se los filtra y evapora y purifica en una columna de gel de sílice utilizando acetato de etilo al 0–100% en hexano para dar **G1**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7,79 (d, *J* = 2,9, 1H), 7,49 (d, *J* = 1,5, 1H), 4,13 (m, 2H), 4,14 (d, *J* = 6,5, 1H), 3,82 (m, 2H), 3,74 (dd, *J* = 6,3,6,3, 2H), 3,49 (m, 2H), 3,26 (m, 2H), 2,78 (s, 3H), 2,73 (m, 2H), 2,07 (m, 2H), 1,94 (m, 1H), 1,79 (m, 1H), 1,46 (s, 9H), 1,25 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{36}N_5O_5S$ calc.: 470,2, resultó: 370,2 ($M–Boc+H^+$).

Ejemplo G2 *terc*–Butil 4–((5–(3–(metilsulfoniloxi)pirrolidin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



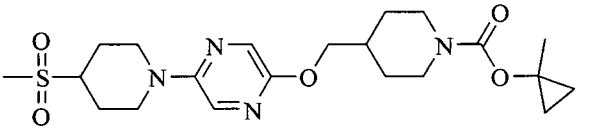
Siguiendo un procedimiento similar al utilizado para la preparación de **G1** a partir de **B4b** excepto que se sustituye homopiperazina por pirrolidin–3–ol, se prepara **G2**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7,82 (d, *J* = 1,5, 1H), 7,38 (d, *J* = 1,5, 1H), 5,43 (m, 1H), 4,03 (m, 2H), 4,06 (d, *J* = 6,6, 1H), 3,82 (m, 21H), 3,74 (dd, *J* = 12,4, 4,4, 1H), 3,58 (m, 2H), 3,05 (s, 3H), 2,72 (m, 2H), 2,47 (m, 1H), 2,33 (m, 1H), 1,93 (m, 1H), 1,79 (m, 2H), 1,46 (s, 9H), 1,26 (m, 2H); ESIMS *m/z* correspondiente a $(M–Boc+H)^+$ $C_{15}H_{25}N_4O_4S$ calc.: 357,2, resultó: 357,2.

Ejemplo G3. *Terc*–butil 4–((5–(4–(metilsulfonil)piperidin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



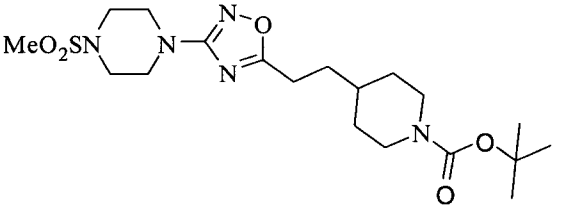
Siguiendo un procedimiento similar al utilizado para la preparación de **G1a** a partir de **B4b** excepto que se sustituye homopiperazina por 4–(metilsulfonil)piperidina, se prepara **G3**; ESIMS *m/z* correspondiente a $(M-{}^{t}Bu+H)^{+}$ $C_{16}H_{27}N_4O_3S$ calc: 355.2, resultó: 355.2

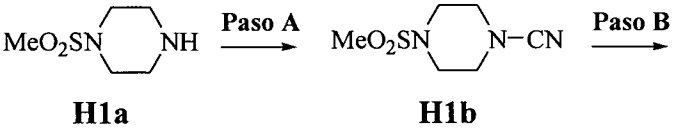
Ejemplo G4. 1–Metilciclopropil 4–((5–(4–(metilsulfonil)piperidin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



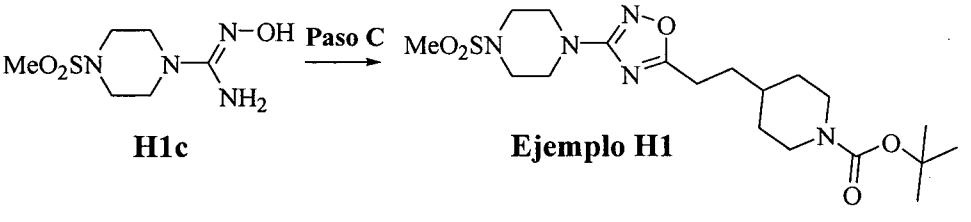
Siguiendo un procedimiento similar al utilizado para la preparación de **E3** a partir de **B4** excepto que se sustituye **B4** por **G3**, se prepara **G4**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{34}N_4O_5S$ calc: 454.2, resultó: 454.2.

Ejemplo H1. *terc*–Butil 4–(2–(3–(4–(metilsulfonil)piperazin–1–il)–1,2,4–oxadiazol–5–il)etil)piperidin–1–carboxilato.





H1a **H1b**



H1c **Ejemplo H1**

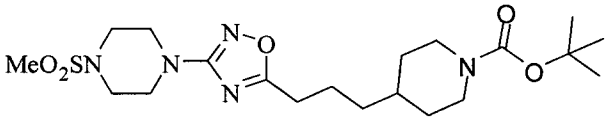
Paso A: A una solución agitada de carbonato de potasio (2,78 g, 20,0 mmol) en agua (20 ml) se agrega **H1a** (3,0 g, 18,3 mmol). Se enfría la solución a 10 °C, luego se agrega por goteo una solución de bromuro de cianógeno (2,12 g, 20,0 mmol) en

diclorometano (20 ml) en un lapso de 30 min. Se calienta la reacción a temperatura ambiente y se la agita por espacio de 2 horas, luego se la extrae en diclorometano. Se lava la capa orgánica con HCl 1 N (30 ml), se la seca sobre $MgSO_4$, se la filtra y concentra. Se utiliza el producto sin más purificación.

Paso B: Se calienta una solución de **H1b** (2,6 g, 13,7 mmol) e hidroxilamina (1 ml, 15,1 mmol) en EtOH (10 ml) en un vial herméticamente cerrado a 90 °C por espacio de 12 horas. Se concentra la mezcla al vacío para producir **H1c**, que es utilizado sin más purificación.

Paso C: Se agita una solución de ácido 1–Boc–piperidin–4–il propiónico (112 mg, 0,44 mmol) y N,N–carbonil dimidazol (71 mg, 0,44 mmol) en N,N–dimetilformamida (0,5 ml) a temperatura ambiente por espacio de 30 min. Se agrega **H1c** (107 mg, 0,48 mmol), se cierra herméticamente el tubo y se lo calienta a 115 °C por espacio de 18 horas. Se enfría la mezcla de reacción, se la extrae en acetato de etilo (10 ml), se la lava con agua (2 x 10 ml), luego con solución salina (10 ml). Se seca la capa orgánica sobre $MgSO_4$, se la filtra, concentra y purifica por HPLC de fase inversa iniciada por la masa para producir **H1**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4,10 (br, s, 2H), 3,59 (m, 4H), 3,32 (m, 4H), 2,82 (s, 3H), 2,79 (t, J = 8,0 Hz, 2H), 2,68 (m, 2H), 1,71 (m, 4H), 1,46 (s, 9H), 1,15 (m, 2H) ; ESIMS *m/z* correspondiente a $(M+H+Na)^+$ $C_{19}H_{33}N_5O_5SNa$ calc.: 466,2, resultó: 466,2.

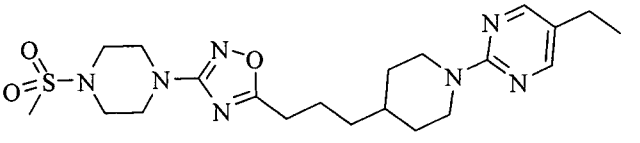
Ejemplo H2. *terc*–Butil 4–(3–(3–(4–(metilsulfonil)piperazin–1–il)–1,2,4–oxadiazol–5–il)propil)piperidin–1–carboxilato.

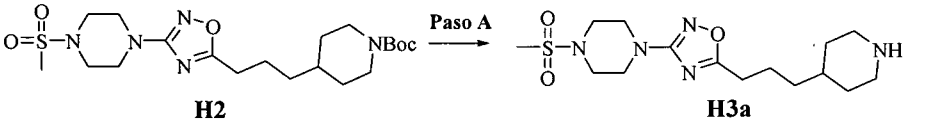


Siguiendo un procedimiento similar al utilizado para la preparación de **H1** a partir de **H1a** excepto que se sustituye el ácido 1–Boc–piperidin–4–il propiónico por ácido 4–(1–Boc–piperidin–4–il) butanoico, se prepara **H2**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4,08 (d, J = 13,2 Hz, 2H), 3,59 (m, 4H), 3,32 (m, 4H), 2,82 (s, 3H), 2,75 (t, J = 7,6 Hz, 2H), 2,68

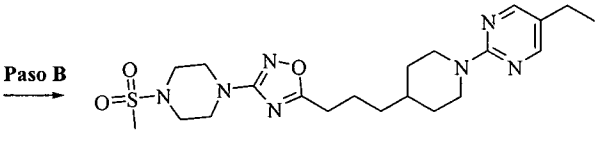
(dt, J = 2,4, 13,2 Hz, 2H), 1,80 (m, 2H), 1,68 (s, 1H), 1,65 (s, 1H), 1,46 (s, 9H), 1,42 (m, 1H), 1,34 (s, 2H), 1,11 (m, 2H) ; ESIMS *m/z* correspondiente a $(M+H+Na)^+$ $C_{20}H_{35}N_5O_5SNa$ calc.: 480,2, resultó: 480,3.

Ejemplo H3. 5–(3–(1–(5–Etilpirimidin–2–il)piperidin–4–il)propil)–3–(4–(metilsulfonil)piperazin–1–il)–1,2,4–oxadiazol.





H2 **H3a**



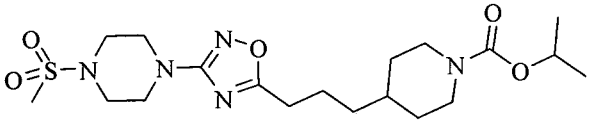
Ejemplo H3

Paso A: Se trata una **solución de H2** (261 mg, 0,57 mmol) en tetrahidrofurano (5 ml) con HCl (5 ml de 4N en dioxano) y se la agita a temperatura ambiente por espacio de 1 hora. Se concentra la reacción, se la disuelve en diclorometano (5 ml) y se la concentra al vacío para eliminar rastros de ácido y producir **H3a**, que es utilizado sin más purificación; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{15}H_{28}N_5O_3S$ calc.: 358,2, resultó: 358,2.

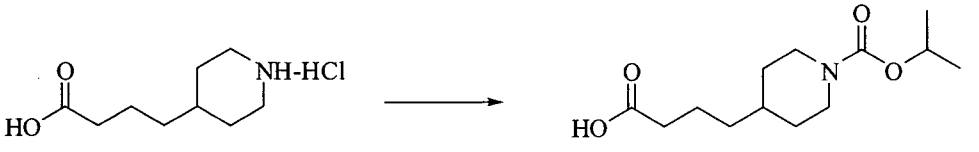
Paso B: Se disuelve **H3a** (53 mg, 0,15 mmol) y 2–cloro–5–etil–pirimidina (22 µl, 0,18 mmol) en 1, 4–dioxano (1 ml). Se agrega carbonato de cesio (120 mg, 0,37 mmol) y se cierra herméticamente el tubo y se lo calienta a 150 °C por espacio de 2 horas. Se enfría la mezcla de reacción, se la filtra y purifica por HPLC de fase inversa iniciada por la masa para producir **H3**; ^1H NMR ($CDCl_3$, 400 MHz): δ 8,27 (s, 2H), 4,70 (d, J = 13,2 Hz, 2H), 3,60 (m, 4H), 3,33 (m, 4H), 2,93 (dt, J = 2,0, 13,2 Hz, 2H), 2,83 (s, 3H), 2,77 (t,

J = 7,6 Hz, 2H), 2,51 (q, J = 7,6 Hz, 2H), 1,84 (m, 4H), 1,58 (m, 1H), 1,37 (m, 3H), 1,22 (t, J = 7,6 Hz, 3H; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{34}N_7O_3S$ calc.: 464,2, resultó: 464,2.

Ejemplo H4. Isopropil 4–(3–(3–(4–(metilsulfonil)piperazin–1–il)–1,2,4–oxadiazol–5–il)propil)piperidin–1–carboxilato.



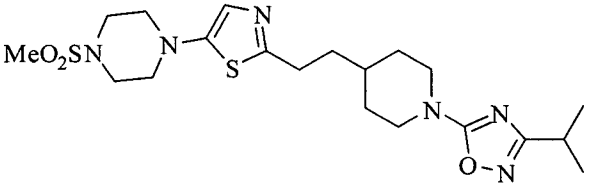
Siguiendo un procedimiento similar al utilizado para la preparación de **H1** a partir de **H1a** excepto que se sustituye el 1–ácido Boc–piperidin–4–il propiónico por **H4b** (ver el esquema siguiente), se prepara **H4**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{19}H_{34}N_5O_5S$ calc.: 444,2, resultó: 480,3.

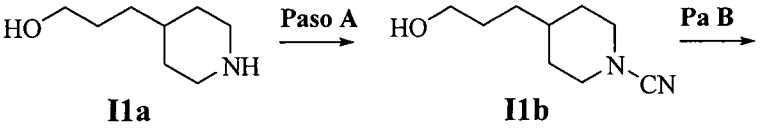


H4a **H4b**

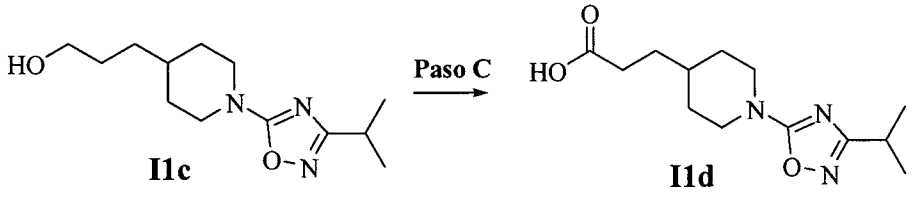
Se suspende el **H4a** existente en el comercio (20 g, 96 mmol) en dimetilacetamida seca (100 ml). Se agrega trietilamina (34 ml, 240 mmol) y se enfría la mezcla así obtenida en un baño de hielo/agua. Se agrega por goteo una solución de isopropil cloroformiato en tolueno (1,0 M, 150 ml) formando un precipitado blanco. Se agita la suspensión a temperatura ambiente por espacio de 18 horas, luego se filtra el precipitado blanco, se lo lava con acetato de etilo y se lo descarta. Se concentra el filtrado al vacío para dar **H4b**.

Ejemplo I1. 3–Isopropil–5–(4–(2–(5–(4–(metilsulfonil)piperazin–1–il)tiazol–2–il)etil)piperidin–1–il)–1,2,4–oxadiazol.

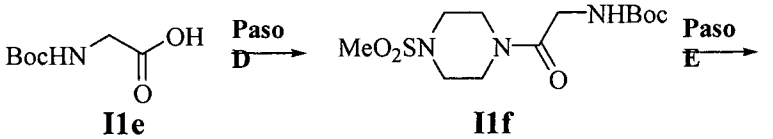




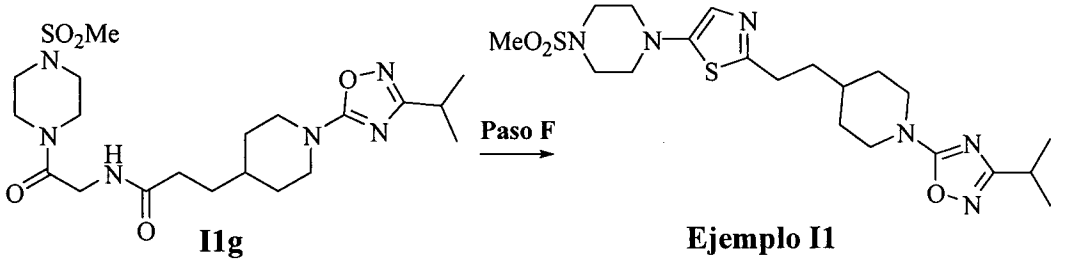
I1a I1b



I1c I1d



I1e I1f



I1g Ejemplo I1

Paso A: A una suspensión agitada de hidrogenocarbonato de sodio (2,80 g, 33,3 mmol) en agua (1,5 ml) se agrega la sal de clorhidrato de **I1a** (2,00 g, 11,1 mmol) y diclorometano (2 ml). Se enfría la mezcla en un baño de hielo/agua y se la agita. Se agrega una solución de bromuro de cianógeno (1,42 g, 13,4 mmol) en diclorometano (3 ml) en el curso de un período de 1 hora. Se retira el baño frío y se agita la reacción de

un día para otro. Se agrega 0,33 g de Na_2CO_3 para garantizar que la reacción sea básica. Se diluye la reacción con diclorometano (20 ml), se la seca con $MgSO_4$. Se filtra la mezcla, se la lava con diclorometano y se evapora para dar **I1b**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_9H_{17}N_2O$ calc.: 169,1, resultó: 169,1.

Paso B: Se trata gota a gota una solución de **I1b** (1,87 g, 11,1 mmol) y N'–hidroxi isobutirimidamida (1,70 g, 16,7 mmol) en acetato de etilo (40 ml) con una solución de $ZnCl_2$ (16,7 ml, 1N en éter). Se forma un precipitado blanco. Después de agitar a temperatura ambiente por espacio de 15 minutos, el precipitado se pega al matraz y se dificulta la agitación. Se tritura el sólido con éter (40 ml) y se lo agita por espacio de 4 horas hasta que se obtiene una suspensión amarilla. Se recoge el sólido por filtración, se lo lava con éter (30 ml) y se lo seca para dar un sólido amarillo que se utiliza sin purificación para el Paso siguiente; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{13}H_{27}N_4O_2$ calc.: 271,2, resultó: 271,2. Se trata el material intermedio (422 mg) con dioxano (10 ml) y HCl 4 M en dioxano (0,5 ml) y lo calienta a 100 °C durante 1 hora. Seguidamente se enfría la reacción a temperatura ambiente y se separa el solvente. Se diluye el residuo con acetato de etilo y se lo extrae con HCl 1 M dos veces, se lo seca sobre $MgSO_4$, filtra y evapora para dar **I1c**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{13}H_{24}N_3O_2$ calc.: 254,2, resultó: 254,2.

Paso C: Se trata una solución de **I1c** (368 mg, 1,45 mmol) en acetonitrilo (8 ml) con NaH_2PO_4 (218 mg, 1,8 mmol), Na_2HPO_4 (258 mg, 1,8 mmol), los radiales libres TEMPO (16 mg, 0,1 mmol), $NaClO_2$ (328 mg de una muestra 80 % pura, 2,91 mmol) y agua (8ml). Una vez incorporados todos los reactivos a la solución, se agrega lavandina al 10 % (22 µl, 0,03 mmol) y se agita la reacción de un día para otro. Se separa el acetonitrilo al vacío y se extrae la solución obtenida una vez con acetato de etilo y se descartan los extractos orgánicos. Se acidifica la fase acuosa (pH<1) con HCl concentrado y se la extrae dos veces con acetato de etilo y se descarta. Se secan los extractos orgánicos combinados sobre $MgSO_4$ y se separa el solvente para dar **I1d**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{13}H_{22}N_3O_3$ calc.: 268,2, resultó: 268,1.

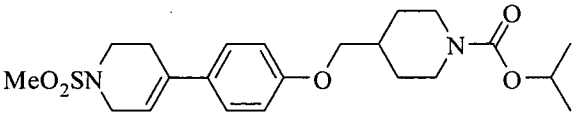
Paso D. Se trata una solución de **I1e** (250 mg, 1,4 mol) y metansulfonil piperazina (258 mg, 1,6 mmol) en diclorometano (4 ml) con HOBt hidrato (328 mg, 2,1 mmol) seguido

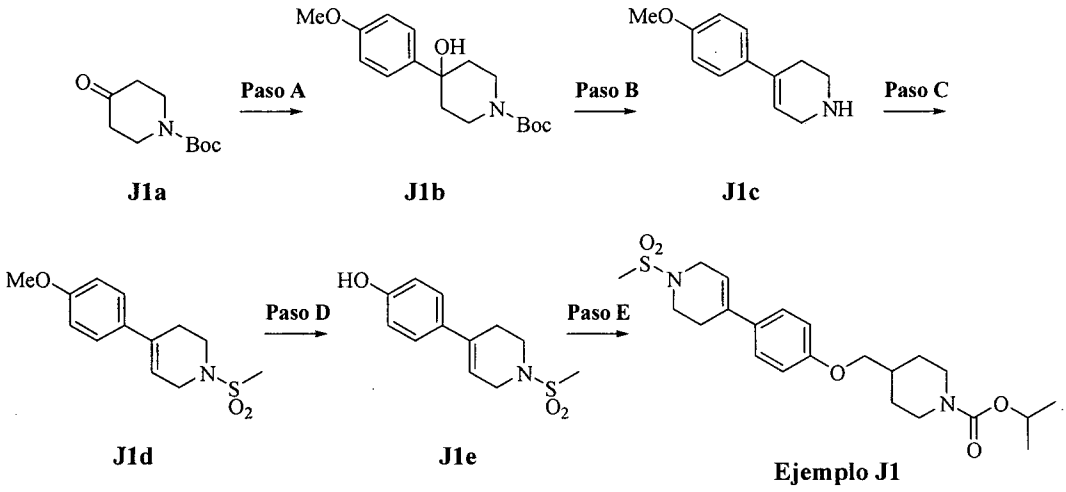
por EDC (356 mg, 1,9 mmol). Después de agitar por espacio de 3 horas, se diluye la reacción con acetato de etilo y se la extrae con agua, HCl 1M y NaOH 1 M, se la seca sobre $MgSO_4$, se la filtra y evapora para dar **I2f** ; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{12}H_{24}N_3O_5S$ calc.: 322,1, resultó: 322.2.

Paso E. Se trata una muestra de **I1f** (388 mg, 1,2 mmol) con HCl 4 M en dioxano (4 ml) y se la deja madurar durante 1 hora. Se separa el solvente y se trata el residuo con **I1d** (298 mg, 1,1 mmol), HATU (502 mg, 1,3 mmol) y N–metilpirrolidinona (4 ml). A continuación se trata la solución con trietilamina (0,39 ml, 2,8 mmol) y se la agita por espacio de 2 horas. Seguidamente se diluye la reacción con NaOH 1M y se la satura con NaCl. Se extrae 4 veces la solución así obtenida con acetato de etilo y se la descarta. Se secan los extractos orgánicos combinados sobre $MgSO_4$, se los filtra, evapora y purifica a su vez en un HPLC iniciado por UV para dar **I1g**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{20}H_{35}N_6O_5S$ calc.: 471,2, resultó: 471,1.

Paso F. Se sumerge una suspensión de **I1g** (354 mg, 0,75 mmol) y reactivo de Lawesson (304 mg, 0,75 mmol) en *m*–xileno (3 ml) en un baño de aceite calentado a 140 °C y se la agita por espacio de 5 minutos. Seguidamente se enfría la reacción a temperatura ambiente y se la carga en gel de sílice y se la purifica utilizando un gradiente lineal de 0–100% de acetato de etilo para dar **F1**; ^1H NMR ($CDCl_3$, 400 MHz): δ 6,86 (s, 1H), 4,12, (2, 2H), 3,38 (m, 4H), 3,19 (m, 4H), 3,02 (m, 2H), 2,99 (m, 3H), 2,83 (s, 3H), 1,80 (m, 2H), 1,73 (dd, *J* = 15,3, 7,1, 21H), 1,40 (m, 1H), 1,24 (m, 2H), 1,28 (d, *J* = 7,0, 6H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{20}H_{33}N_6O_3S_2$ calc.: 469,2, resultó: 469,1.

Ejemplo J1: Isopropil 4–((4–(1–metansulfonil–1,2,3,6–tetrahidropiridin–4–il)fenoxi)metil)piperidin–1–carboxilato.





Paso A: Se disuelve 4–Bromoanisol (4.5 ml, 36,0 mmol) en tetrahidrofurano seco (50 ml) y se lo enfría a –78 °C bajo nitrógeno. Se agrega lentamente una solución de *n*–butil litio (1,6 M en hexano (22,0 ml, 35,2 mmol) con agitación. Se agita la mezcla a –78 °C por espacio de 2 horas. Se enfría una solución de **J1a** (7,28 g, 36,5 mmol) en tetrahidrofurano seco (80 ml) bajo nitrógeno a –78 °C. Se transfiere lentamente la suspensión de organolitio preparada anteriormente mediante una cánula, con agitación, a la solución de **J1a**, utilizando un enjuague de tetrahidrofurano de 20 ml. Se agita la mezcla así obtenida a –78 °C por espacio de 30 minutos, luego a 0 °C durante 15 min. La adición de una solución de cloruro de amonio saturado (60 ml) y la extracción con acetato de etilo, lavado con solución salina y concentración al vacío da un aceite. Se purifica el residuo empleando un gradiente lineal de 10–80% de acetato de etilo en hexano para dar **J1b**; ^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 7,39 (d, *J* = 8,9 Hz, 2H), 6,89 (d, *J* = 8,9 Hz, 2H), 3,99 (br,, 2H), 3,81 (s, 3H), 1,96 (br, 2H), 1,71 (m, 4H), 1,49 (s, 9H); no se pudieron obtener espectros de masas.

Paso B: A una solución de **J1b** (6,29 g, 20 mmol) en diclorometano (120 ml) se agrega ácido trifluoracético (20 ml), lentamente, con agitación. Se agita la solución así obtenida a temperatura ambiente por espacio de 3 horas. La concentración, dilución con diclorometano (50 ml), lavado con una solución acuosa saturada de hidrogenocarbonato de sodio, secado sobre $MgSO_4$ y concentración, dan origen a **J1c**; ^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 7,30 (d, *J* = 8,8 Hz, 2H), 6,88 (d, *J* = 8,8 Hz, 2H), 5,93

(m, 1H), 3,82 (s, 5H), 3,40 (t, J = 6,0 Hz, 2H), 2,77 (m, 2H); ESIMS calc, para $C_{12}H_{16}NO$ ($M+H^+$) 190,1, resultó 190,0,

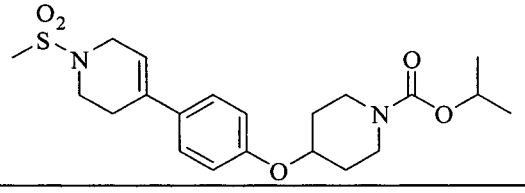
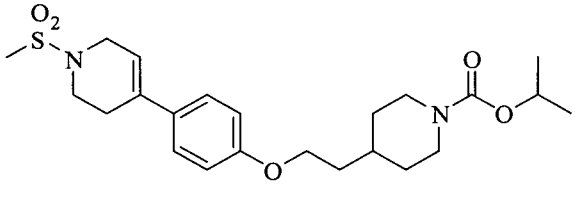
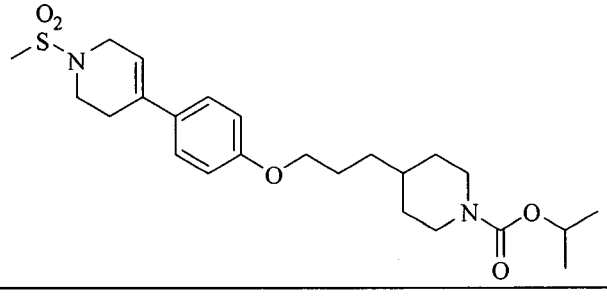
Paso C: A una solución de **J1c** (3.41 g, 18 mmol) en diclorometano (80 ml) se agrega trietilamina (4,5 ml, 32,0 mmol) en una porción. Se enfría la mezcla así obtenida en un baño de hielo/agua y se agrega gota a gota cloruro de metansulfonilo (1,75 ml, 22,5 mmol) con agitación, en un lapso de 5 minutos. Se agita la solución así obtenida a temperatura ambiente por espacio de 30 min. Se agrega la mezcla de reacción a agua (40 ml) y se la extrae con diclorometano (2 x 40 ml). Se lavan los extractos orgánicos combinados con una solución acuosa saturada de cloruro de amonio, se la seca sobre $MgSO_4$ y se la concentra para dar **J1d**; ^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 7,31 (d, J = 8,8 Hz, 2H), 6,88 (d, J = 8,8 Hz, 2H), 5,98 (m, 1H), 3,96 (q, J = 3,2 Hz, 2H), 3,82 (s, 3H), 3,52 (t, J = 5,7 Hz, 2H), 2,86 (s, 3H), 2,64 (m, 2H); ESIMS calc, para $C_{13}H_{18}NO_3S$ ($M+H^+$) 268,1, resultó 268,1.

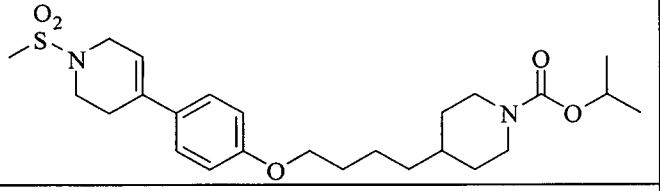
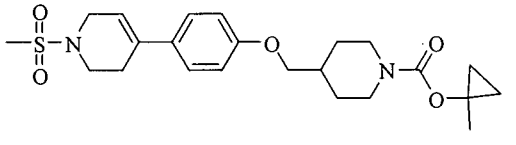
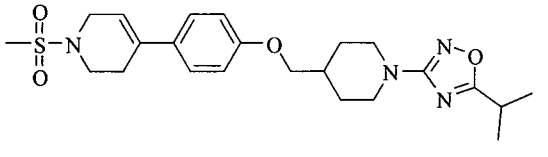
Paso D: Se trata una solución de **J1d** (3,71 g, 13,9 mmol) en diclorometano (100 ml) con tribromuro de boro (5,0 ml, 51,9 mmol) lentamente y se la agita a temperatura ambiente por espacio de 3 horas. Se vierte la mezcla sobre hielo triturado y, una vez que funde el hielo, se la extrae con diclorometano. El lavado con una solución acuosa saturada de hidrogenocarbonato de sodio, agua y cloruro de amonio saturado, el secado sobre $MgSO_4$ y concentración, dan origen a **J1e**; ^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 7,27 (d, J = 8,7 Hz, 2H), 6,81 (d, J = 8,7 Hz, 2H), 5,97 (m, 1H), 4,85 (s, 1H), 3,95 (q, J = 3,2 Hz, 2H), 3,52 (t, J = 5,7 Hz, 2H), 2,86 (s, 3H), 2,63 (m, 2H); ESIMS calc, para $C_{12}H_{16}NO_3S$ ($M+H^+$) 254,1, resultó 254,1.

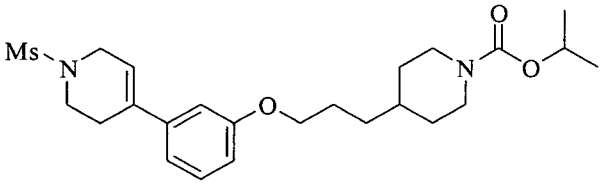
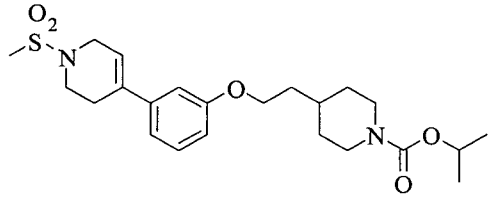
Paso E: Se trata una solución de **J1e** (0,12 g, 0,47 mmol) en acetonitrilo (3 ml) con **A1c** (0,16 g, 0,57 mmol) seguido por carbonato de cesio en polvo (0,20 g, 0,6 mmol) y se la agita a 60 °C por espacio de 5 horas. El enfriamiento, filtración y purificación utilizando HPLC de fase inversa iniciada por la masa da **J1**; ^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 7,30 (d, J = 8,7 Hz, 2H), 6,86 (d, J = 8,7 Hz, 2H), 5,97 (m, 1H), 4,92 (septet, J = 6,2 Hz, 1H), 4,19 (br, 2H), 3,95 (dd, J = 2,6, 5,9 Hz, 2H), 3,81 (d, J = 6,3 Hz, 2H), 3,52 (t, J = 5,8 Hz, 2H), 2,85 (s, 3H), 2,78 (m, 2H), 2,63 (m, 2H), 1,97 (m, 1H), 1,83 (dd, J =

1,0, 13,4 Hz, 2H), 1,25 (m, 2H), 1,24 (d, *J* = 6,2 Hz, 6H); ESIMS calc, para $C_{22}H_{33}N_2O_5S$ ($M+H^+$) 437,2, resultó 437,1.

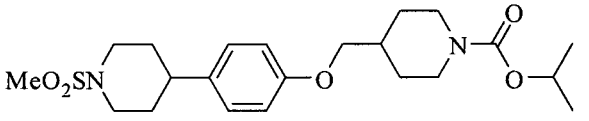
Siguiendo un procedimiento similar al utilizado para la preparación de **J1** a partir de **HJ1a** excepto que, en el **Paso E** se sustituye el intermediario **A1c** por el metansulfonato apropiado y/o 4–bromoanisol por 3–bromoanisol, se preparan los siguientes ejemplos;

Ejemplo	Estructura	Datos Analíticos
J2		ESIMS calc, para $C_{21}H_{31}N_2O_5S$ ($M+H^+$) 423,2, resultó 423,1.
J3		^1H NMR ($CDCl_3$, 400,13 MHz): δ7,30 (d, *J* = 8,7 Hz, 2H), 6,86 (d, *J* = 8,7 Hz, 2H), 5,97 (m, 1H), 4,92 (septete, *J* = 6,2 Hz, 1H), 4,12 (br, 2H), 4,02 (t, *J* = 5,8, 2H), 3,95 (dd, *J* = 2,6, 5,9 Hz, 2H), 3,52 (t, *J* = 5,8 Hz, 2H), 2,85 (s, 3H), 2,74 (m, 2H), 2,64 (m, 2H), 1,85 (m, 1H), 1,73 (dd, *J* = 1,0, 13,4 Hz, 2H), 1,24 (d, *J* = 6,2 Hz, 6H), 1,18 (m, 2H); ESIMS calc, para $C_{23}H_{35}N_2O_5S$ ($M+H^+$) 451,2, resultó 451,2.
J4		^1H NMR ($CDCl_3$, 400,13 MHz): δ7,29 (d, *J* = 8,7 Hz, 2H), 6,86 (d, *J* = 8,7 Hz, 2H), 5,97 (m, 1H), 4,91 (septete, *J* = 6,2 Hz, 1H), 4,13 (br, 2H), 3,52 (t, *J* = 5,8 Hz,

		2H), 2,85 (s, 3H), 2,71 (m, 2H), 2,63 (m, 2H), 1,81 (m, 2H), 1,70 (m, 5H), 1,42 (m, 4H), 1,24 (d, *J* = 6,2 Hz, 6H), 1,12 (m, 2H); ESIMS calc, para $C_{24}H_{37}N_2O_5S$ ($M+H^+$) 465,2, resultó 465,1.
J5		ESIMS calc, para $C_{25}H_{39}N_2O_5S$ ($M+H^+$) 479,3, resultó 479,1.
J6		^{1}H–NMR (400MHz, DMSO–d6) δ 7,37 (m, 2H), 6,90 (m, 2H), 6,08 (m, 1H), 3,70–4,05 (m, 6H), 2,92 (s, 3H), 2,75 (m, 2H), 2,56 (m, 2H), 1,91 (m, 1H), 1,73 (m, 2H), 1,46 (s, 3H), 1,13 (m, 2H), 0,76 (m, 2H), 0,59 (m, 2H); ESIMS calc, para $C_{23}H_{33}N_2O_5S$ ($M+H^+$) 449,2, resultó 448,8.
J7		^{1}H–NMR (400MHz, DMSO–d6) δ 7,38 (m, 2H), 6,92 (m, 2H), 6,08 (m, 1H), 3,86 (m, 6H), 3,10 (h, 1H, J = 7,0 Hz), 2,92 (s, 3H), 2,91 (m, 2H), 2,56 (m, 2H), 1,97 (m, 1H), 1,82 (m, 2H), 1,30 (m, 2H), 1,26 (d, 6H, J = 7,0 Hz); ESIMS calc, para $C_{23}H_{33}N_4O_4S$ ($M+H^+$) 461,2, resultó 460,8.

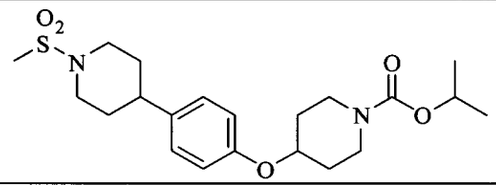
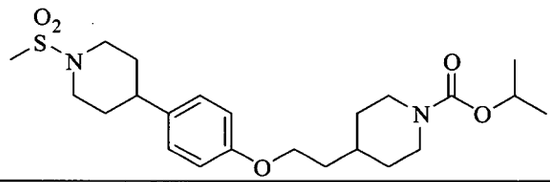
J8		^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 7,25 (dd, *J* = 7,8, 8,2 Hz, 1H), 6,95 (dd, *J* = 2,2, 7,8 Hz, 1H), 6,89 (dd, *J* = 1,9, 2,2 Hz, 1H), 6,81 (dd, *J* = 1,9, 8,2 Hz, 1H), 6,07 (tt, *J* = 1,5, 3,5 Hz, 1H), 4,91 (septete, *J* = 6,2 Hz, 1H), 4,13 (br, s, 2H), 3,96 (m, 4H), 3,52 (t, *J* = 5,7 Hz, 2H), 2,86 (s, 3H), 2,73 (t, *J* = 12,4 Hz, 2H), 2,65 (m, 2H), 1,81 (m, 2H), 1,71 (d, *J* = 12,7 Hz, 2H), 1,46 (m, 1H), 1,41 (m, 2H), 1,24 (d, J = 6,3 Hz, 6H), 1,12 (ddd, *J* = 4,2, 12,7, 13,0 Hz, 2H); ESIMS calc, para $C_{24}H_{37}N_2O_5S$ ($M+H^+$) 465,2, resultó 465,2.
J9		^{1}H NMR ($CDCl_3$, 400,13 MHz): δ. 7,26 (dd, *J* = 7,9, 8,1 Hz, 1H), 6,96 (d, *J* = 7,8 Hz, 1H), 6,89 (dd, *J* = 1,8, 2,2 Hz, 1H), 6,82 (dd, *J* = 2,0, 7,8 Hz, 1H), 6,07 (m, 1H), 4,91 (septete, *J* = 6,2 Hz, 1H), 4,13 (br, 2H), 4,02 (t, *J* = 5,8 Hz, 2H), 3,97 (dd, *J* = 2,7, 6,0 Hz, 2H), 3,52 (t, J = 5,7 Hz, 2H), 2,86 (s, 3H), 2,74 (t, *J* = 12,4 Hz, 2H), 2,66 (m, 2H), 1,80 (m, 2H), 1,74 (m, 3H), 1,24 (d, *J* = 6,2 Hz, 6H), 1,20 (m, 2H); ESIMS calc, para $C_{23}H_{35}N_2O_5S$ ($M+H^+$) 451,2, resultó 451,2.

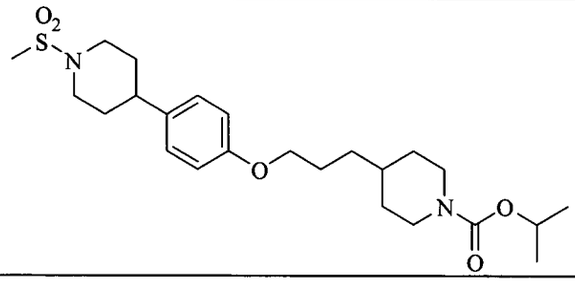
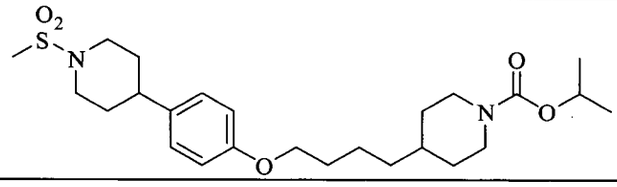
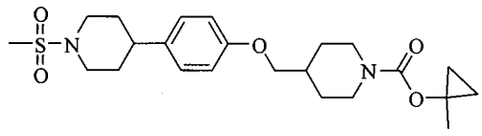
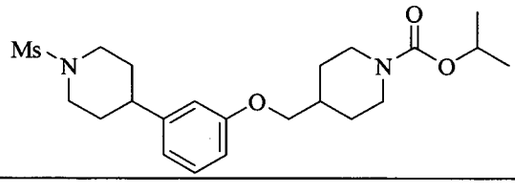
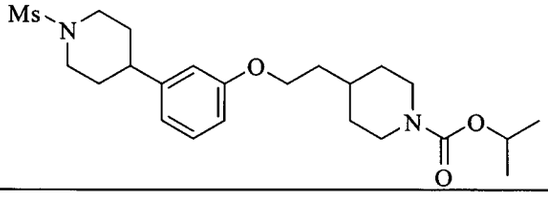
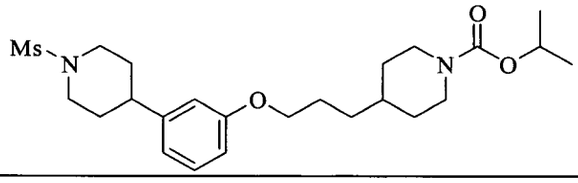
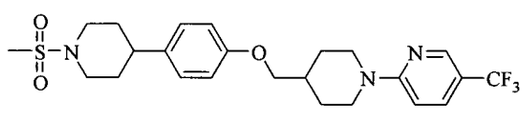
Ejemplo J10: Isopropil 4–((4–(1–metansulfonilpiperidin–4–il)fenoxi)metil)piperidin–1–carboxilato.

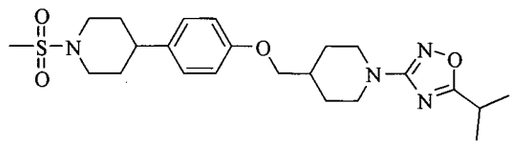
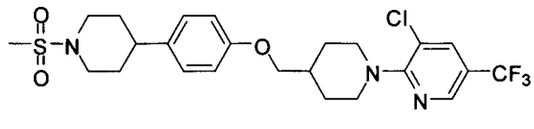


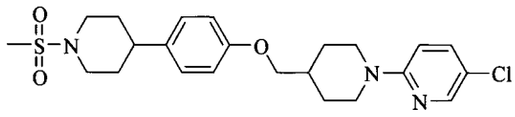
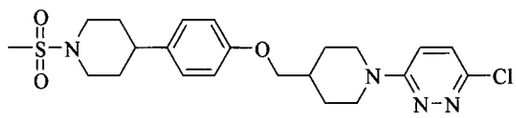
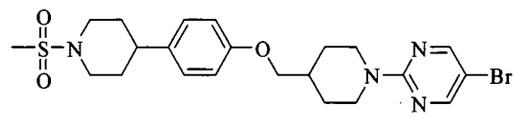
Se trata una solución de **J1** (0,18 g, 0,4 mmol) en etanol (10 ml) y acetato de etilo (2 ml) con paladio(0) sobre carbón (5 %, 0,12 g). Se agita la mezcla bajo 1 atm de hidrógeno por espacio de 18 horas. La filtración, concentración, y purificación empleando HPLC de fase inversa iniciada por la masa dan **J9**; ^{1}H NMR (CD_3CN, 400,13 MHz): δ 7,19 (d, *J* = 8,7 Hz, 2H), 6,88 (d, *J* = 8,7 Hz, 2H), 4,95 (septete, *J* = 6,2 Hz, 1H), 4,16 (br, 2H), 3,83 (d, *J* = 6,4 Hz, 2H), 3,78 (m, 2H), 2,81 (s, 3H), 2,78 (m, 4H), 2,61 (tt, *J* = 3,6, 12,1 Hz, 1H), 2,01 (m, 1H), 1,90 (m, 2H), 1,81 (m, 2H), 1,71 (m, 2H), 1,23 (d, *J* = 6,2 Hz, 6H), 1,22 (m, 2H); ESIMS calc, para $C_{22}H_{35}N_2O_5S$ ($M+H^+$) 439,2, resultó 439,2.

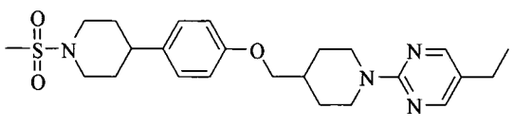
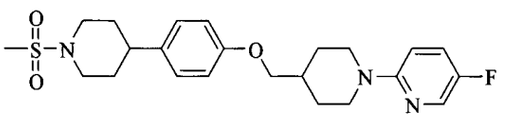
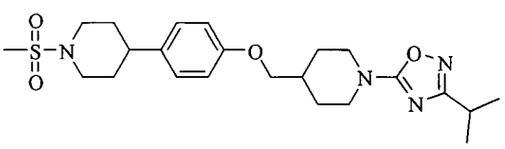
Siguiendo un procedimiento similar al utilizado para la preparación de **J10** a partir de **J1** excepto que se sustituye el intermediario **J1** por la olefina o siguiendo un procedimiento similar al utilizado para la preparación de **J1** a partir de **J1a** excepto que se sustituye **J1c** por 4–(4–metoxifenil)piperidina o 4–(3–metoxifenil)piperidina, se preparan los siguientes ejemplos;

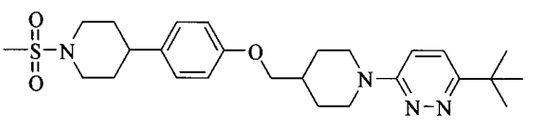
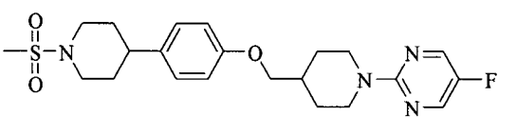
Ejemplo	Estructura	Datos Analíticos
J11		ESIMS calc, para $C_{21}H_{33}N_2O_5S$ ($M+H^+$) 425,2, resultó 425,0,
J12		ESIMS calc, para $C_{23}H_{37}N_2O_5S$ ($M+H^+$) 453,2, resultó 453,2.

J13		ESIMS calc, para $C_{24}H_{39}N_2O_5S$ ($M+H^+$) 467,3, resultó 467,2.
J14		ESIMS calc, para $C_{25}H_{41}N_2O_5S$ ($M+H^+$) 481,3, resultó 481,1.
J15		^{1}H–NMR (400MHz, $CDCl_3$) δ 7,11 (m, 2H), 6,83 (m, 2H), 4,12 (m, 2H), 3,93 (m, 2H), 3,77 (d, 2H, J = 6,3 Hz), 2,81 (s, 3H), 2,75 (m, 2H), 2,55 (tt, 1H, J = 3,5, 12,1 Hz), 1,93 (m, 2H), 1,81 (m, 4H), 1,55 (s, 3H), 1,26 (m, 2H), 0,86 (m, 2H). 0,62 (m, 2H), ESIMS calc, para $C_{23}H_{35}N_2O_5S$ ($M+H^+$) 451,2, resultó 451,2.
J16		ESIMS calc, para $C_{22}H_{35}N_2O_5S$ ($M+H^+$) 439,2, resultó 439,1.
J17		ESIMS calc, para $C_{23}H_{37}N_2O_5S$ ($M+H^+$) 453,2, resultó 453,1.
J18		ESIMS calc, para $C_{24}H_{39}N_2O_5S$ ($M+H^+$) 467,3, resultó 467,1.
J19		^{1}H–NMR (400MHz, DMSO–d6) δ 8,38 (m, 1H), 7,75 (dd, 1H, J = 2,5, 9,2 Hz), 7,16 (m,

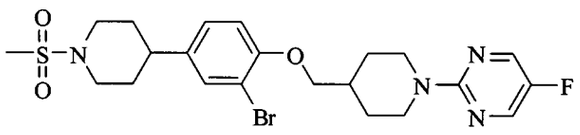
		2H), 6,96 (d, 1H, J = 9,2 Hz), 6,86 (m, 2H), 4,46 (m, 2H), 3,82 (d, 2H, J = 6,4 Hz), 3,65 (m, 2H), 2,95 (m, 2H), 2,88 (s, 3H), 2,78 (m, 2H), 2,56 (tt, 1H, J = 3,5, 12,3 Hz), 2,07 (m, 1H), 1,83 (m, 4H), 1,62 (m, 2H), 1,24 (m, 2H), ESIMS calc, para $C_{24}H_{31}F_3N_3O_3S$ ($M+H^+$) 498,2, resultó 497,8.
J20		^{1}H–NMR (400MHz, DMSO–d6) δ 7,16 (m, 2H), 6,86 (m, 2H), 3,87 (m, 2H), 3,82 (d, 2H, J = 6,5 Hz), 3,65 (m, 2H), 3,10(h, 1H, J = 7,0Hz), 2,90 (m, 2H), 2,89 (s, 3H), 2,78 (m, 3H), 2,56 (tt, 1H, J = 3,4, 12,2 Hz), 1,95 (m, 1H), 1,82 (m, 4H), 1,62 (m, 2H), 1,29 (m, 2H), 1,26 (d, 6H, J = 7,0 Hz), ESIMS calc, para $C_{23}H_{35}N_4O_4S$ ($M+H^+$) 463,2, resultó 463,2.
J21		^{1}H–NMR (400MHz, DMSO–d6) δ 8,54 (m, 1H), 8,16 (d, 1H, J = 2,0 Hz), 7,17 (m, 2H), 6,88 (m, 2H), 4,04 (m, 2H), 3,86 (d, 2H, J = 6,4 Hz), 3,65 (m, 2H), 2,93 (m, 2H), 2,89 (s, 3H), 2,78 (m, 2H), 2,56 (tt, 1H, J = 3,5, 12,2 Hz), 2,01 (m, 1H), 1,86 (m, 4H), 1,62 (m, 2H), 1,43 (m, 2H), ESIMS calc, para $C_{24}H_{30}ClF_3N_3O_3S$ ($M+H^+$) 532,2, resultó 531,9.

J22		^{1}H–NMR (400MHz, DMSO–d6) δ 8,08 (d, 1H, J =2,5 Hz), 7,56 (dd, 1H, J = 2,7, 9,1 Hz), 7,16 (m, 2H), 6,87 (m, 3H), 4,29 (m, 2H), 3,81 (d, 2H, J = 6,4 Hz), 3,65 (m, 2H), 2,88 (s, 3H), 2,81 (m, 4H), 2,56 (tt, 1H, J = 3,4, 11,9 Hz), 2,00 (m, 1H), 1,82 (m, 4H), 1,62 (m, 2H), 1,25 (m, 2H), ESIMS calc, para $C_{23}H_{31}ClN_3O_3S$ ($M+H^+$) 464,2, resultó 464,2.
J23		^{1}H–NMR (400MHz, DMSO–d6) δ 7,50 (d, 1H, J =9,6 Hz), 7,41 (d, 1H, J = 9,7 Hz), 7,16 (m, 2H), 6,87 (m, 2H), 4,37 (m, 2H), 3,82 (d, 2H, J = 6,4 Hz), 3,64 (m, 2H), 2,96 (m, 2H), 2,88 (s, 3H), 2,78 (m, 2H), 2,56 (tt, 1H, J = 3,4, 11,9 Hz), 2,06 (m, 1H), 1,84 (m, 4H), 1,62 (m, 2H), 1,29 (m, 2H), ESIMS calc, para $C_{22}H_{30}ClN_4O_3S$ ($M+H^+$) 465,2, resultó 465,2.
J24		^{1}H–NMR (400MHz, DMSO–d6) δ 8,43 (s, 2H), 7,16 (m, 2H), 6,86 (m, 2H), 4,61 (m, 2H), 3,81 (d, 2H, J = 6,6 Hz), 3,65 (m, 2H), 2,93 (m, 2H), 2,88 (s, 3H), 2,78 (m, 2H), 2,55 (m, 1H), 2,05 (m, 1H), 1,82 (m, 4H), 1,62 (m, 2H), 1,22 (m, 2H), ESIMS calc, para $C_{22}H_{30}BrN_4O_3S$

		(M+H$^+$) 509,1, resultó 508,9.
J25		^{1}H–NMR (400MHz, DMSO–d6) δ 8,24 (s, 2H), 7,16 (m, 2H), 6,86 (m, 2H), 4,65 (m, 2H), 3,81 (d, 2H, J = 6,4 Hz), 3,65 (m, 2H), 2,87 (m, 2H), 2,89 (s, 3H), 2,78 (m, 2H), 2,56 (tt, 1H, J = 3,5, 11,9 Hz), 2,42 (q, 2H, J = 7,6 Hz), 2,03 (m, 1H), 1,82 (m, 4H), 1,62 (m, 2H), 1,20 (m, 2H), 1,12 (t, 3H, J = 7,6), ESIMS calc, para $C_{24}H_{35}N_4O_3S$ (M+H$^+$) 459,2, resultó 459,2.
J26		^{1}H–NMR (400MHz, DMSO–d6) δ 8,07 (d, 1H, J = 3,1 Hz), 7,49 (ddd, 1H, J = 3,1, 8,4,9,2 Hz), 7,16 (m, 2H), 6,88 (m, 3H), 4,23 (m, 2H), 3,82 (d, 2H, J = 6,4 Hz), 3,65 (m, 2H), 2,89 (s, 3H), 2,79 (m, 4H), 2,57 (tt, 1H, J = 3,5, 12,0 Hz), 1,98 (m, 1H), 1,82 (m, 4H), 1,62 (m, 2H), 1,27 (m, 2H), ESIMS calc, para $C_{23}H_{31}FN_3O_3S$ (M+H$^+$) 448,2, resultó 448,2,
J27		^{1}H–NMR (400MHz, DMSO–d6) δ 7,16 (m, 2H), 6,87 (m, 2H), 3,99 (m, 2H), 3,83 (d, 2H, J = 6,4 Hz), 3,65 (m, 2H), 3,12(m, 2H), 2,89 (s, 3H), 2,79 (m, 3H), 2,56 (tt, 1H, J = 3,5, 11,9 Hz), 1,99 (m, 1H), 1,84 (m, 4H), 1,62 (m, 2H), 1,31 (m,

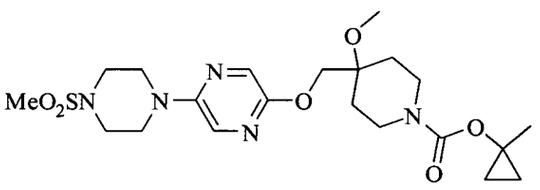
		2H), 1,18 (d, 6H, J = 6,9 Hz), ESIMS calc, para $C_{23}H_{35}N_4O_4S$ ($M+H^+$) 463,2, resultó 463,2.
J28		^{1}H–NMR (400MHz, DMSO–d6) δ 8,10 (d, 1H, J = 10,0 Hz), 8,01 (d, 1H, J = 10,0 Hz), 7,17 (m, 2H), 6,87 (m, 2H), 4,31 (m, 2H), 3,84 (d, 2H, J = 6,4 Hz), 3,66 (m, 2H), 3,25 (m, 2H), 2,89 (s, 3H), 2,78 (m, 2H), 2,56 (tt, 1H, J = 3,4, 12,3 Hz), 2,16 (m, 1H), 1,92 (m, 2H), 1,82 (m, 2H), 1,62 (m, 2H), 1,41 (m, 2H), 1,32 (s, 9H), ESIMS calc, para $C_{26}H_{39}N_4O_3S$ ($M+H^+$) 486,3, resultó 486,3.
J29		^{1}H–NMR (400MHz, DMSO–d6) δ 8,42 (d, 2H, J = 0,8 Hz), 7,16 (m, 2H), 6,86 (m, 2H), 4,60 (m, 2H), 3,82 (d, 2H, J = 6,4 Hz), 3,65 (m, 2H), 2,91 (m, 2H), 2,88 (s, 3H), 2,78 (m, 2H), 2,56 (tt, 1H, J = 3,5, 11,9 Hz), 2,03 (m, 1H), 1,82 (m, 4H), 1,62 (m, 2H), 1,21 (m, 2H), ESIMS calc, para $C_{22}H_{30}FN_4O_3S$ ($M+H^+$) 449,2, resultó 448,8.

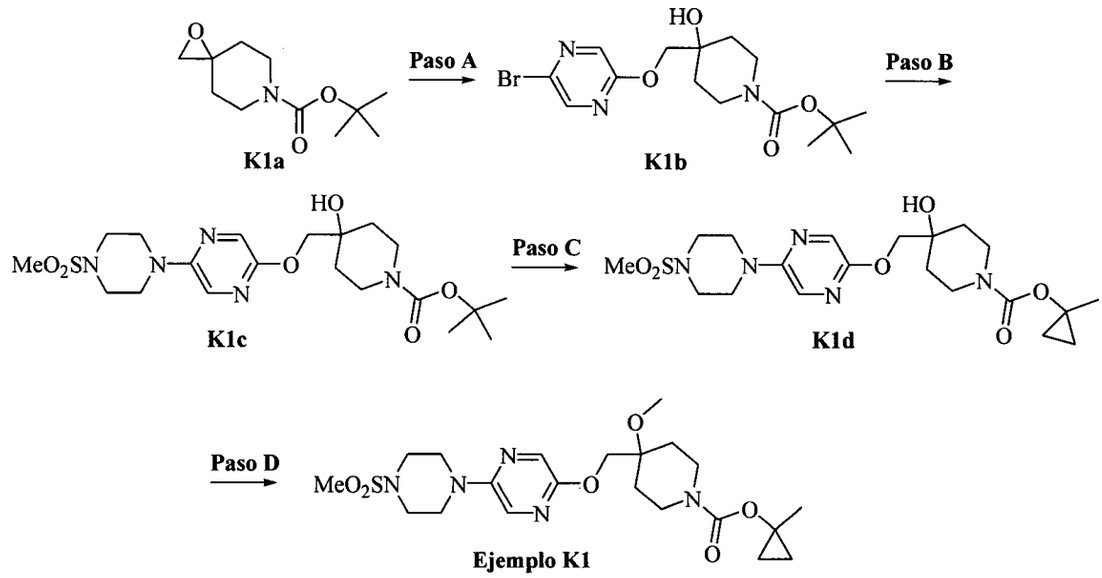
Ejemplo J30: 2–(4–((2–Bromo–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)–5–fluoropirimidina



Se prepara este material cuando la preparación en gran escala de **J28** a partir de 4–(4–metoxifenil)piperidina en lugar de **J1c** siguiendo un esquema similar al esquema esbozado para **J1** da un subproducto bromado en el **Paso D:** ^{1}H–NMR (400MHz, DMSO–d6) δ 8,43 (d, 2H, J = 0,8 Hz), 7,45 (d, 1H, J = 2,1 Hz), 7,21 (dd, 1H, J = 2,1, 8,6 Hz), 7,04 (d, 1H, J = 8,6 Hz), 4,61 (m, 2H), 3,91 (d, 2H, J = 6,3 Hz), 3,65 (m, 2H), 2,93 (m, 2H), 2,89 (s, 3H), 2,77 (m, 2H), 2,59 (tt, 1H, J = 3,5, 12,0 Hz), 2,07 (m, 1H), 1,84 (m, 4H), 1,62 (m, 2H), 1,27 (m, 2H), ESIMS calc, para $C_{22}H_{29}BrFN_4O_3S$ ($M+H^+$) 527,1, resultó 527,1.

Ejemplo K1: 1–Metilciclopropil 4–metoxi–4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.





Paso A: Se trata una solución de **K1a** (2,22 g, 10,4 mmol) y 2–bromo–5–hidroxipirazina (2 g, 11,4 mmol) en N–metilpirrolidinona (10 ml) con K_2CO_3 (2,37 g, 17,1 mmol) y se la calienta a 80 °C de un día para otro. Después del enfriamiento a temperatura ambiente, se diluye la reacción con acetato de etilo y se la extrae con agua dos veces. Se secan los extractos orgánicos sobre $MgSO_4$, se los filtra, evapora y purifica con gel de sílice empleando un gradiente lineal de 0–100% de acetato de etilo en hexano para producir **K1b**; ESIMS *m/z* correspondiente a $(M+H^+)$ $C_{15}H_{23}BrN_3O_4$ calc.: 388.1, resultó: 388.2.

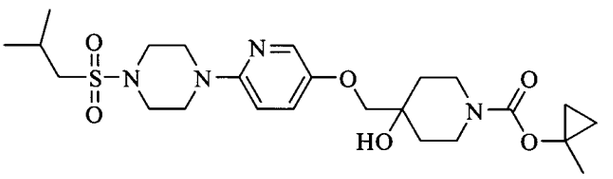
Paso B: Siguiendo un procedimiento similar al utilizado para la preparación de **B1** a partir de isopropil 4–((6–cloropiridin–3–iloxi)metil)piperidin–1–carboxilato excepto que se sustituye **K1b** por isopropil 4–((6–cloropiridin–3–iloxi)metil)piperidin–1–carboxilato, se prepara **K1c**; ESIMS *m/z* correspondiente a $(M+H^+)$ $C_{20}H_{34}N_5O_6S$ calc.: 472.2, resultó: 472.2.

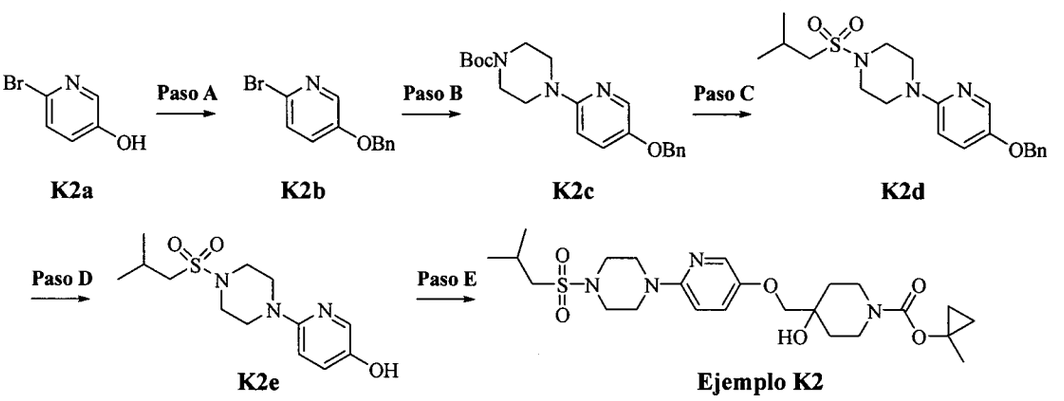
Paso C: **:** Siguiendo un procedimiento similar al utilizado para la preparación de **E3** a partir de **B4** excepto que se sustituye **B4** por **K1c**, se prepara **K1d**; ESIMS *m/z* correspondiente a $(M+H^+)$ $C_{20}H_{32}N_5O_6S$ calc.: 470,2, resultó: 470,2.

Paso D: Se trata una solución de **K1d** (75 mg, 0,16 mmol) en N, N–dimetilformamida con dimetilsulfato (80 mg, 0,63 mmol) seguido por NaH (30 mg, 1,25 mmol). Después de agitar a temperatura ambiente por espacio de 1 hora, se trata la reacción con agua y acetato de etilo. Se aíslan los extractos orgánicos, se

los lava con agua, se los seca sobre $MgSO_4$, filtra, evapora y purifica por gel de sílice empleando un gradiente lineal de 50–100% de acetato de etilo en hexano para producir **K1**; ^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 7,94 (d, *J* = 1,5 Hz, 1H), 7,61 (d, *J* = 1,4 Hz, 1H), 4,20 (m, 2H), 3,91 (m, 2H), 3,54 (m, 4H), 3,37 (m, 4H), 3,29 (s, 3H), 3,13 (m, 2H), 2,82 (s, 3H), 1,89 (m, 2H), 1,55 (m, 2H), 1,55 s, 3H), 0,87 (m, 2H), 0,62 (m, 2H); ESIMS calc, para $C_{21}H_{34}N_5O_6S$ ($M+H^+$) 484,2, resultó 484,1.

Ejemplo K2: 1–metilciclopropil 4–hidroxi–4–((6–(4–(isobutilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato.





Paso A: Se trata una solución de **K2a** (2,0 g, 11,5 mmol) y bromuro de bencilo (2,36 g, 13,8 mmol) en N–metilpirrolidinona (15 ml) con K_2CO_3 (2,38 g, 17,2 mmol) y se la agita a 60 °C de un día para otro. Se enfría la reacción a temperatura ambiente, se la diluye con acetato de etilo y se la extrae dos veces con agua. A continuación se secan los extractos orgánicos sobre $MgSO_4$, se los filtra, evapora y purifica en gel de sílice empleando un gradiente lineal de 0–100 % de acetato de etilo en hexano para producir **K2b**; ^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 8,13 (d, *J* =

3,1 Hz, 1H), 7,38 (m, 6H), 7,15 (dd, *J* = 3,2, 8,7 Hz, 1H), 5,09 (s, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{12}H_{11}BrNO$ calc.: 264,0, resultó: 264,0.

Paso B: Se carga un matraz de fondo redondo con **K2b** (2,55 g, 9,65 mmol), Pd_2dba_3 (177 mg, 0,19 mmol), xantfos (335 mg, 0,58 mmol) y terc–butil piperazin–1–carboxilato (2,16 g, 11,6 mmol) seguidos por tolueno seco (30 ml). Se rocía el matraz con nitrógeno seco, se lo trata con NaO*t*Bu (1.39 g, 14,5 mmol), se lo cierra herméticamente, se lo sumerge en un baño de aceite precalentado a 100 °C y se agita por espacio de 2 horas. A continuación se enfría la reacción a temperatura ambiente, se la diluye con acetato de etilo y se la extrae dos veces con agua. Seguidamente se secan los extractos orgánicos sobre $MgSO_4$, se los filtra, evapora y purifica en gel de sílice empleando un gradiente lineal de 0–100% de acetato de etilo en hexano para producir **K2c**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{28}N_3O_3$ calc: 370,2, resultó: 370,1.

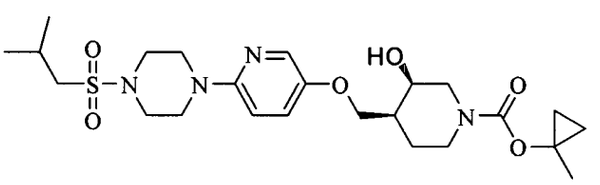
Paso C: Se madura una solución de **K2c** (970 mg, 2,2 mmol) en 1:1 TFA/ diclorometano (10 ml) por espacio de 1 hora y se separa el solvente. Se reparte el residuo obtenido entre acetato de etilo y HCl 1 M. Se recoge la fase acuosa y se extraen los extractos orgánicos una vez más con HCl 1 M y se los descarta. Se basifican los extractos acuosos combinados con Na_2CO_3 sólido y se los extrae tres veces con diclorometano. Se secan los extractos orgánicos combinados sobre $MgSO_4$, se los filtra, evapora, disuelve en diclorometano (10 ml) y se los trata con trietilamina (337 mg, 3,33 mmol) seguida por cloruro de isobutansulfonilo (452 mg, 2,89 mmol). Después de agitar por espacio de 30 minutos, se diluye la reacción con acetato de etilo, se la extrae con hidrogenocarbonato de sodio acuoso saturado, se la seca sobre $MgSO_4$, filtra y evapora para producir **K2d**; ^1H NMR ($CDCl_3$, 400,13 MHz): δ 7,99 (d, *J* = 2,8 Hz, 1H), 7,38 (m, 5H), 7,22 (dd, *J* = 3,2, 9,1 Hz, 1H), 6,64 (d, *J* = 9,0 Hz, 1H), 5,04 (s, 2H), 3,52 (m, 4H), 3,37 (m, 4H), 2,76 (d, *J* = 6,6 Hz, 2H), 1,12 (d, *J* = 6,7 Hz, 6H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{20}H_{28}N_3O_3S$ calc.: 390,2, resultó: 390,2.

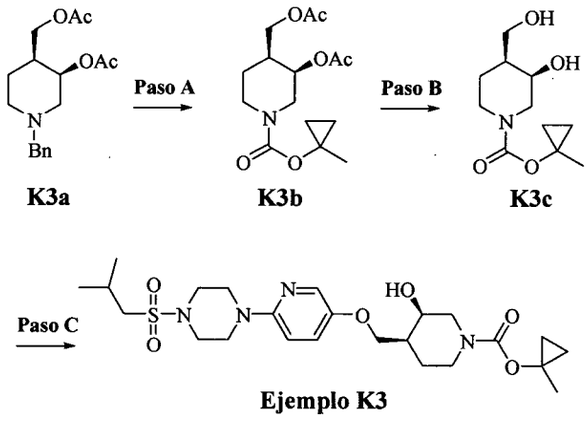
Paso D: Se trata una solución de **K2d** (0,80 g, 2,0 mmol) en etanol (10 ml) con $Pd(OH)_2$ (50 mg) y se la hidrogena de un día para otro. Se retira el catalizador por filtración a través de Celite® y se la vuelve a someter a hidrogenación con 100 mg

de Pd/C al 10% de un día para otro. Se separa el catalizador por filtración a través de y se separa el solvente. Se suspende el material obtenido en hexano, se lo recoge y seca para producir **K2e**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{13}H_{22}N_3O_3S$ calc.: 300,1, resultó: 300,1.

Paso E: Se trata una solución de **K2e** (75 mg, 0,25 mmol) y **K1a** (64 mg, 0,30 mmol) en N–metilpirrolidinona (2 ml) con K_2CO_3 (52 mg, 0,38 mmol) y se la agita a 80 °C de un día para otro. A continuación se enfría la reacción a temperatura ambiente, se la reparte entre acetato de etilo y agua y se la extrae con agua una vez más. Se secan los extractos orgánicos sobre $MgSO_4$, se la filtra, evapora, disuelve en diclorometano (2 ml) y se la trata con TFA (2 ml). Después de agitar por espacio de 1 hora, se separa el solvente y se disuelve el residuo en diclorometano, se lo trata con **E3b** (59 mg, 0,25 mmol) y exceso de trietilamina y se agita de un día para otro. A continuación se reparte el residuo entre acetato de etilo y agua y se lo extrae con agua una vez más. Se secan los extractos orgánicos sobre $MgSO_4$, se los filtra, evapora y purifica en gel de sílice empleando un gradiente lineal de 0–100% de acetato de etilo en hexano para producir **K2;** ^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 7,93 (d, *J* = 3,0 Hz, 1H), 7,18 (dd, *J* = 3,1, 9,1 Hz, 1H), 6,65 (d, *J* = 9,2 Hz, 1H), 3,99 (m, 2H), 3,77 (s, 2H), 3,52 (m, 4H), 3,37 (m, 4H), 3,20 (m, 2H), 2,77 (d, *J* = 6,6 Hz, 2H), 2,32 (m, 1 H), 2,12 (s, 1H), 1,72 (m, 2H), 1,55 (m, 3H), 1,12 (d, *J* = 6,7 Hz, 6H), 0,87 (m, 2H), 0,63 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{24}H_{38}N_4O_6S$ calc.: 510,3, resultó: 511,5.

Ejemplo K3: (+/–)–(cis)–1–metilciclopropil 3–hidroxi–4–((6–(4–(isobutilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato





K3a **K3b** **K3c**

Ejemplo K3

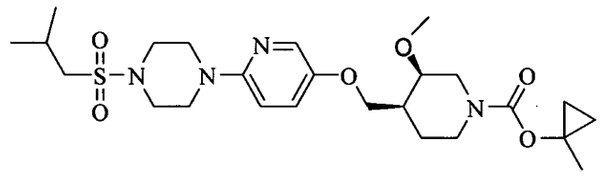
Paso A: Se hidrogena una solución de **K3a** (420 mg, 1,4 mmol) (Helv. Chim. Acta **2004**, 87, 2629) en EtOH que contiene 1% en volumen de TFA (150 ml) en un aparato H–Cube a 50 atmósferas de H_2 y a 70 °C. A continuación se separa el solvente y se coevapora el residuo dos veces con tolueno, se lo disuelve en diclorometano (10 ml) y se lo trata con **E3b** (342 mg, 1,4 mmol), exceso de trietilamina y unos pocos cristales de DMAP. Se agita la reacción de un día para otro, se la reparte entre acetato de etilo e hidrogenocarbonato de sodio acuoso saturado y se la extrae dos veces con carbonato de sodio acuoso saturado. A continuación se secan los extractos orgánicos sobre $MgSO_4$, se los filtra y evapora y se los purifica en gel de sílice empleando un gradiente lineal de 0–100% de acetato de etilo en hexano para producir **K3b**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{15}H_{24}NO_6$ calc.: 314.2, resultó: 314.1.

Paso B: Se trata una solución de **K3b** (333 mg, 1,1 mmol) en MeOH con una solución de $Mg(OMe)_2$ (5,6 ml de una solución con 0,57 M, 3,2 mmol) y se agita por espacio de 1 hora. A continuación se inactiva la reacción con exceso de la resina Amberlite IR–120 H^+ prelavada y se la filtra. Se separa el solvente para producir **K3c**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{11}H_{20}NO_4$ calc.: 230,1, resultó: 230,1.

Paso C: Se enfría una solución de DIAD (88 mg, 0,22 mmol) en diclorometano (0,5 ml) en un baño de hielo y se la trata con una solución de PPh_3 (114 mg, 0,44 mmol) en diclorometano (1 ml). Se agita la solución por espacio de 15 minutos y se la trata con una solución de **K3c** (50 mg, 0,22 mmol) y **K2d** (65 mg, 0,22 mmol)

en diclorometano (1,5 ml). Se sella la reacción y se la calienta a 50 °C de un día para otro. Se enfría la reacción a temperatura ambiente y se la carga en una columna de gel de sílice y se la purifica empleando un gradiente lineal de 0–100% de acetato de etilo en hexano. Se reparten las fracciones de producto entre acetato de etilo y HCl 1 M. Se recoge la fase acuosa y se extraen los extractos orgánicos una vez más con HCl 1 M y se los descarta. Se basifican los extractos acuosos combinados con Na_2CO_3 sólido y se los extrae tres veces con acetato de etilo. Se secan los extractos orgánicos sobre $MgSO_4$, se los filtra y evapora para producir **K3**; ^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 7,93 (d, *J* = 2,9 Hz, 1H), 7,17 (dd, *J* = 3,1, 9,1 Hz, 1H), 6,64 (d, *J* = 9,1 Hz, 1H), 4,19 (m, 2H), 4,09 (m, 1H), 4,03 (dd, *J* = 7,6, 9,1 Hz, 1H), 3,84 (dd, *J* = 6,0, 9,1 Hz, 1H), 3,51 (m, 4H), 3,37 (m, 4H), 2,91 (m, 1H), 2,78 (m, 1H), 2,76 (d, *J* = 6,6 Hz, 2H), 2,32 (m, 1H), 2,00 (m, 1H), 1,86 (m, 1H), 1,68 (m, 1H), 1,55 (s, 3H), 1,12 (d, *J* = 6,7 Hz, 6H), 0,88 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{24}H_{39}N_4O_6S$ calc.: 511,3, resultó: 511,4.

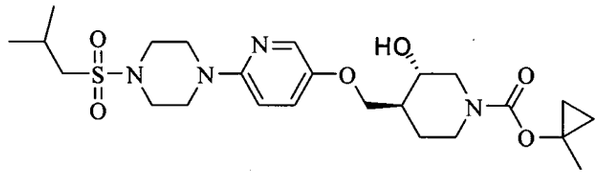
Ejemplo K4: (+/–)–(cis)–1–Metilciclopropil 4–((6–(4–(isobutilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)–3–metoxipiperidin–1–carboxilato



Se trata una solución de **K3** (25 mg, 0,22 mmol) en N, N–dimetilformamida (2 ml) con exceso (~100 ul) de dimetilsulfato y exceso (~40 mg) de NaH. Se agita la reacción por espacio de 1 hora y luego se la diluye con acetato de etilo y agua. Se aíslan los extractos orgánicos y se los lava una vez más con agua, se los seca sobre MgSO4, filtra, evapora y purifica en gel de sílice empleando un gradiente lineal de 0–100% de acetato de etilo en hexano para producir **K4**; ^{1}H NMR ($CDCl_3$, 400,13 MHz): □ 7.93 (d, *J* = 2.9 Hz, 1H), 7.16 (dd, *J* = 3.0, 9.1 Hz, 1H),

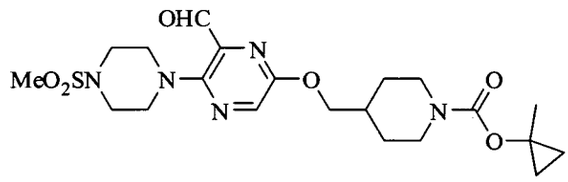
6.64 (d, *J* = 9.1 Hz, 1H), 4.53 (m, 0,5H), 4.28 (m, 1H), 4.00 (m, 1.5 H), 3.78 (m, 1H), 3.52 (m, 4H), 3.75 (m, 7H), 2.76 (d, *J* = 6.6 Hz, 2H), 2.72 (m, 2H), 2.32 (m, 1H), 2.03 (m, 1H), 1.59 (m, 1H), 1.55 (s, 3H), 1.48 (m, 1H), 1.12 (d, *J* = 6.7 Hz, 6H), 0,87 (m, 2H), 0,61 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{25}H_{41}N_4O_6S$ calc.: 525.3, resultó: 525.2.

Ejemplo K5: (+/–)–(Trans)–1–metilciclopropil 3–hidroxi–4–((6–(4–(isobutilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato



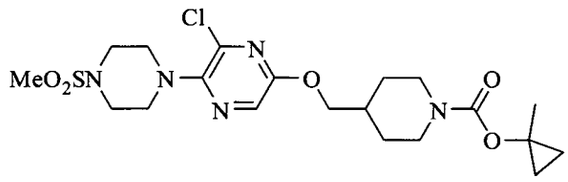
Siguiendo un procedimiento similar al utilizado para la preparación de **K3** a partir de **K3a** excepto que se sustituye **K3a** por el isómero trans de **K3a** (Helv. Chim. Acta **2004**, 87, 2629), se prepara **K5**; ^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 7,93 (d, *J* = 3,0 Hz, 1H), 7,24 (dd, *J* = 3,0, 9,1 Hz, 1H), 6,69 (d, *J* = 9,2 Hz, 1H), 4,17 (m, 3H), 4,05 (m, 2H), 3,56 (m, 5 H), 3,37 (m, 4H), 2,77 (d, *J* = 6,6 Hz, 2H), 2,72 (m, 1H), 2,58 (m, 1H), 2,31 (m, 1H), 1,90 (m, 1H), 1,78 (m, 1H), 1,55 (s, 3H), 1,40 (m, 1H), 1,12 (d, *J* = 6,7 Hz, 6H), 0,87 (m, 2H), 0,61 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{24}H_{39}N_4O_6S$ calc.: 511,3, resultó: 511,4.

Ejemplo L1: 1–metilciclopropil 4–((6–formil–5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



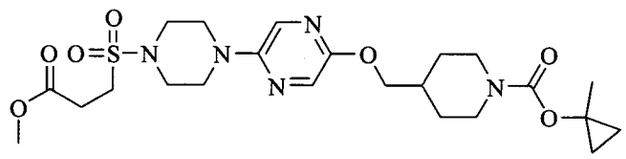
Se trata una solución de **E3** (109 mg, 0,24 mmol) en N,N–dimetilformamida (2,2 ml) con $POCl_3$ (165 mg, 1,1 mmol) y se la calienta a 70 °C por espacio de 2 horas. A continuación se enfría la reacción a temperatura ambiente, se la inactiva con agua y diluye con acetato de etilo. Se extrae la fase orgánica con agua dos veces más, se la seca sobre $MgSO_4$, filtra evapora y purifica por gel de sílice empleando un gradiente lineal de 50–100% de acetato de etilo en hexano para producir **L1**; ^1H NMR ($CDCl_3$, 400,13 MHz): δ 9,93 (s, 1H), 8,04 (s, 1H), 4,19 (d, *J* = 6,4 Hz, 1H), 4,15 (m, 2H), 3,50 (m, 4H), 3,43 (m, 4H), 2,83 (s, 3H), 2,74 (m, 2H), 1,97 (m, 1H), 1,81 (m, 2H), 1,55 (s, 3H), 1,27 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS calc, para $C_{21}H_{32}N_5O_6S$ $(M+H^+)$ 482,2, resultó 482,1.

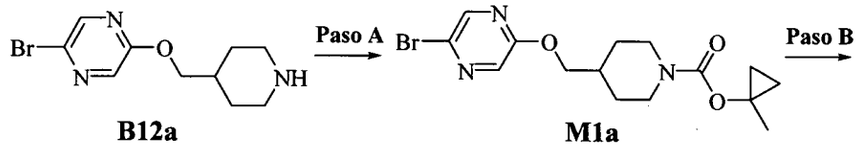
Ejemplo L2: 1–Metilciclopropil 4–((6–cloro–5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



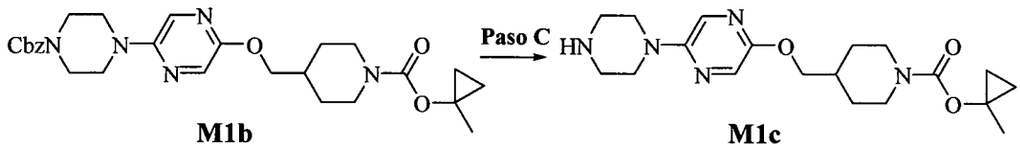
Siguiendo un procedimiento similar al utilizado para la preparación de **L1** a partir de **E3** excepto que se utiliza NCS a 50 °C en dicloroetano de un día para otro como condiciones de reacción, se prepara **K5**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{20}H_{31}ClN_5O_5S$ calc.: 488.2, resultó: 487.7.

Ejemplo M1: 1–Metilciclopropil 4–((5–(4–(3–metoxi–3–oxopropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.

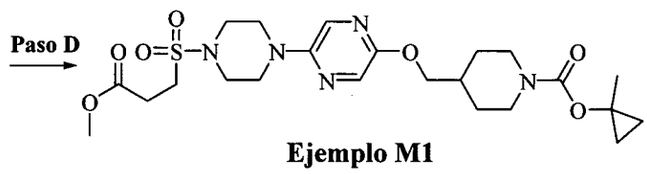




B12a M1a



M1b M1c



Ejemplo M1

Paso A: Siguiendo un procedimiento similar al utilizado para la preparación de **E3** a partir de **E3a** excepto que se sustituye **E3a** por **B12a**, se prepara **M1a**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{15}H_{22}BrN_3O_3$ calc.: 371.2, resultó: 371,1.

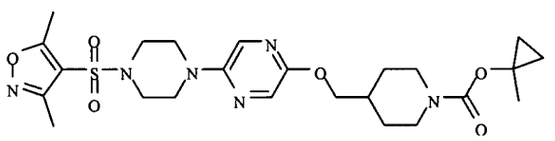
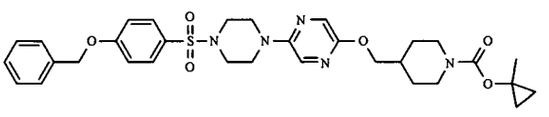
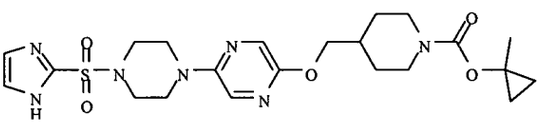
Paso B: : Siguiendo un procedimiento similar al utilizado para la preparación de **B1** a partir de isopropil 4–((6–cloropiridin–3–iloxi)metil)piperidin–1–carboxilato excepto que se sustituye isopropil 4–((6–cloropiridin–3–iloxi)metil)piperidin–1–carboxilato por **M1a** y 1–(metilsulfonil)piperazina por bencil piperazin–1–carboxilato, se prepara **M1b**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7,85 (d, *J* = 1,5 Hz, 1H), 7,59 (d, *J* = 1,4 Hz, 1H), 7,35 (m, 5H), 5,16 (s, 2H), 4,18 (m, 2H), 4,06 (d, *J* = 6,6 Hz, 2H), 3,65 (m, 4H), 3,38 (m, 4H), 2,74 (m, 2H), 1,94 (m, 1H), 1,79 (m, 2H), 1,54 (s, 3H), 1,24 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{27}H_{36}N_5O_5$ calc.: 510,3, resultó: 510,0,

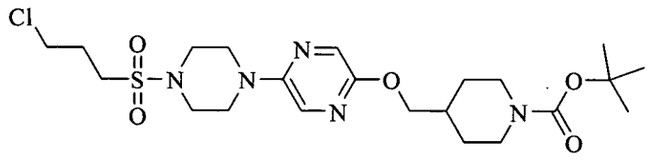
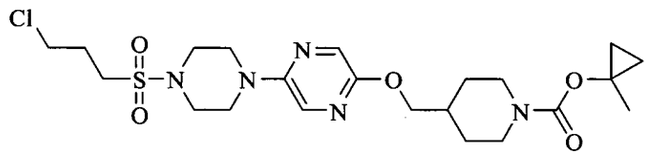
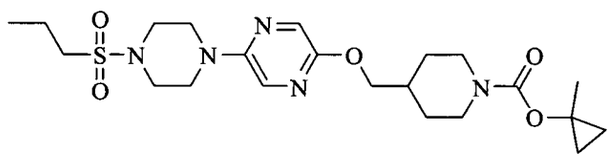
Paso C: Se purga una mezcla de **M1b** (494 mg, 0,969 mmol) y Pd/C al 10% (45 mg) en etanol (5 ml) con H_2 (g) por espacio de 30 minutos y luego se lo deja agitar a temperatura ambiente bajo atmósfera de H_2 de un día para otro. Seguidamente

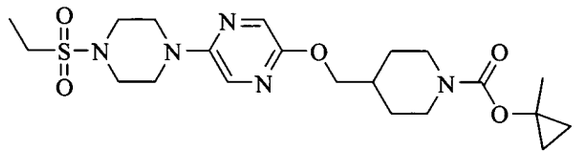
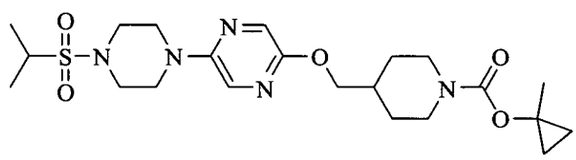
se filtra la reacción cruda a través de una plancha de Celite® y se obtiene **M1c** con una pureza de 95%+. ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{19}H_{30}N_5O_3$ calc.: 376.2, resultó: 376.0,

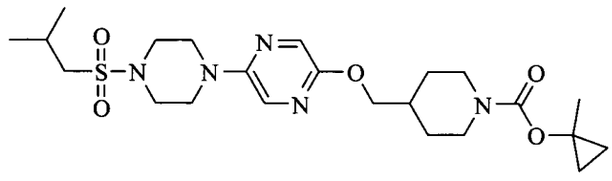
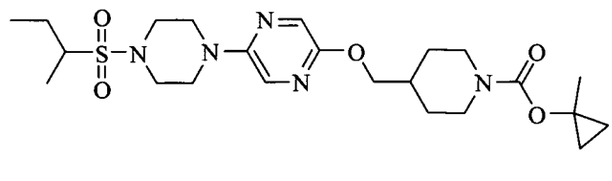
Paso D: Se trata una solución de **M1c** (100 mg, 0,266 mmol) en diclorometano (1 ml) con trietilamina (74.2 ml, 0,533 mmol) seguida por metil 3–(clorosulfonil)propanoato (50 mg, 0,27 mmol) y se la agita a temperatura ambiente por espacio de 4 horas. Seguidamente se concentra la reacción cruda y se la purifica directamente por HPLC dirigida a la masa para producir **M1**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7,86 (d, J = 1,5 Hz, 1H), 7,61 (d, J = 1,5 Hz, 1H), 4,18 (m, 2H), 4,07 (d, J = 6,5 Hz, 2H), 3,73 (s, 3H), 3,49 (m, 4H), 3,42 (m, 4H), 3,28 (t, J = 7,3 H, 2H), 2,85 (t, J = 7,7 Hz, 2H), 2,74 (m, 2H), 1,93 (m, 1H), 1,81 (m, 2H), 1,54 (s, 3H), 1,24 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{23}H_{36}N_5O_7S$ calc.: 526,2, resultó: 526,2.

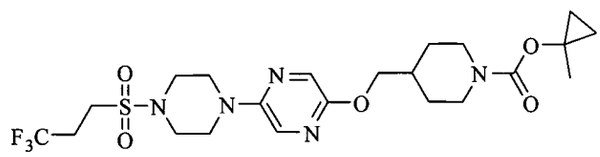
Siguiendo un procedimiento similar al utilizado para la preparación de **M1** a partir de **E12a** excepto que se sustituye el metil 3–(clorosulfonil)propanoato por cloruros de sulfonilo existentes en el comercio (en el caso de **M5**, también se sustituye **M1a** por **B4bB)**, se preparan los siguientes ejemplos;

Ejemplo	Estructura	Datos Analíticos
M2		ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{24}H_{35}N_6O_6S$ calc.: 535,2, resultó: 535,2.
M3		ESIMS *m/z* correspondiente a $(M)^+$ $C_{32}H_{39}N_5O_6S$ calc.: 621,3, resultó: 621,7,
M4		ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{22}H_{32}N_7O_5S$ calc.: 506,2, resultó: 506,2.

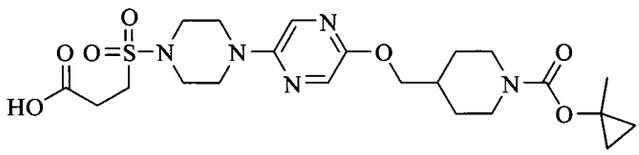
M5		^{1}H NMR (400 MHz, CD_3CN) δ 7,87 (d, J = 1,4 hz, 1H), 7,62 (d, J – 1,5 Hz, 1H), 4,15 (m, 2H), 4,08 (d, J = 6,6 Hz, 2H), 3,70 (t, J = 6,1 Hz, 2H), 3,51 (m, 4H), 3,43 (m, 4H), 3,11 (t, J = 7,4 Hz, 2H), 2,73 (m, 2H), 2,32 (m, 2H), 1,94 (m, 1H), 1,79 (m, 2H), 1,46 (s, 9H), 1,26 (m, 2H); ESIMS *m/z* correspondiente a $(M–Boc+H)^+$ $C_{17}H_{29}ClN_5O_3S$ calc.: 418,2, resultó: 418,2,
M6		^{1}H–NMR (400MHz, $CDCl_3$) δ 7,87 (d, *J* = 1,4 Hz, 1H), 7,63 (d, *J* = 1,4 Hz, 1H), 4,21 (m, 2H), 4,08 (d, *J* = 6,5Hz, 2H), 3,70 (t, *J* = 6,1 Hz, 2H), 3,51 (m, 4H), 3,44 (m, 4H), 3,12 (m, 2H), 2,74 (dd, *J* = 12,3, 12,2 Hz, 2H), 2,32 (m, 2H), 1,95 (m, 1H), 1,79 (m, 2H), 1,55 (s, 3H), 1,25 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS calc, para $C_{22}H_{35}ClN_5O_5S$ $[M]^+$ 516,2, resultó 516,0,
M7		^{1}H NMR (400 MHz, CD_3CN) δ 7,89 (d, J = 1,4 Hz, 1H), 7,82 (d, J = 1,2 Hz, 1H), 4,19 (m, 2H), 4,10 (d, J = 6,5 Hz, 2H), 3,51 (m, 8H), 2,93 (m, 2H), 2,74 (dd,

		J= 12,7, 12,0 Hz, 1H), 1,91 (m, 3H), 1,79 (m, 2H), 1,55 (s, 3H), 1,25 (m, 2H), 1,07 (t, J = 7,4 Hz, 3H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{22}H_{36}N_5O_5S$ calc.: 482,3 , resultó: 482,2,
M8		^{1}H NMR (400 MHz, CD_3CN) δ 7,96 (s, 1H), 7,91 (d, J = 1,4 Hz, 1H), 4,17 (m, 2H), 4,11 (d, J = 6,5 Hz, 2H), 3,58 (m, 4H), 3,54 (m, 4H), 3,01 (m, 2H), 2,74 (dd, J = 12,2, 11,9 Hz, 2H), 1,95 (m, 1H), 1,79 (m, 2H), 1,55 (s, 3H), 1,40 (t, J = 7,4 Hz, 3H), 1,25 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{34}N_5O_5S$ calc.: 468,2 , resultó: 468,2,
M9		^{1}H NMR (400 MHz, CD_3CN) δ 7,91 (m, 2H), 4,18 (m, 2H), 4,11 (d, J = 6,5 Hz, 2H), 3,63 (m, 4H), 3,50 (m, 4H), 3,25 (sept,, J = 6,8 Hz, 1H), 2,74 (dd, J = 12,2, 12,1 Hz, 2H), 1,94 (m, 1H), 1,78 (m, 2H), 1,55 (s, 3H), 1,37 (d, J = 6,9 Jz, 6H), 1,25 (m, 2H), 0,86 (m, 2H),

		0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{22}H_{36}N_5O_5S$ calc.: 482,2 , resultó: 482,2,
M10		^{1}H NMR (400 MHz, CD_3CN) δ 7,89 (d, J = 1,4 Hz, 1H), 7,81 (d, J = 1,1 Hz, 1H), 4,18 (m, 2H), 4,10 (d, J = 6,5 Hz, 2H), 3,53 (m, 4H), 3,47 (m, 4H), 2,79 (d, J = 6,6 Hz, 2H), 2,74 (m, 2H), 2,32 (m, 1H), 1,95 (m, 1H), 1,78 (m, 2H), 1,55 (s, 3H), 1,24 (m, 2H), 1,12 (d, J = 6,7 Hz, 6H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{23}H_{38}N_5O_5S$ calc.: 496,3 , resultó: 496,3,
M11		^{1}H NMR (400 MHz, CD_3CN) δ 7,87 (d, J = 1,5 Hz, 1H), 7,62 (d, J = 1,5 Hz, 1H), 4,19 (m, 2H), 4,07 (d, J = 6,5 Hz, 2H), 3,50 (m, 4H), 3,46 (m, 4H), 2,98 (m, 1H), 2,75 (dd, J = 12,2, 12,1 Hz, 2H), 2,03 (m, 1H), 1,80 (m, 1H), 1,79 (m, 2H), 1,56 (m, 1H), 1,55 (s, 3H), 1,35 (d, J = 6,9 Hz, 3H), 1,26 (m, 2H), 1,03 (t, J = 7,5 hz, 3H), 0,87 (m, 2H), 0,62 (m, 2H); ESIMS *m/z*

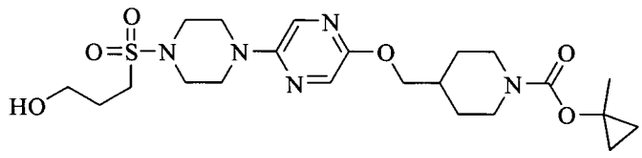
		correspondiente a $(M+H)^+$ $C_{23}H_{38}N_5O_5S$ calc.: 496,3 , resultó: 496,2,
M12		^{1}H–NMR (400MHz, $CDCl_3$) δ 7,87 (d, *J* = 1,4Hz, 1H), 7,62 (d, *J* = 1,4Hz, 1H), 4,20 (m, 2H), 4,08 (d, *J* = 6,5Hz, 2H), 3,52 (m, 4H), 3,45 (m, 2H), 3,13 (m, 2H), 2,74 (dd, *J* = 12,2, 12,2 Hz, 2H), 2,66 (m, 2H), 1,94 (m, 1H), 1,79 (m, 2H), 1,56 (s, 3H), 1,25 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS calc., $C_{22}H_{33}F_3N_5O_5S$ $[M+H]^+$ 536,2, resultó 536,3,

Ejemplo M13: Ácido 3–(4–(5–((1–((1–Metilciclopropoxi)carbonil)piperidin–4–il)metoxi)pirazin–2–il)piperazin–1–ilsulfonil)propanoico.



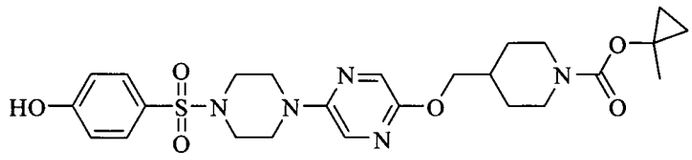
Se trata una solución de **M1** (18.8 mg, 0,035 mmol) en tetrahidrofurano (1 ml) y agua (0,25 ml) con LiOH (3 mg) y se la agita de un día para otro. A continuación se concentra la reacción cruda y se la purifica por HPLC dirigida a la masa para producir **M13**. ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{22}H_{34}N_5O_7S$ calc.: 512.2, resultó: 512.3.

Ejemplo M14: 1–Metilciclopropil 4–((5–(4–(3–hidroxipropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



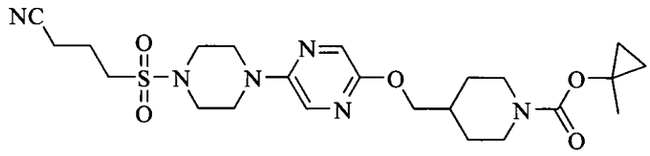
Se calienta una solución de **M1** (18,8 mg, 0,035 mmol) en $LiBH_4$ 2 M en tetrahidrofurano (1 ml) a 50 °C y se la agita de un día para otro. A continuación se concentra la reacción cruda y se la purifica por HPLC dirigida a la masa para producir **M14**. ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{22}H_{36}N_5O_6S$ calc.: 498,2, resultó: 498,3.

Ejemplo M15: 1–Metilciclopropil 4–((5–(4–(4–hidroxifenilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



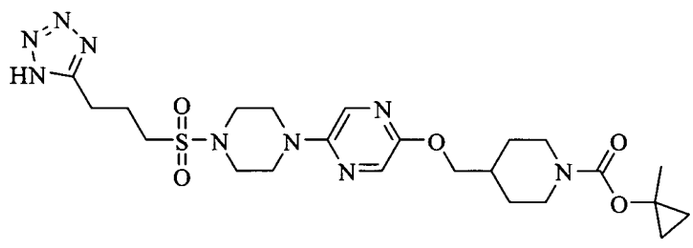
Se trata una solución de **M3** (44,5 mg, 0,071 mmol) en etanol (2 ml) con Pd/C al 5% (10 mg) y se la hidrogena a presión atmosférica de un día para otro. Se separa el catalizador mediante filtración a través de Celite® y se concentra y purifica directamente la reacción por HPLC dirigida a la masa para producir **M15**. ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{25}H_{33}N_5O_6S$ calc.: 531.2, resultó: 531.7.

Ejemplo M16: 1–Metilciclopropil 4–((5–(4–(3–cianopropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



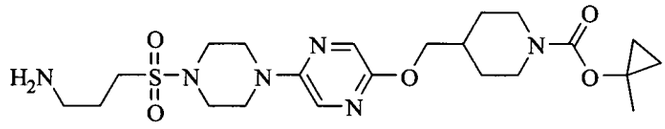
Se trata una solución de **M6** (19 mg, 0,037 mmol) en N,N–dimetilformamida (0,5 ml) con KCN (3,6 mg, 0,055 mmol) y carbonato de cesio (24 mg, 0,077 mmol) y se la calienta a 80 °C por espacio de 1,5 horas. A continuación se diluye la reacción con agua y se la extrae con acetato de etilo tres veces y dos veces con éter dietílico. Se secan los extractos orgánicos combinados sobre $MgSO_4$, se los filtra, evapora y purifica por gel de sílice empleando un gradiente lineal de 50–100% de acetato de etilo en hexano para producir **M16**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7,87 (d, *J* = 1,6 Hz, 1H), 7,62 (d, *J* = 1,6 Hz, 1H), 4,28–3,95 (m, 2H), 4,08 (d, *J* = 6,4 Hz, 2H), 3,53–3,50 (m, 4H), 3,44–3,42 (m, 4H), 3,07 (t, *J* = 6,8 Hz, 2H), 2,74 (br t, *J* = 12,0 Hz, 2H), 2,64 (t, *J* = 7,2 Hz, 2H), 2,24 (quintete, *J* = 7,2 Hz, 2H), 2,01–1,89 (m, 1H), 1,81–1,77 (m, 2H), 1,54 (s, 3H), 1,30–1,17 (m, 2H), 0,88–0,84 (m, 2H), 0,64–0,60 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{23}H_{35}N_6O_5S$ calc.: 507,2, resultó: 507,2.

Ejemplo M17: 1–Metilciclopropil 4–((5–(4–(3–(1H–tetrazol–5–il)propilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



Se trata una solución de **M16** (12 mg, 0,024 mmol) en isopropanol (0,1 ml) y agua (0,3 ml) con $ZnBr_2$ (27 mg, 0,12 mmol) y NaN_3 (7,7 mg, 0,12 mmol) y se la calienta a 150 °C de un día para otro. Se filtra la solución a través de un filtro de jeringa y se la purifica directamente por HPLC dirigida a la masa para producir **M17**; ^1H NMR (400 MHz, CD_3CN) δ 7,83 (d, *J* = 1,6 Hz, 1H), 7,71 (d, *J* = 1,6 Hz, 1H), 4,16–3,89 (m, 2H), 4,06 (d, *J* = 6,4 Hz, 2H), 3,49–3,46 (m, 4H), 3,35–3,32 (m, 4H), 3,12–3,04 (m, 4H), 2,81–2,70 (m, 2H), 2,28–2,20 (m, 2H), 1,78–1,71 (m, 3H), 1,48 (s, 3H), 1,22–1,12 (m, 2H), 0,81–0,78 (m, 2H), 0,60–0,57 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{23}H_{36}N_9O_5S$ calc.: 550,3, resultó: 550,3.

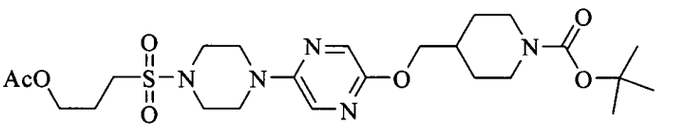
Ejemplo M18: 1–Metilciclopropil 4–((5–(4–(3–aminopropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



Se trata una solución de **M6** (113 mg, 0,22 mmol) en N,N–dimetilformamida (1 ml con NaN_3 (42,7 mg, 0,67 mmol) y se la calienta a 90 °C de un día para otro. Se enfría la reacción a temperatura ambiente, se la reparte entre agua y acetato de etilo. Se extraen los extractos orgánicos con agua dos veces more, se los seca sobre $MgSO_4$, se los filtra y evapora y purifica por gel de sílice empleando un gradiente lineal de 0–100% de acetato de etilo en hexano para producir el intermediario azida, al que se disuelve en etanol (1 ml) y se trata con Pd/C al 10% (20 mg) y se hidrogena a temperatura ambiente de un día para otro. Se separa el catalizador mediante filtración a través de Celite® y se concentra y purifica la reacción por HPLC dirigida a la masa para producir **M18.** ^1H NMR (400 MHz, CD_3CN) δ 7,86 (d, J = 1,4 Hz, 1H), 7,61 (d, J = 1,5 Hz, 1H), 4,19 (m, 2H), 4,07 (d, J = 6,5 Hz, 2H), 3,50 (m, 4H), 3,42 (m, 4H), 3,05 (m, 2H), 2,88 (t, J = 6,7

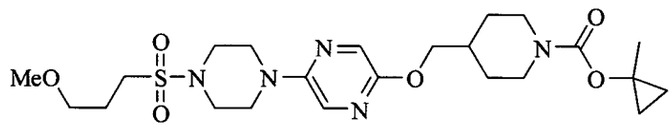
Hz, 2H), 2,74 (dd, J = 13,0, 12,0 Hz, 2H), 1,98 (m, 3H), 1,79 (m, 2H), 1,54 (s, 3H), 1,24 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{22}H_{37}N_6O_5S$ calc.: 497,3 , resultó: 497,6.

Ejemplo M19: *Terc*–butil 4–((5–(4–(3–acetoxipropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



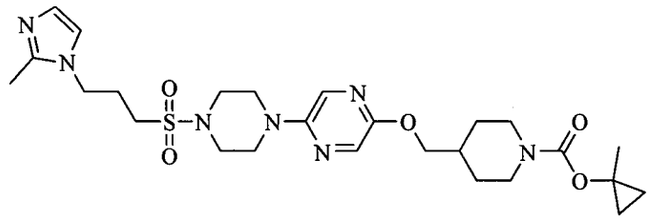
Se trata una solución de **M5** (154 mg, 0,30 mmol) en N,N–dimetilformamida (2 ml) con acetato de sodio (73 mg, 0,89 mmol) y yoduro de sodio (45 mg, 0,30 mmol) y se la calienta a 120 °C de un día para otro . Se enfría la reacción a temperatura ambiente, se la reparte entre agua y acetato de etilo. Se extraen los extractos orgánicos con agua dos veces más, se los seca sobre $MgSO_4$, filtra, evapora y purifica por gel de sílice empleando un gradiente lineal de 0–100% de acetato de etilo en diclorometano para producir **M19;** ^{1}H NMR (400 MHz, CD_3CN) δ 7,87 (d, J = 1,4 Hz, 1H), 7,83 (d, J = 1,5 Hz, 1H), 4,20 (t, J = 6,1 Hz, 2H), 1,14 (m, 2H), 4,08 (d, J = 6,6 Hz, 1H), 3,51 (m, 4H), 3,44 (m, 4H), 3,02 (m, 2H), 2,74 (m, 2H), 2,19 (m, 2H), 2,07 (s, 3H), 1,95 (m, 1H), 1,80 (m, 2H), 1,46 (s, 9H), 1,26 (m, 2H); ESIMS *m/z* correspondiente a $(M–Boc+H)^+$ $C_{19}H_{32}N_5O_5S$ calc.: 442,2 , resultó: 442,3.

Ejemplo M20: 1–Metilciclopropil 4–((5–(4–(3–metoxipropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



Se trata una solución de **M6** (26 mg, 0,049 mmol) in metanol (1 ml) con una solución de metóxido de sodio 0,5 M en metanol (0,2 ml, 0,1 mmol) y se la calienta a 65 °C de un día para otro y a 95 °C por espacio de 10 horas. Se enfría la reacción a temperatura ambiente, se separa el solvente al vacío y se purifica el residuo crudo por gel de sílice empleando un gradiente lineal de 0–80% de acetato de etilo en hexano para producir **M20,** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7,86 (d, J = 1,2 Hz, 1H), 7,61 (d, J = 1,6 Hz, 1H), 4,15 (m, 2H), 4,07 (d, J = 6,4 Hz, 2H), 3,49 (m, 6H), 3,42 (m, 4H), 3,33 (s, 3H), 3,04 (m, 2H), 2,74 (t, J = 12,4 Hz, 2H), 2,09 (m, 2H), 1,94 (m, 1H), 1,79 (d, J = 12,4 Hz, 2H), 1,54 (s, 3H), 1,24 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{23}H_{37}N_5O_6S$ calc.: 511,3, resultó: 512,2.

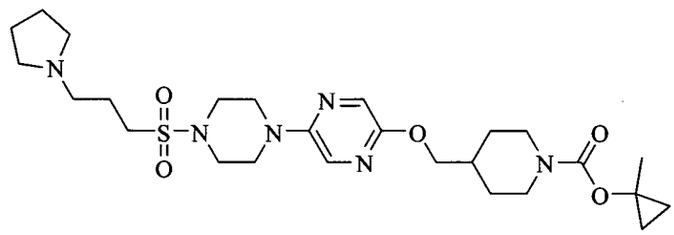
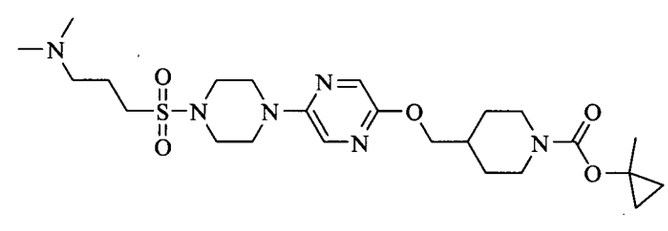
Ejemplo M21: 1–Metilciclopropil 4–((5–(4–(3–(2–metil–1H–imidazol–1–il)propilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.

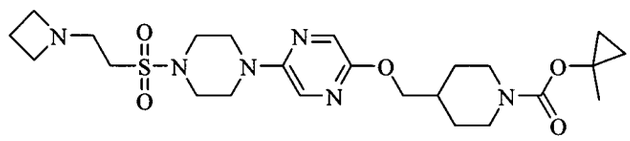
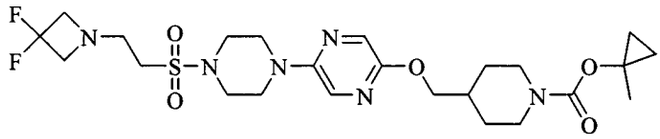


Se trata una solución de **M6** (53 mg, 0,10 mmol) en tetrahidrofurano (1 ml) con 2–metilimidazol (8,5 mg, 0,10 mmol) y se la calienta a 65 °C de un día para otro. Se enfría la reacción a temperatura ambiente, se separa el solvente al vacío y se purifica el residuo crudo directamente por HPLC dirigida a la masa para producir **M21**. ^{1}H NMR (400 MHz, CD_3CN) δ 7,86 (d, J = 1,4 Hz, 1H), 7,62 (d, J = 1,4 Hz,

1H), 7,29 (d, J = 2,0 Hz, 1H), 7,18 (d, J = 1,8 Hz, 1H), 4,34 (t, J = 7,0 Hz, 2H), 4,18 (m, 2H), 4,07 (d, J = 6,5 Hz, 2H), 3,51 (m, 4H), 3,41 (m, 4H), 2,93 (m, 2H), 2,83 (s, 3H), 2,74 (m, 2H), 2,42 (m, 2H), 1,94 (m, 1H), 1,79 (m, 2H), 1,54 (s, 3H), 1,25 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{26}H_{40}N_7O_5S$ calc.: 562,3 , resultó: 562,5.

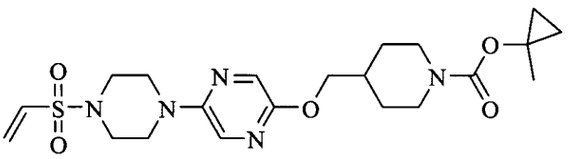
Siguiendo el mismo procedimiento que para **M21** usando los amino nucleófilos apropiados se obtienen los siguientes ejemplos:

Ejemplo	Estructura	Datos Analíticos
M22		^{1}H NMR (400 MHz, CD_3CN) δ 7,85 (d, J = 1,4 Hz, 1H), 7,61 (d, J = 1,5 Hz, 1H), 4,18 (m, 2H), 4,07 (d, J = 6,5 Hz, 2H), 3,51 (m, 4H), 3,43 (m, 4H), 3,19 (m, 6H), 2,74 (dd, J = 12,4, 12,3 Hz, 2H), 2,36 (m, 2H), 2,08 (m, 5H), 1,94 (m, 2H), 1,79 (m, 2H), 1,54 (s, 3H), 1,25 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{26}H_{43}N_6O_5S$ calc.: 551,3 , resultó: 551,5.
M23		^{1}H NMR (400 MHz, CD_3CN) δ 7,85 (d, J = 1,5 Hz, 1H), 7,61 (d, J = 1,5 Hz, 1H), 4,18 (m, 2H), 4,07 (d, J = 6,6 Hz, 2H), 3,51 (m, 4H), 3,44 (m, 4H), 3,18 (m, 2H), 2,98 (m, 2H), 2,74 (dd, J = 12,4,

		12,3, Hz, 2H), 2,63 (s, 6H), 2,30 (m, 2H), 1,94 (m, 1H), 1,79 (m, 2H), 1,54 (s, 3H), 1,25 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{24}H_{41}N_6O_5S$ calc.: 525,3 , resultó: 525,3.
M–24		^{1}H NMR (400 MHz, CD_3CN) δ 7,86 (d, J = 1,2 Hz, 1H), 7,82 (d, J = 1,6 Hz, 1H), 4,10 (d, J = 6,4 Hz, 2H), 4,07 (m, 2H), 3,55 (m, 2H), 3,41 (m, 2H), 3,15 (t, J = 7,2 Hz, 4H), 3,01 (m, 2H), 2,83 (m, 2H), 2,74 (m, 2H), 1,95 (m, 3H), 1,78 (m, 2H), 1,50 (s, 3H), 1,22 (m, 2H), 0,79 (m, 2H), 0,58 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{24}H_{38}N_6O_5S$ calc.: 522,3, resultó: 523,2.
M–25		^{1}H NMR (400 MHz, CD_3CN) δ 7,83 (d, J = 1,2 Hz, 1H), 7,71 (d, J = 1,6 Hz, 1H), 4,06 (d, J = 6,8 Hz, 2H), 4,00 (m, 2H), 3,59 (t, J = 12,4 Hz, 4H), 3,48 (m, 4H), 3,32 (m, 4H), 3,06 (m, 2H), 2,95 (m, 2H), 2,74 (m, 2H), 2,10 (m, 1H), 1,76 (m, 2H), 1,49 (s,

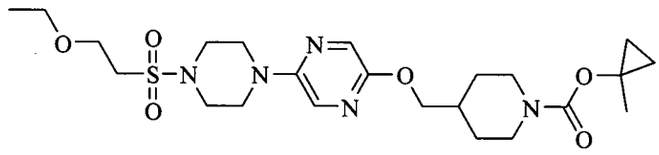
		3H), 1,17 (m, 2H), 0,79 (m, 2H), 0,59 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{24}H_{36}F_2N_6O_5S$ calc.: 558,2, resultó: 559,2.

Ejemplo M26: 1–Metilciclopropil 4–((5–(4–(vinilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



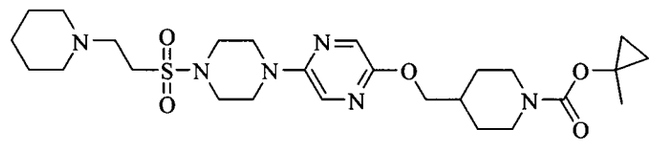
Se enfría una solución de **M1c** (308 mg, 0,82 mmol) en tetrahidrofurano (4 ml) en un baño de hielo/agua y se la trata con trietilamina (299 mg, 3,0 mmol) seguida por cloruro de 2–cloroetansulfonilo (401 mg, 2,5 mmol) agregado en un lapso de 10 minutos. Se agita la reacción por espacio de una hora y luego se la evapora y reparte entre agua y acetato de etilo. Se extrae la fase orgánica con agua dos veces más, se la seca sobre $MgSO_4$, se la filtra, evapora y purifica por gel de sílice empleando un gradiente lineal de 0–100% de acetato de etilo en hexano para producir **M26**; ^{1}H NMR (400 MHz, CD_3CN) δ 7,91 (d, J = 2,9Hz, 1H), 7,15 (dd, J = 9,1, 3,1 Hz, 1H), 6,65 (d, J = 9,1 Hz, 1H), 4,19 (m, 2H), 3,81 (d, J = 6,3 Hz, 2H), 3,54 (m, 4H), 3,34 (m, 4H), 3,08 (ddd, J = 13,1, 2,8, 2,8 Hz, 2H), 2,80 (s, 3H), 2,04 (m, 1H), 1,92 (m, 2H), 1,44 (m, 2H), 1,28 (m, 6H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{32}N_5O_5S$ calc.: 466,2, resultó: 466,2.

Ejemplo M27: 1–Metilciclopropil 4–((5–(4–(2–etoxietilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



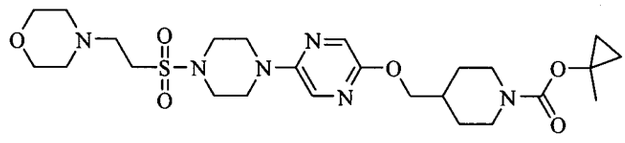
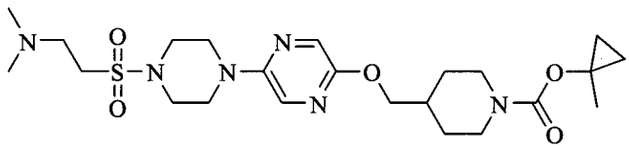
Siguiendo un procedimiento similar al utilizado para la preparación de **M20** a partir de **M6** excepto que se sustituye **M6** por **M26**, se prepara **M27**; ^{1}H NMR (400 MHz, CD_3CN) δ 7,86 (d, J = 1,5 Hz, 1H), 7,61 (d, J = 1,5 Hz, 1H), 4,18 (m, 2H), 4,07 (d, J = 6,6 Hz, 2H), 3,80 (t, J = 6,0 Hz, 2H), 3,51 (m, 6H), 3,43 (m, 4H), 3,24 (t, J = 5,9 Hz, 2H), 2,74 (dd, J = 12,3, 12,0 Hz, 2H), 1,94 (m, 1H), 1,79 (m, 2H), 1,54 (s, 3H), 1,23 (m, 2H), 1,17 (t, J = 7,0 Hz, 3H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{23}H_{38}N_5O_6S$ calc.: 512,3 , resultó: 512,6.

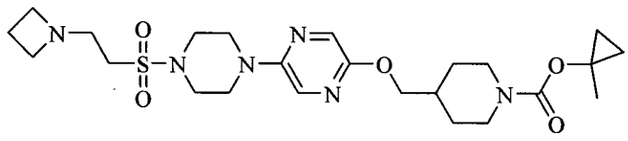
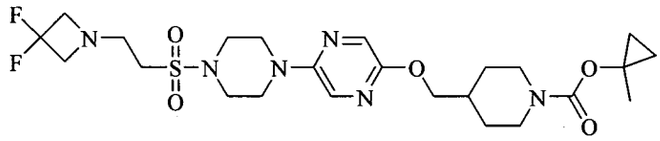
Ejemplo M28: 1–Metilciclopropil 4–((5–(4–(2–(piperidin–1–il)etilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



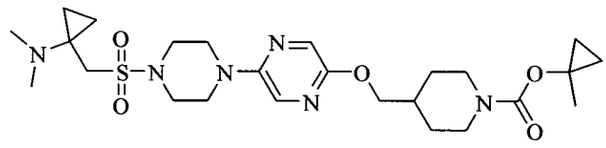
Se trata una solución de **M26** (27 mg, 0,058 mmol) en etanol (0,5 ml) con piperidina (13,3 mg, 0,12 mmol) y se la agita a temperatura ambiente de un día para otro. Se diluye la reacción con N,N–dimetilformamida y se la purifica directamente por HPLC dirigida a la masa para producir **M27**; ^{1}H NMR (400 MHz, CD_3CN) δ 7,87 (d, J = 1,4 Hz, 1H), 7,64 (d, J = 1,4 Hz, 1H), 4,19 (m, 2H), 4,07 (d, J = 6,5 Hz, 2H), 3,70 (m, 2H), 3,49 (m, 8H), 3,42 (m, 4H), 2,75 (m, 4H), 1,93 (m, 6H), 1,80 (m, 2H), 1,54 (s, 3H), 1,45 (m, 1H), 1,24 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{26}H_{43}N_6O_5S$ calc.: 551,3, resultó: 551,3.

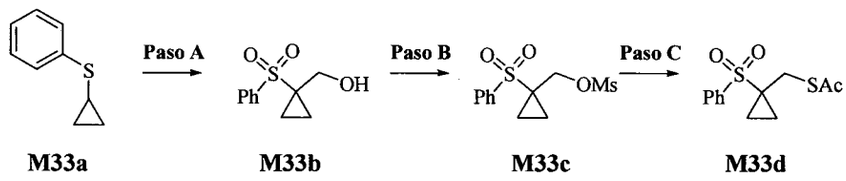
Siguiendo un procedimiento similar al utilizado para la preparación de **M28** a partir de **M26** excepto que se sustituye la piperidina por una amina existente en el comercio, se preparan los siguientes ejemplos;

Ejemplo	Estructura	Datos analíticos
M29		^{1}H NMR (400 MHz, CD_3CN) δ 7,86 (s, 1H), 7,62 (s, 1H), 4,19 (m, 2H), 4,07 (d, J = 6,5 Hz, 2H), 3,97 (m, 5H), 3,49 (m, 5H), 3,42 (m, 5H), 2,74 (m, 2H), 1,94 (m, 1H), 1,79 (m, 2H), 1,54 (s, 3H), 1,24 (m, 2H), 0,86 (m, 2H), 0,61 (m, 2); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{25}H_{41}N_6O_6S$ calc.: 553,3, resultó: 553,2.
M30		^{1}H NMR (400 MHz, CD_3CN) δ 7,88 (s, 1H), 7,64 (s, 1H), 4,18 (m, 2H), 4,07 (d, J = 6,5 Hz, 2H), 3,51 (m, 8H), 3,44 (m, 4H), 2,94 (s, 6H), 2,76 (m, 2H), 1,96 (m, 1H), 1,80 (m, 2H), 1,54 (s, 3H), 1,24 (m, 2H), 0,87 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{23}H_{39}N_6O_5S$ calc.: 511,3, resultó: 511,2.

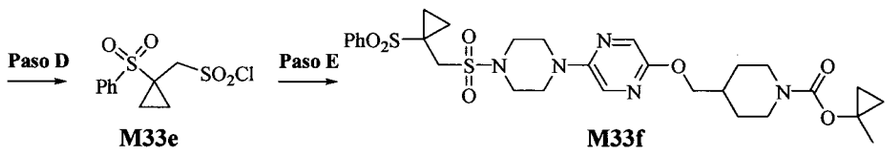
M31		^{1}H NMR (400 MHz, CD_3CN) δ 7,86 (d, J = 1,2 Hz, 1H), 7,82 (d, J = 1,6 Hz, 1H), 4,10 (d, J = 6,4 Hz, 2H), 4,07 (m, 2H), 3,55 (m, 2H), 3,41 (m, 2H), 3,15 (t, J = 7,2 Hz, 4H), 3,01 (m, 2H), 2,83 (m, 2H), 2,74 (m, 2H), 1,95 (m, 3H), 1,78 (m, 2H), 1,50 (s, 3H), 1,22 (m, 2H), 0,79 (m, 2H), 0,58 (m, 2H). ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{24}H_{38}N_6O_5S$ calc.: 522,3, resultó: 523,2,
M32		^{1}H NMR (400 MHz, CD_3CN) δ 7,83 (d, J = 1,2 Hz, 1H), 7,71 (d, J = 1,6 Hz, 1H), 4,06 (d, J = 6,8 Hz, 2H), 4,00 (m, 2H), 3,59 (t, J = 12,4 Hz, 4H), 3,48 (m, 4H), 3,32 (m, 4H), 3,06 (m, 2H), 2,95 (m, 2H), 2,74 (m, 2H), 2,10 (m, 1H), 1,76 (m, 2H), 1,49 (s, 3H), 1,17 (m, 2H), 0,79 (m, 2H), 0,59 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{24}H_{36}F_2N_6O_5S$ calc.: 558,2, resultó: 559,2.

Ejemplo M33: 1–Metilciclopropil 4–((5–(4–((1–(dimetilamino)ciclopropil)metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.

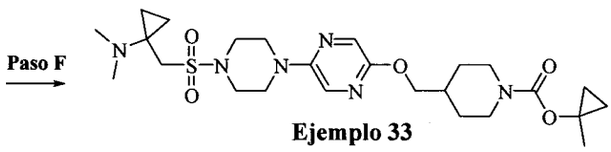




M33a M33b M33c M33d



M33e M33f



Ejemplo 33

Paso A: Se trata una solución de **M33a** (5,0 g, 33 mmol) en ácido acético (50 ml) con peróxido de hidrógeno acuoso al 30% (7,92 g de solución, 70 mmol) y se la agita a 100 °C por espacio de 1 hora. A continuación se separa el solvente y se coevapora la reacción con tolueno 3 veces..

Se enfría una muestra de **M33a** (4 g, 22 mmol) en tetrahidrofurano (40 ml) en un baño de hielo/agua y se la trata con BuLi en hexano (13,2 ml de una solución 2 M, 26 mmol) y se la agita por espacio de 20 minutos. Se trata la solución amarilla obtenida con paraformaldehído (1.65 g, 55 mmol) y se la deja agitar durante 1 hora. A continuación se inactiva la reacción con cloruro de amonio acuoso saturado y se la filtra a través de una plancha de Celite® empleando acetato de

etilo. Se aísla la fase orgánica, se la seca sobre $MgSO_4$, filtra, evapora y purifica en gel de sílice empleando un gradiente lineal de 0–100% de acetato de etilo en hexano para producir **M33b**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7,91 (m, 2H), 7,68 (m, 1H), 7,59 (m, 2H), 3,64 (d, J = 6,4 Hz, 2H), 2,72 (dd, J = 6,4, 6,4 Hz, 1H), 1,64 (m, 2H), 1,07 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{10}H_{13}O_3S$ calc,: 213,1, resultó: 213,0,

Paso B: Se trata una solución de **M33b** (4,2 g, 20 mmol) en diclorometano (40 ml) con trietilamina (3,0 g de solución, 30 mmol), se la enfría en un baño de hielo/agua y se la trata con cloruro de metansulfonilo (2,95 g, 26 mmol). Se agita la solución de un día para otro y se la deja llegar a temperatura ambiente. A continuación se inactiva la reacción con HCl acuoso 1 M y se la extrae dos veces con diclorometano. Se secan los extractos orgánicos sobre $MgSO_4$, se los filtra, evapora y tritura con éter dietílico para producir **M33c**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7,92 (m, 2H), 7,68 (m, 1H), 7,59 (m, 2H), 4,41 (s, 2H), 2,82 (s, 3H), 1,80 (m, 2H), 1,21 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{11}H_{15}O_5S_2$ calc.: 291,0, resultó: 291,0,

Paso C: Se trata una solución de **M33c** (3 g, 10 mmol) en N, N–dimetilformida (30 ml) con tioacetato de potasio (1,3 g, 11 mmol) y agua (20 ml) y se la agita a 60 °C de un día para otro. Se diluye la reacción con acetato de etilo y se la extrae con agua dos veces. Se aísla la fase orgánica, se la seca sobre $MgSO_4$, filtra, evapora y purifica en gel de sílice empleando un gradiente lineal de 0–100% de acetato de etilo en hexano para producir **M33d**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7,88 (m, 2H), 7,69 (m, 1H), 7,59 (m, 2H), 3,26 (s, 2H), 2,26 (m, 3H), 1,68 (m, 2H), 1,02 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{12}H_{15}O_3S_2$ calc,: 271,1, resultó: 271,0,

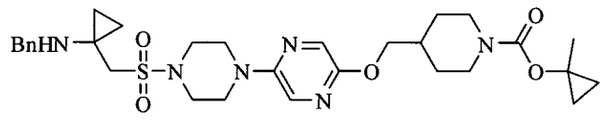
Paso D: Se trata una solución fría (baño de hielo/agua) de acetonitrilo (2,1 ml) y HCl 2 M (419 µl, 0,84 mmol) con NCS (838 mg, 6,27 mmol), se la deja agitar por espacio de 5 minutos y se la trata gota a gota con una solución de **M33d** (358 mg, 1,6 mmol) en acetonitrilo (419 µl). Al cabo de 30 minutos de agitación, se diluye la reacción con éter dietílico y se la extrae con solución salina, agua y tiosulfato de sodio saturado. Se aísla la fase orgánica, se la seca sobre sulfato de magnesio,

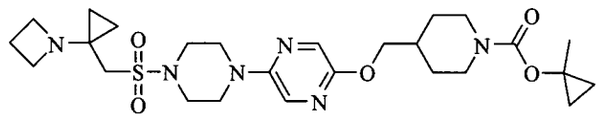
filtra y para producir **M33e**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{10}H_{12}ClO_4S_2$ calc.: 295,0, resultó: 294,9.

Paso E: Se trata una solución fría (baño de hielo/agua) de **M1c** (524 mg, 1,4 mmol) y trietilamina (282 mg, 2,8 mmol) en diclorometano (5 ml) con una solución de **M33e** (solución del crudo obtenida en el último Paso) en diclorometano. Después de 2 horas de agitación, se evapora la reacción y se la purifica en gel de sílice empleando un gradiente lineal de 0–100% de acetato de etilo en hexano para producir **M33f**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{29}H_{40}N_5O_7S_2$ calc.: 634,2, resultó: 634,2.

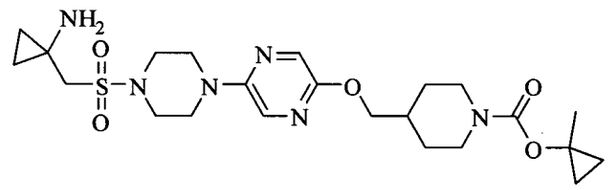
Paso F: Se trata una solución de **M33f** (157 mg, 0,25 mmol) en dimetilamina 2 M en tetrahidrofurano (2 ml, 4 mmol) con *terc*–butóxido de potasio (28 mg, 0,25 mmol) y se la agita durante 1 hora. Se evapora la reacción, se la diluye con metanol y purifica directamente por HPLC dirigida a la masa para producir **M33;** ^{1}H–NMR (400MHz, $CDCl_3$) δ 7,86 (d, *J* = 1,4 Hz, 1H), 7,61 (d, *J* = 1,4 Hz, 1H), 4,20 (m, 2H), 4,07 (d, *J* = 6,5 Hz, 2H), 3,50 (m, 4H), 3,39 (m, 4H), 3,07 (s, 2H), 2,74 (dd, *J* = 12,4, 12,3 Hz, 2H), 2,37 (s, 6H), 1,94 (m, 1H), 1,79 (m, 2H), 1,55 (s, 3H), 1,25 (m, 2H), 0,93 (m, 2H), 0,86 (m, 4H); ESIMS calc, para $C_{25}H_{41}N_6O_5S$ $[M+H]^+$ 537,3, resultó 537,4.

Siguiendo el procedimiento utilizado para **M33** utilizando los nucleófilos de amina apropiados en el Paso F, se obtienen los siguientes ejemplos:

Ejemplo	Estructura	Datos analíticos
M34		^{1}H–NMR (400MHz, $CDCl_3$) δ 7,86 (d, *J* = 1,5 Hz, 1H), 7,61 (d, *J* = 1,5 Hz, 1H), 7,31 (m, 5H), 4,14 (m, 2H), 4,09 (d, *J* = 6,5 Hz, 2H), 3,83 (s, 2H), 3,49 (m, 4H), 3,38 (m, 4H), 3,06 (s, 2H), 2,75 (m, 2H), 1,94 (m, 1H), 1,79 (m, 2H), 1,55

		(s, 3H), 1,26 (m, 2H), 0,92 (m, 2H), 0,87 (m, 2H), 0,71 (m, 2H), 0,62 (m, 2H); ESIMS calc, para $C_{30}H_{43}N_6O_5S$ $[M+H]^+$ 599,3. resultó 599,5,
M35		^{1}H–NMR (400MHz, $CDCl_3$) δ 7,86 (d, *J* = 1,4 Hz, 1H), 7,61 (d, *J* = 1,4 Hz, 1H), 3,82–4,21 (m, 6H), 4,07 (d, *J* = 6,5 Hz, 2H), 3,49 (m, 7H), 3,41 (m, 5H), 2,74 (dd, *J* = 12,5, 12,3 Hz, 2H), 1,94 (m, 1H), 1,79 (m, 2H), 1,55 (s, 3H), 1,24 (m, 6H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS calc, para $C_{26}H_{41}N_6O_5S$ $[M+H]^+$ 549,3, resultó 549,4.

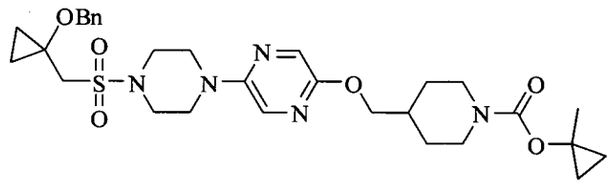
Ejemplo M36: 1–Metilciclopropil 4–((5–(4–((1–aminociclopropil)metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



Se trata una solución de **M34** (29 mg, 0,048 mmol) en etanol (1 ml) y ácido acético (0,1 ml) con Pd/C al 10% (tipo Degussa) y se la hidrogena a presión ambiente por espacio de 2 horas. Se intercambia la atmósfera por nitrógeno y se

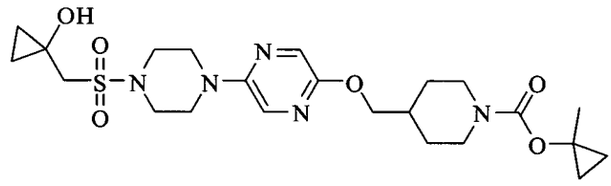
separa el catalizador mediante filtración a través de Celite®. Se diluye el material crudo con metanol y se lo purifica directamente por HPLC dirigida a la masa para producir **M36;** ^{1}H–NMR (400MHz, $CDCl_3$) δ 7,86 (d, *J* = 1,4 Hz, 1H), 7,61 (d, *J* = 1,4 Hz, 1H), 4,20 (m, 2H), 4,07 (d, *J* = 6,5 Hz, 2H), 3,50 (m, 4H), 3,39 (m, 4H), 3,07 (s, 2H), 2,74 (dd, *J* = 12,4, 12,3 Hz, 2H), 2,37 (s, 6H), 1,94 (m, 1H), 1,79 (m, 2H), 1,55 (s, 3H), 1,25 (m, 2H), 0,93 (m, 2H), 0,86 (m, 4H); ESIMS calc, para $C_{23}H_{37}N_6O_5S$ $[M+H]^+$ 509,3, resultó 509,5.

Ejemplo M37: 1–metilciclopropil 4–((5–(4–((1–(benciloxi)ciclopropil)metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



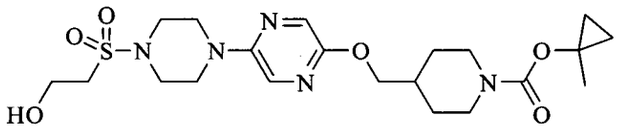
Se trata una solución de **M33f** (147 mg, 0,23 mmol) en alcohol bencílico (1 ml) con hidruro de sodio (12 mg, 0,5 mmol) y se la agita por espacio de 24 horas. Se purifica la reacción directamente por HPLC dirigida a la masa para producir **M37**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 7,84 (d, *J* = 1,4 Hz, 1H), 7,56 (d, *J* = 1,4 Hz, 1H), 7,25 (m, 5H), 4,55 (s, 2H), 4,20 (m, 2H), 4,07 (d, *J* = 6,5 Hz, 2H), 3,46 (m, 8H), 3,31 (s, 2H), 2,75 (dd, *J* = 12,3, 12,3 Hz, 2H), 1,94 (m, 1H), 1,80 (m, 2H), 1,54 (s, 3H), 1,25 (m, 2H), 1,08 (m, 2H), 0,87 (m, 4H), 0,62 (m, 2H); ESIMS calc, para $C_{30}H_{42}N_5O_6S$ $[M+H]^+$ 600,3, resultó 600,5.

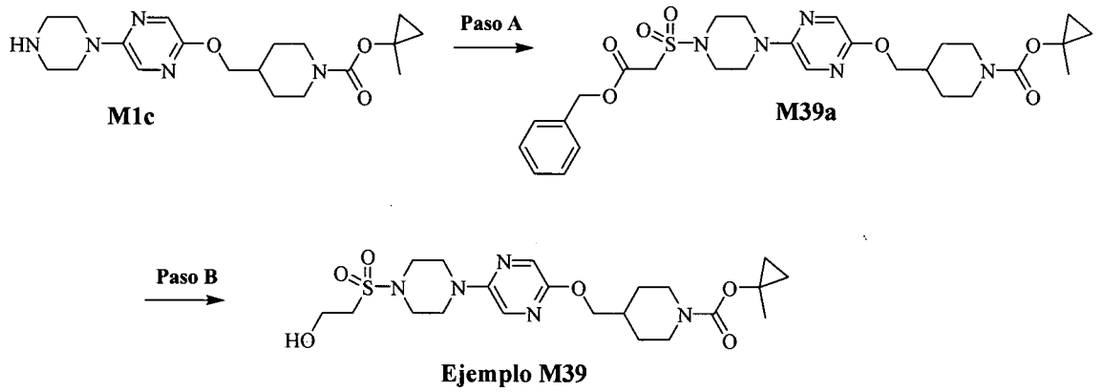
Ejemplo M38: 1–Metilciclopropil 4–((5–(4–((1–hidroxiciclopropil)metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



Se trata una solución de **M33f** (11,6 mg, 0,018 mmol) en tetrahidrofurano (0,5 ml) con *terc*–butóxido de potasio (2 mg, 0,02 mmol) y se la agita por espacio de 5 minutos. A continuación se trata la reacción con agua (50 µl) y trimetilfosfina (9 µl de una solución 1 M en tetrahidrofurano, 0,009 mmol) y se la agita a 45 °C de un día para otro. Se diluye la reacción con acetato de etilo y se la lava con agua. Se secan la fase orgánica sobre $MgSO_4$, se la filtra, evapora y purifica por HPLC dirigida a la masa para producir **M38**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 7,87 (s, 1H), 7,62 (s, 1H), 4,18 (m, 2H), 4,07 (d, *J* = 6,5 Hz, 2H), 3,51 (m, 8H), 3,21 (s, 2H), 2,75 (dd, *J* = 12,4, 12,4 Hz, 2H), 2,34 (bs, 1H), 1,94 (m, 1H), 1,79 (m, 2H), 1,54 (s, 3H), 1,28 (m, 2H), 1,10 (m, 2H), 0,86 (m, 4H), 0,62 (m, 2H); ESIMS calc, para $C_{23}H_{36}N_5O_6S$ $[M+H]^+$ 510,2, resultó 510,4.

Ejemplo M39: 1–Metilciclopropil 4–((5–(4–(2–hidroxietilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato



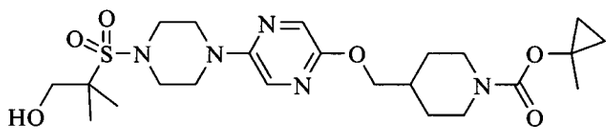


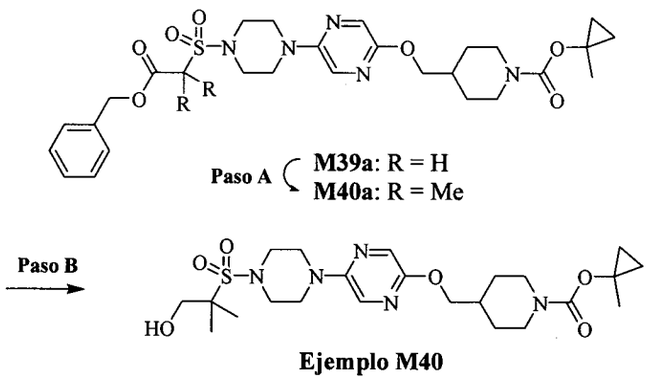
Ejemplo M39

Paso A: Siguiendo un procedimiento similar al utilizado para la preparación de **M1** a partir de **M1c** excepto que se sustituye metil 3–(clorosulfonil)propanoato por bencil 2–(clorosulfonil)acetato, se prepara **M39a**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{28}H_{38}N_5O_7S$ calc.: 588,3, resultó: 588,2.

Paso B: Se trata una solución de **M39a** (20 mg, 0,034 mmol) en metanol (3 ml) con borohidruro de sodio (13 mg, 0,34 mmol) y se la calienta a 80 °C por espacio de 2 horas. Se enfría la mezcla, se la diluye con agua y se la extrae con acetato de etilo. Se lava la capa orgánica con solución salina, se la seca ($MgSO_4$) filtra, concentra y purifica empleando HPLC de fase inversa iniciada por la masa para producir **M39**; ^1H NMR (400 MHz, $CDCl_3$) δ 7,89 (d, J = 1,6 Hz, 1H), 7,64 (d, J = 1,6 Hz, 1H), 4,11 (s, 4H), 3,54 (m, 4H), 3,47 (m, 4H), 3,21 (m, 2H), 2,77 (m, 2H), 1,96 (m, 1H), 1,82 (m, 2H), 1,57 (s, 3H), 1,28 (m, 2H), 0,89 (m, 2H), 0,65 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{34}N_5O_6S$ calc.: 484,2, resultó: 484,2.

Ejemplo M40: 1–Metilciclopropil 4–((5–(4–(1–hidroxi–2–metilpropan–2–ilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



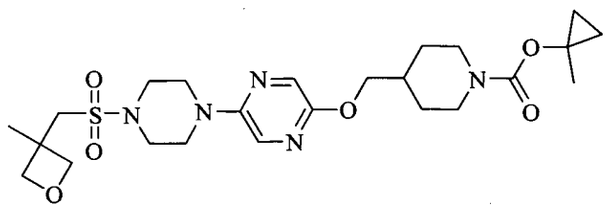


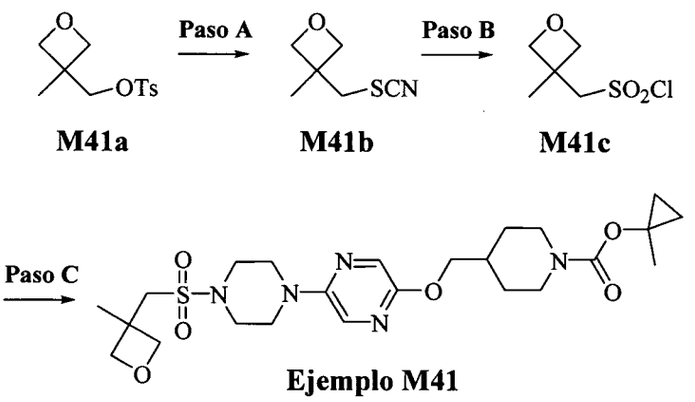
Ejemplo M40

Paso A: Se trata una solución de **M39a** (40 mg, 0,068 mmol) en dimetilformamida (2 ml) con carbonato de potasio (50 mg, 0,36 mmol) y yoduro de metilo (46 mg, 0,32 mmol) y se la calienta a 60 °C por espacio de 2 horas. A continuación se reparte la reacción entre acetato de etilo y agua. Se lava la fase orgánica con agua y solución salina, se la seca sobre $MgSO_4$, filtra y evapora y se la utiliza cruda para el siguiente Paso; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{30}H_{42}N_5O_7S$ calc.: 616,3, resultó: 616,3.

Siguiendo un procedimiento similar al utilizado para la preparación de **M39** a partir de **M39a** excepto que se sustituye **M39a** por **M40a**, se prepara **M40**; ^1H NMR (400 MHz, $CDCl_3$) δ 7,89 (d, J = 1,6 Hz, 1H), 7,62 (d, J = 1,6 Hz, 1H), 4,10 (d, J = 6,4 Hz, 2H), 3,75 (s, 2H), 3,59 (m, 4H), 3,48 (m, 4H), 2,76 (m, 2H), 1,97 (m, 1H), 1,81 (m, 2H), 1,57 (s, 3H), 1,40 (m, 6H), 1,27 (m, 2H), 0,89 (m, 2H), 0,64 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{23}H_{38}N_5O_6S$ calc.: 512,3, resultó: 512,2.

Ejemplo M41: 1–Metilciclopropil 4–((5–(4–((3–metiloxetan–3–il)metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.





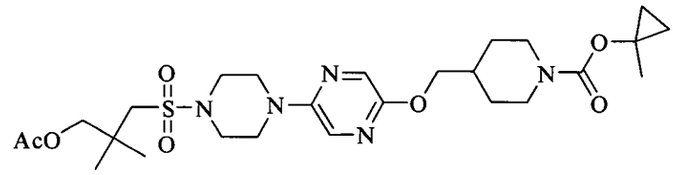
Ejemplo M41

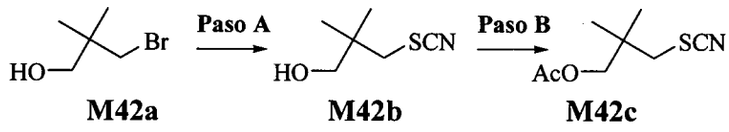
Paso A: Se trata una solución de **M41a** (1.01 g, 3,9 mmol) en etanol (25 ml) con tiocianato de potasio (767 mg, 7,9 mmol) y se la agita a reflujo de un día para otro. A continuación se separa el solvente para producir **M41b** que es utilizado crudo. ESIMS *m/z* correspondiente a $(M+H)^+$ $C_6H_{10}NOS$ calc.: 144,1, resultó: 144,0,

Paso B: Se enfría una suspensión de **M41b** (cruda del Paso A) en agua (5 ml) en un baño de hielo/agua y se la trata con una corriente lenta de gas cloro por espacio de 30 minutos. A continuación se extrae la reacción con éter dietílico y se lavan los extractos orgánicos con una solución acuosa saturada de bisulfato de sodio seguida por una solución acuosa saturada de hidrogenocarbonato de sodio. Seguidamente se secan los extractos orgánicos sobre Na_2SO_4, se los filtra y evapora para producir **M41b** que fue utilizado crudo en la siguiente reacción; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_5H_{10}ClO_3S$ calc.: 185,0, resultó: 185,0,

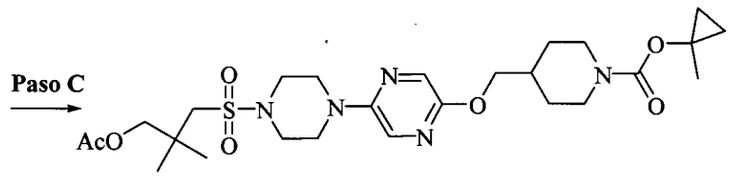
Paso C: Siguiendo un procedimiento similar al utilizado para la preparación de **M1** a partir de **M1c** excepto que se sustituye metil 3–(clorosulfonil)propanoato por **M41c**, se prepara **M41**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 7,87 (d, *J* = 1,4 Hz, 1H), 7,62 (d, *J* = 1,5 Hz, 1H), 4,64 (d, *J* = 6,3 Hz, 2H), 4,46 (d, *J* = 6,4 Hz, 2H), 4,22 (m, 2H), 4,08 (d, *J* = 6,6 Hz, 2H), 3,53 (m, 4H), 3,40 (m, 4H), 3,25 (s, 2H), 2,74 (dd, *J* = 12,4, 12,4 Hz, 2H), 1,94 (m, 1H), 1,79 (m, 2H), 1,65 (s, 3H), 1,55 (s, 3H), 1,25 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS calc, para $C_{24}H_{38}N_5O_6S$ $[M+H]^+$ 524,3, resultó 524,2.

Ejemplo M42: 1–Metilciclopropil 4–((5–(4–(3–acetoxi–2,2–dimetilpropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.





M42a **M42b** **M42c**



Ejemplo M42

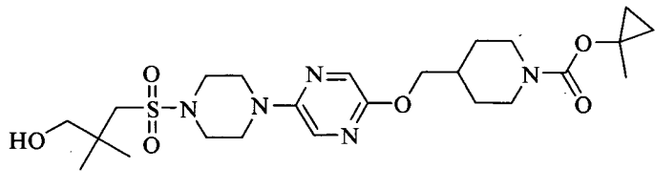
Paso A: Se trata una solución de **M42a** (2 g, 12 mmol) en N,N–dimetilformamida (7,2 ml) con tiocianato de potasio (1,75 g, 18 mmol) y se la agita a 140 °C por espacio de 4 horas. Se enfría la reacción a temperatura ambiente y se la reparte entre éter dietílico y agua. Se extrae la fase acuosa con éter dietílico una vez más y se la descarta. Se secan los extractos orgánicos combinados sobre $MgSO_4$, se los filtra, evapora y destila en un aparato Kugelrohr para producir **M42b**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_6H_{12}NOS$ calc.: 146,1, resultó: 146,1.

Paso B: Se enfría una solución de **M42b** (1,54 g, 10,6 mmol) en piridina (10 ml) en un baño de hielo/agua y se la trata con anhídrido acético (10 ml). Se deja agitar la reacción de un día para otro al fundir el baño de hielo. Se separa el solvente y se reparte el residuo entre acetato de etilo y agua. Se lavan los extractos orgánicos con HCl 1 M dos veces y luego con una solución acuosa saturada de hidrogenocarbonato de sodio. A continuación se secan los extractos

orgánicos sobre $MgSO_4$, se los filtra y evapora para producir **M42c** que fue utilizado crudo en la siguiente reacción; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_8H_{14}NO_2S$ calc.: 188,1, resultó: 188,1.

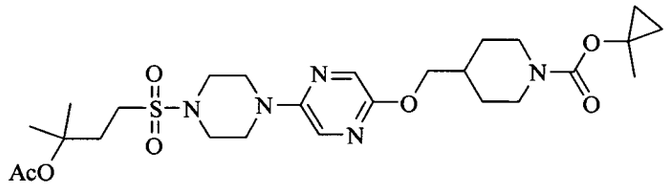
Paso C: Siguiendo un procedimiento similar al utilizado para la preparación de **M41** a partir de **M41b** excepto que se sustituye **M41b** por **M42c**, se obtiene **M42**; ^1H NMR (400 MHz, CD_3CN) δ 7,86 (d, J = 1,4 Hz, 1H), 7,61 (d, J = 1,4 Hz, 1H), 4,19 (m, 2H), 4,07 (d, J = 6,5 Hz, 2H), 4,00 (s, 2H), 3,50 (m, 5H), 3,37 (m, 4H), 2,86 (s, 2H), 2,73 (dd, J = 12,4, 12,3 Hz, 2H), 2,08 (s, 3H), 1,94 (m, 1H), 1,79 (m, 2H), 1,54 (s, 3H), 1,27 (m, 2H), 1,22 (s, 6H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{26}H_{42}N_5O_7S$ calc.: 568,3 , resultó: 568,4.

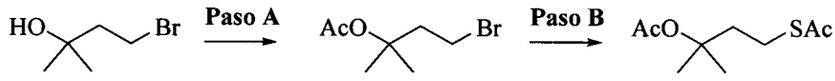
Ejemplo M43: 1–Metilciclopropil 4–((5–(4–(3–hidroxi–2,2–dimetilpropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



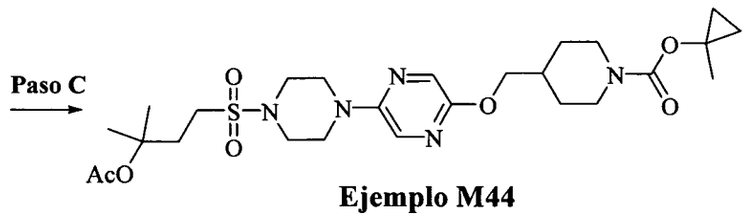
Paso A: Se trata una solución de **M42** (48 mg, 0,085 mmol) en tetrahidrofurano (1,5 ml) con hidróxido de litio (7 mg, 0,17 mmol) y se la agita durante 1 día. Se separa el solvente y se purifica el residuo en gel de sílice empleando un gradiente lineal de 0–100% de acetato de etilo en hexano para producir **M43;** ^1H NMR (400 MHz, CD_3CN) δ 7,89 (d, J = 1,4 Hz, 1H), 7,67 (s, 1H), 4,36 (s, 2H), 4,17 (m, 2H), 4,07 (d, J = 6,5 Hz, 2H), 3,51 (m, 4H), 3,37 (m, 4H), 2,87 (s, 2H), 2,76 (dd, J = 12,2, 11,6 Hz, 2H), 1,94 (m, 2H), 1,80 (m, 2H), 1,53 (s, 3H), 1,26 (m, 2H), 1,24 (s, 6H), 1,14 (s, 1H), 0,87 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{24}H_{40}N_5O_6S$ calc.: 526,3 , resultó: 526,2.

Ejemplo M44: 1–Metilciclopropil 4–((5–(4–(3–acetoxi–3–metilbutilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.





M44a **M44b** **M44c**



Ejemplo M44

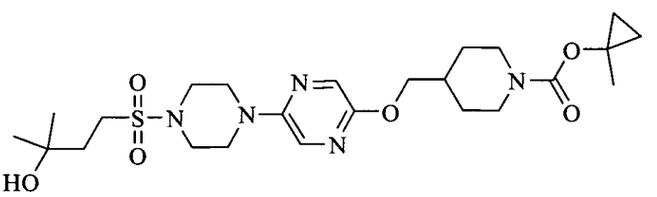
Paso A: Se enfría una solución de **M44a** (1,48 g, 8,9 mmol) en diclorometano (49 ml) en un baño de hielo/agua y se la trata con piridina (913 mg, 12 mmol) y acetil cloruro (868 mg, 11 mmol) y se deja que la reacción se agita de un día para otro al fundir el baño de hielo. A continuación se inactiva con agua la reacción. Se aísla la fase orgánica, se la seca sobre $MgSO_4$, se la filtra, evapora y se purifica el residuo en gel de sílice empleando un gradiente lineal de 0–100% de acetato de etilo en hexano para producir **M44b**; No se pudo obtener una ESIMS satisfactoria.

Paso B: Se enfría una solución de **M44b** (750 mg, 3,6 mmol) en N,N–dimetilfromamida (10 ml) en un baño de hielo/agua y se la trata con tioacetato de potasio (410 mg, 3,6 mmol). Se agita la reacción de un día para otro y se la reparte entre acetato de etilo y agua. Se extraen los extractos orgánicos con agua una vez más, se los seca sobre $MgSO_4$, filtra y evapora para producir **M44c**

que es utilizado crudo en el siguiente Paso; ESIMS *m/z* correspondiente a $(M+Na)^+$ $C_9H_{16}NaO_3S$ calc.: 227,1, resultó: 227,0;

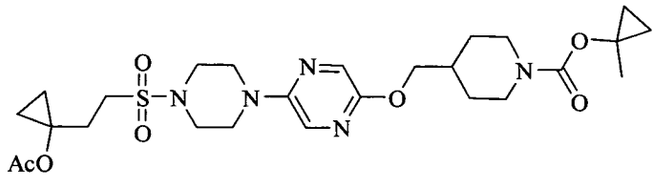
Paso C: Siguiendo un procedimiento similar al utilizado para la preparación de **M32** a partir de **M32d** excepto que se sustituye **M32d** por **M44c**, se prepara **M44**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 7,86 (d, *J* = 1,4 Hz, 1H), 7,61 (d, *J* = 1,5 Hz, 1H), 4,20 (m, 2H), 4,07 (d, *J* = 6,5 Hz, 2H), 3,50 (m, 4H), 3,44 (m, 4H), 3,02 (m, 2H), 2,74 (dd, *J* = 13,2, 12,6 Hz, 2H), 2,22 (m, 2H), 1,98 (s, 3H), 1,96 (m, 1H), 1,80 (m, 2H), 1,55 (s, 3H), 1,48 (s, 6H), 1,25 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS calc, para $C_{24}H_{38}N_5O_5S$ $[M–OAc]^+$ 508,3, resultó 508,4.

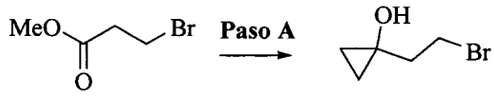
Ejemplo M45: 1–Metilciclopropil 4–((5–(4–(3–hidroxi–3–metilbutilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



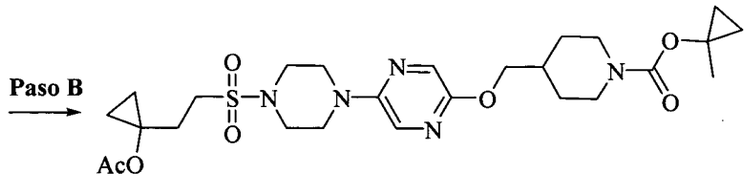
Se trata una solución de **M44** (199 mg, 0,35 mmol) en metanol (3,9 ml) con NaOMe (1,1 ml de una solución 6,4M, 7 mmol) y se la agita durante 2,5 horas. Se inactiva la reacción con cloruro de amonio acuoso saturado y se separa el solvente. Se disuelve el residuo en diclorometano y se lo lava con agua, se lo seca sobre $MgSO_4$, filtra, evapora y se purifica el residuo en gel de sílice empleando un gradiente lineal de 0–100% de acetato de etilo en hexano para producir **M45**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 7,86 (d, *J* = 1,5 Hz, 1H), 7,62 (d, *J* = 1,5Hz, 1H), 4,20 (m, 2H), 4,07 (d, *J* = 6,5 Hz, 2H), 3,50 (m, 4H), 3,44 (m, 4H), 3,09 (m, 2H), 2,74 (dd, *J* = 12,9, 12,7 Hz, 2H), 1,92–2,01 (m, 3H), 1,79 (m, 2H), 1,55 (s, 3H), 1,27 (m, 8H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS calc. para $C_{24}H_{40}N_5O_6S$ $[M+H]^+$ 526,3, resultó 526,2.

Ejemplo M46: 1–Metilciclopropil 4–((5–(4–(2–(1–acetoxiciclopropil)etilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.





M46a **M46b**



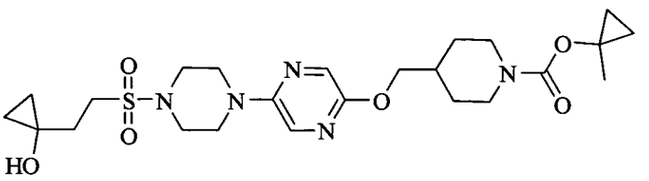
Ejemplo M46

Paso A: Se trata una solución de **M46a** (1.99 g, 12 mmol) en éter dietílico (40 ml) con isopropóxido de titanio(IV) (369 mg, 1,2 mmol) seguido por la adición gota a gota de bromuro de etilmagnesio (8,8 ml de una solución 3 M en éter dietílico, 26 mmol). Se inactiva la reacción en ácido sulfúrico helado al 10 % y se extrae la fase acuosa con éter una vez más. Se secan los extractos orgánicos combinados sobre $MgSO_4$, se los filtra y evapora y se purifica el residuo en gel de sílice empleando un gradiente lineal de 0–100% de acetato de etilo en hexano para producir **M46b**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 3,60 (dd, *J* = 7,3, 7,3 Hz, 2H), 2,41 (s, 1H), 2,10 (dd, *J* = 7,3, 7,3 Hz, 2H), 0,78 (m, 2H), 0,52 (m, 2H); No se pudo obtener un espectro de ESIMS satisfactorio.

Paso B: Siguiendo un procedimiento similar al utilizado para la preparación de **M33** a partir de **M33c** excepto que se sustituye **M33c** por **M46b**, se prepara **M46**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 7,86 (d, *J* = 1,4 Hz, 1H), 7,61 (d, *J* = 1,4 Hz, 1H), 4,20 (m, 2H), 4,07 (d, *J* = 6,5 Hz, 2H), 3,49 (m, 4H), 3,41 (m, 4H), 3,11 (ddd, *J* =

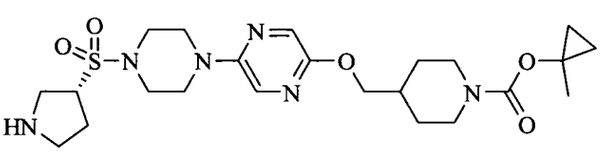
8,2, 5,2, 5,2 Hz, 2H), 2,74 (dd, *J* = 12,2, 12,0 Hz, 2H), 2,25 (ddd, J = 8,2, 4,7, 4,7 Hz, 2H), 2,00 (s, 3H), 1,94 (m, 1H), 1,79 (m, 2H), 1,54 (s, 3H), 1,25 (m, 2H), 0,93 (m, 2H), 0,86 (m, 2H), 0,76 (m, 2H), 0,62 (m, 2H); ESIMS calc, para $C_{26}H_{40}N_5O_7S$ $[M+H]^+$ 566,3, resultó 566,4.

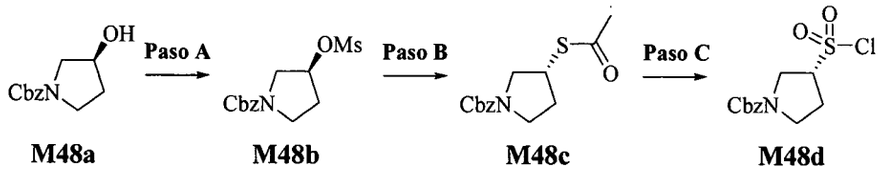
Ejemplo M47: 1–Metilciclopropil 4–((5–(4–(2–(1–hidroxiciclopropil)etilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



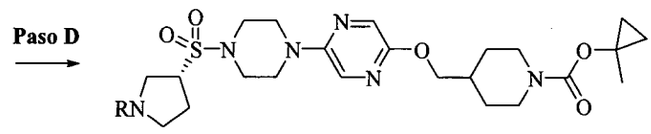
Siguiendo un procedimiento similar al utilizado para la preparación de **M43** a partir de **M42** excepto que se sustituye **M42** por **M46**, se prepara **M47**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 7,87 (d, *J* = 1,5 Hz, 1H), 7,62 (d, *J* = 1,4 Hz, 1H), 4,19 (m, 2H), 4,08 (d, *J* = 6,5 Hz, 2H), 3,51 (m, 4H), 3,43 (m, 4H), 3,21 (m, 2H), 2,74 (dd, *J* = 12,3, 12,3 Hz, 2H), 2,27 (bs, 1H), 2,08 (m, 2H), 1,94 (m, 1H), 1,79 (m, 2H), 1,55 (s, 3H), 1,25 (m, 2H), 0,86 (m, 4H), 0,62 (m, 2H), 0,56 (m, 2H); ESIMS calc, para $C_{24}H_{38}N_5O_6S$ $[M+H]^+$ 524,3, resultó 524,5.

Ejemplo M48: (R)–1–metilciclopropil 4–((5–(4–(pirrolidin–3–ilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato





M48a **M48b** **M48c** **M48d**



Paso E **M48e**: R=Cbz
Ejemplo M48: R=H

Paso A: Se enfría una solución de **M48a** (10 g, 45,2 mmol) en diclorometano (200 ml) en un baño de hielo/agua y se la trata con diisopropiletilamina (9,4 ml, 54,3 mmol) seguida por la adición gota a gota de cloruro de metansulfonilo (3,8 ml, 50 mmol). Se agita la solución así obtenida a 0 °C por espacio de 1 hora, se la concentra y purifica en gel de sílice empleando un gradiente lineal de 0–100% de acetato de etilo en hexano para producir **M48b**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{13}H_{18}NO_5S$ calc.: 300,1, resultó: 300,0.

Paso B: Se trata una solución de **M48b** (14,1 g, 45 mmol) y ácido tiolacético (6,4 ml, 90 mmol) en dimetilformamida (200 ml) con Cs_2CO_3 (30 g, 90 mmol) y se la calienta a 60 °C por espacio de 14 horas. Se diluye la mezcla con agua y se la extrae con acetato de etilo (3x). Se combinan las capas orgánicas, se las lava con agua (2x) y solución salina, se las seca sobre $MgSO_4$, filtra, concentra y purifica en gel de sílice empleando un gradiente lineal de 0–100% de acetato de etilo en hexano para producir **M48c**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{14}H_{18}NO_3S$ calc.: 280,1, resultó: 280,0,

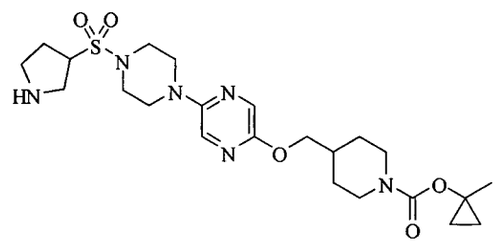
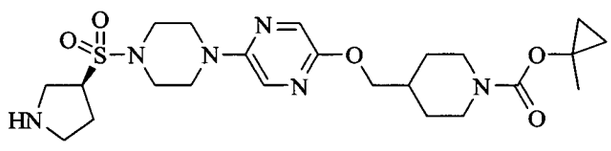
Paso C: Se enfría una solución de N–clorosuccinimida (16,7 g, 125 mmol) en HCl 2N (24 ml) y acetonitrilo (120 ml) en un baño de hielo/agua y se la trata gota a gota con una solución de **M48c** (9,2 g, 31 mmol) en acetonitrilo (20 ml) en el curso de 1 hora. Se concentra la solución y se la reparte entre acetato de etilo y una solución acuosa saturada de hidrogenocarbonato de sodio. Se lava la capa orgánica con tiosulfato de sodio acuoso y solución salina, se la seca ($MgSO_4$) y

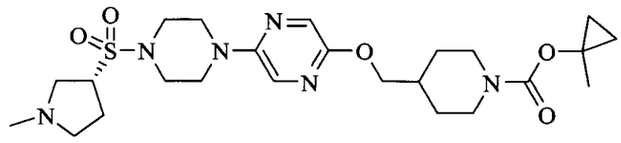
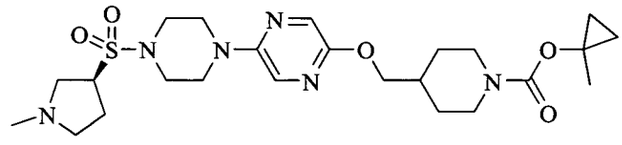
concentra para producir **M48d** en forma de aceite dorado; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{12}H_{15}ClNO_4S$ calc.: 304,0, resultó: 304,0,

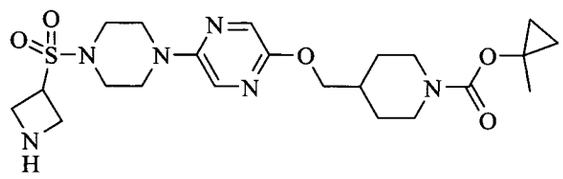
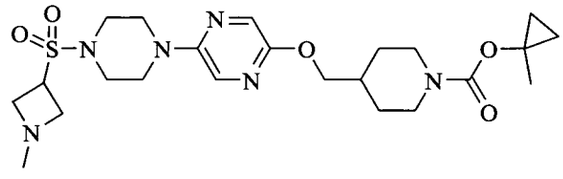
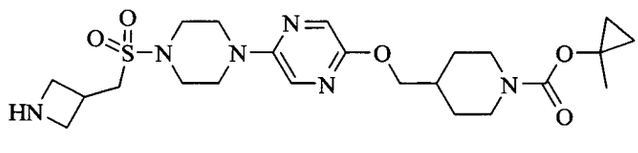
Paso D: Se trata una solución de **M1c** (74 mg, 0,2 mmol) y **M48d** (67 mg, 0,22 mmol) en diclorometano (5 ml) con diisopropiletilamina (69 µl, 0,4 mmol) y se la agita a temperatura ambiente por espacio de 3 horas. Se concentra la mezcla y se la purifica en gel de sílice empleando 0–100% de acetato de etilo en hexano para producir **M48e**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{31}H_{43}N_6O_7S$ calc.: 643,3, resultó: 643,2.

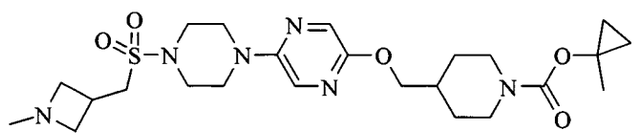
Paso E: Se trata una solución de **M48e** (104 mg, 0,16 mmol) en metanol (10 ml) con Pd/C (al 10%, húmedo) y se la agita bajo 1 atm de H_2 por espacio de 14 horas. Se filtra la mezcla a través de Celite®, se la concentra y purifica en gel de sílice empleando 0–10% de MeOH en diclorometano para producir **M48**: ^1H NMR (400 MHz, $CDCl_3$) δ 7,79 (d, J = 1,2 Hz, 1H), 7,54 (d, J = 1,2 Hz, 1H), 4,01 (d, J = 4,8 Hz, 2H), 3,52 (m, 1H), 3,40 (m, 9H), 3,14 (m, 1H), 3,07 (dd, J = 5,2, 8,4 Hz, 1H), 2,80 (m, 1H), 2,67 (m, 2H), 2,08 (m, 2H), 1,98 (s, 2H), 1,87 (m, 1H), 1,72 (m, 2H), 1,48 (s, 3H), 1,18 (m, 2H), 0,79 (m, 2H), 0,55 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{23}H_{37}N_6O_5S$ calc.: 509,3, resultó: 509,2.

Siguiendo el procedimiento para la preparación de **M48** a partir de **M48a** utilizando los alcoholes de partida apropiados existentes en el comercio en lugar de **M48a** y, en algunos casos efectuando metilaciones reductivas, se preparan los siguientes ejemplos;

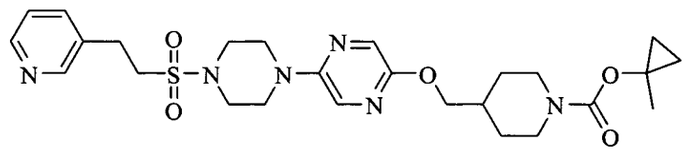
Ejemplo	Estructura	Datos analíticos
M49		^{1}H NMR (400 MHz, CD_3CN) δ 7,82 (d, J = 1,6 Hz, 1H), 7,70 (d, J = 1,6 Hz, 1H), 4,06 (d, J = 6,8 Hz, 2H), 4,00 (m, 2H), 3,63 (m, 1H), 3,46 (m, 4H), 3,36 (m, 4H), 3,12 (m, 2H), 2,95 (m, 1H), 2,77 (m, 3H), 2,10 (m, 5H), 1,76 (m, 2H), 1,73 (s, 3H), 1,18 (m, 2H), 0,79 (m, 2H), 0,59 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{23}H_{37}N_6O_5S$ calc.: 509,3, resultó: 509,2.
M50		^{1}H NMR (400 MHz, $CDCl_3$) δ 7,79 (d, J = 0,8 Hz, 1H), 7,54 (d, J = 0,8 Hz, 1H), 4,01 (d, J = 4,8 Hz, 2H), 3,53 (m, 1H), 3,40 (m, 9H), 3,14 (m, 1H), 3,08 (dd, J = 5,2, 8,4 Hz, 1H), 2,81 (m, 1H), 2,68 (m, 2H), 2,08 (m, 2H), 2,00 (s, 2H), 1,87 (m, 1H), 1,72 (m, 2H), 1,48 (s, 3H), 1,18 (m, 2H), 0,79 (m, 2H), 0,55 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{23}H_{37}N_6O_5S$ calc.: 509,3, resultó: 509,2.

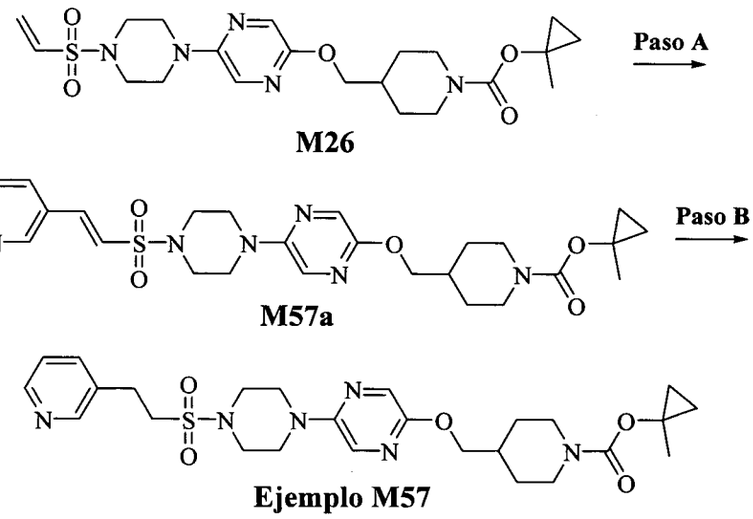
M51		^{1}H NMR (400 MHz, $CDCl_3$) δ 7,79 (d, J = 1,2 Hz, 1H), 7,54 (d, J = 1,2 Hz, 1H), 4,01 (d, J = 4,8 Hz, 2H), 3,64 (m, 1H), 3,40 (m, 8H), 2,87 (m, 1H), 2,73 (m, 1H), 2,67 (m, 2H), 2,61 (m, 1H), 2,31 (s, 3H), 2,00 (m, 2H), 1,98 (s, 2H), 1,72 (m, 2H), 1,48 (s, 3H), 1,18 (m, 2H), 0,79 (m, 2H), 0,55 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{24}H_{39}N_6O_5S$ calc.: 523,3, resultó: 523,2.
M52		^{1}H NMR (400 MHz, $CDCl_3$) δ 7,79 (d, J = 1,2 Hz, 1H), 7,54 (d, J = 1,2 Hz, 1H), 4,01 (d, J = 4,8 Hz, 2H), 3,64 (m, 1H), 3,40 (m, 8H), 2,87 (m, 1H), 2,73 (m, 1H), 2,67 (m, 2H), 2,61 (m, 1H), 2,31 (s, 3H), 2,00 (m, 2H), 1,98 (s, 2H), 1,72 (m, 2H), 1,48 (s, 3H), 1,18 (m, 2H), 0,79 (m, 2H), 0,55 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{24}H_{39}N_6O_5S$ calc.: 523,3, resultó: 523,2.

M53		^{1}H NMR (400 MHz, $CDCl_3$) δ 7,78 (d, J = 1,0 Hz, 1H), 7,53 (d, J = 1,0 Hz, 1H), 4,09 (m, 1H), 4,05 (m, 2H), 4,01 (d, J = 4,4 Hz, 2H), 3,40 (m, 4H), 3,38 (m, 4H), 2,67 (m, 2H), 1,94 (br s, 1H), 1,87 (m, 1H), 1,71 (m, 2H), 1,48 (s, 3H), 1,18 (m, 2H), 0,79 (m, 2H), 0,55 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{22}H_{35}N_6O_5S$ calc.: 495,2, resultó: 495,2.
M54		^{1}H NMR (400 MHz, $CDCl_3$) δ 7,79 (d, J = 0,8 Hz, 1H), 7,53 (d, J = 0,8 Hz, 1H), 4,00 (d, J = 4,4 Hz, 2H), 3,85 (m, 1H), 3,57 (m, 2H), 3,41 (m, 4H), 3,34 (m, 4H), 2,67 (m, 2H), 2,29 (s, 3H), 1,87 (m, 1H), 1,72 (m, 2H), 1,48 (s, 3H), 1,18 (m, 2H), 0,79 (m, 2H), 0,55 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{23}H_{37}N_6O_5S$ calc.: 509,3, resultó: 509,2.
M55		^{1}H NMR (400 MHz, $CDCl_3$) δ 7,79 (d, J = 1,4 Hz, 1H), 7,53 (d, J = 1,4 Hz, 1H), 4,01 (d, J = 6,8 Hz, 2H), 3,75 (m, 2H), 3,43 (m, 6H), 3,33 (m, 4H), 3,16 (m,

		2H), 2,67 (m, 2H), 1,87 (m, 1H), 1,72 (m, 2H), 1,48 (s, 3H), 1,18 (m, 3H), 0,79 (m, 2H), 0,54 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{23}H_{37}N_6O_5S$ calc.: 509,3, resultó: 509,2
M56		^{1}H NMR (400 MHz, $CDCl_3$) δ 7,79 (d, J = 1,6 Hz, 1H), 7,53 (d, J = 1,6 Hz, 1H), 4,01 (d, J = 6,8 Hz, 2H), 3,42 (m, 6H), 3,33 (m, 4H), 3,14 (d, J = 7,2 Hz, 2H), 2,98 (m, 2H), 2,69 (m, 2H), 2,25 (s, 3H), 1,87 (m, 1H), 1,72 (m, 2H), 1,48 (s, 3H), 1,18 (m, 3H), 0,80 (m, 2H), 0,54 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{24}H_{39}N_6O_5S$ calc.: 523,3, resultó: 523,2

Ejemplo M57: 1–Metilciclopropil 4–((5–(4–(2–(piridin–3–il)etilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato

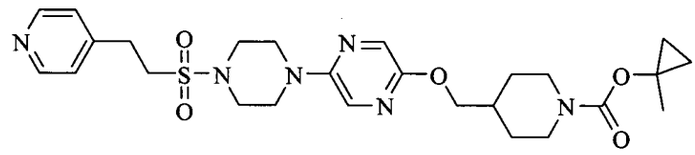




Paso A: Se calienta un recipiente hermético que contiene **M26** (50 mg, 0,11 mmol), 3–bromopiridina (10 µl, 0,11 mmol), Pd_2dba_3 (3,0 mg, 0,0032 mmol), tetrafluoroborato de tri–butilfosfonio (2,0 mg, 0,0064 mmol), diciclohexilmetilamina (45 ml, 0,21 mmol), y dioxano (1 ml) a 120 °C de un día para otro. Se enfría la reacción a temperatura ambiente y se la diluye con agua y se la extrae con acetato de etilo. Se seca la fase orgánica sobre $MgSO_4$, se la filtra, evapora y purifica en gel de sílice empleando un gradiente lineal de 0 a 100% de acetato de etilo en diclorometano para producir **M57a**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{26}H_{34}N_6O_5S$ calc.: 543.2 , resultó: 543.2.

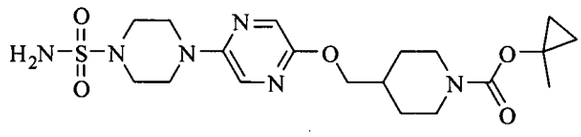
Paso B: Se rocía H_2 (g)sobre una solución de **M57a** del Paso anterior en etanol (1ml) por espacio de 30 minutos y luego se la deja bajo atmósfera de H_2 (g) de un día para otro. Se filtra la reacción a través de Celite®, se la concentra y purifica por HPLC dirigida a la masa empleando un gradiente lineal de 10 a 90% de acetonitrilo in agua para producir **M57**; ^1H NMR ($CDCl_3$, 400 MHz): δ 8,79 (s, 1H), 8,65 (m, 1H), 8,09 (m, 1H), 7,86 (d, J = 1,4 Hz, 1H), 7,68 (m, 1H), 7,61 (d, J = 1,4 Hz, 1H), 4,20 (m, 2H), 4,08 (d, J = 6,5 Hz, 2H), 3,50 (m, 4H), 3,42 (m, 2H), 3,33 (m, 2H), 3,24 (m, 2H), 2,74 (m, 2H), 1,79 (m, 2H), 1,55 (s, 3H), 1,25 (m, 3H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{26}H_{37}N_6O_5S$ calc.,: 545,3, resultó: 545,3.

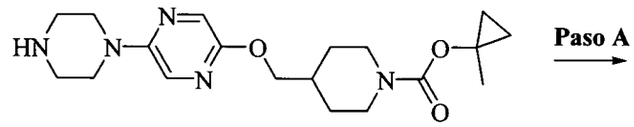
Ejemplo M58: 1–Metilciclopropil 4–((5–(4–(2–(piridin–4–il)etilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato



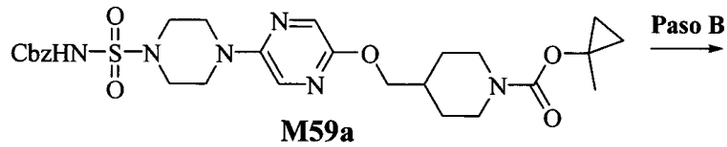
Siguiendo un procedimiento similar al de la preparación de **M57** a partir de **M26** excepto que se sustituye 3–bromopiridina por 4–bromopiridina, se prepara **M58**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8,80 (s, 2H), 7,87 (s, 1H), 7,74 (s, 2H), 7,63 (s, 1H), 4,20 (m, 2H), 4,07 (d, J = 6,5 Hz, 2H), 3,50 (m, 4H), 3,43 (m, 4H), 3,40 (m, 2H), 3,26 (m, 2H), 2,74 (m, 2H), 1,94 (m, 1H), 1,78 (m, 2H), 1,54 (s, 3H), 1,24 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{26}H_{37}N_6O_5S$ calc.,: 545,3, resultó: 545,4.

Ejemplo M59: 1–Metilciclopropil 4–((5–(4–sulfamoilpiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato

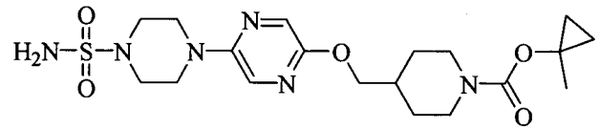




M1c



M59a

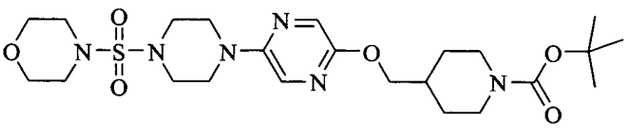


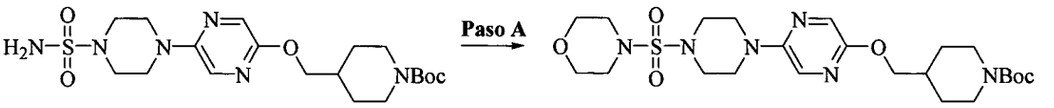
Ejemplo M59

Paso A: Se agrega gota a gota una solución de clorosulfonil isocianato (230 µl, 2,65 mmol) en N–hexanos (2,4 ml) a una solución de **M1c** (1,0 g, 2,7 mmol) en N–hexanos (5 ml) y se la agita a temperatura ambiente por espacio de 45 minutos. A continuación se introduce gota a gota una solución de alcohol bencílico (274 µl, 2,65 mmol) y trietilamina (554 µl, 3,97 mmol) en tetrahidrofurano (10 ml). Al cabo de 2 h, se trata la reacción con agua y se la extrae con diclorometano. Se seca la fase orgánica ($MgSO_4$), se la filtra, evapora y cromatografía en gel de sílice empleando un gradiente lineal de 0 a 100% de acetato de etilo en diclorometano para producir **M59a**. ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{27}H_{37}N_6O_7S$ calc.: 589.2, resultó: 589.3.

Paso B: Se trata una solución de **M59a** (300 mg, 0,509 mmol) en etanol (5 ml) con Pd/C al 5% (30 mg) y se la somete a lavado con H_2 (g) por espacio de 30 minutos. Se deja la reacción bajo atmósfera de H_2 (g) de un día para otro y luego se la filtra a través de Celite® y se la concentra para producir **M59**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{19}H_{31}N_6O_5S$ calc.: 455,2, resultó: 455,3.

Ejemplo M60: *terc*–Butil 4–((5–(4–(morfolinosulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato

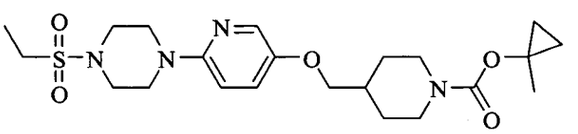


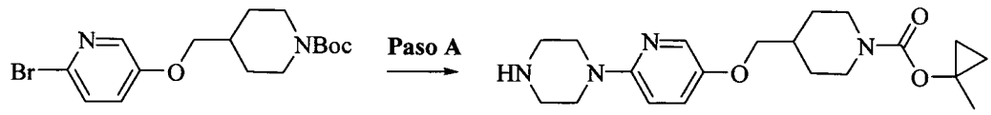


M60a **Ejemplo 60**

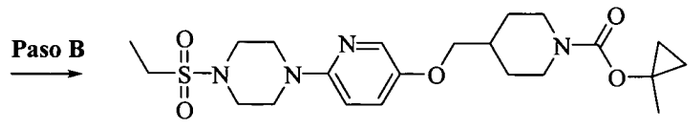
Se prepara una muestra de **M60a** de manera análoga a **M30.** Se carga en un vial de microondas **M60a** (64 mg, 0,14 mmol), 2–bromoetil éter (18 µl, 0,14 mmol), carbonato de potasio (40 mg, 0,28 mmol) y N,N–dimetilformamida (2 ml), se lo cierra herméticamente y se lo calienta a 150 °C por espacio de 5 minutos por medio de microondas. Se enfría la reacción a temperatura ambiente y se la vierte sobre agua y se la extrae con acetato de etilo. Se seca la fase orgánica ($MgSO_4$), se la filtra, evapora y purifica en gel de sílice empleando un gradiente lineal de 0 a 100% de acetato de etilo en hexano para producir **M60**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7,95 (s, 1H), 7,91 (s, 1H), 4,16 (m, 2H), 4,11 (d, *J* = 6,5 Hz, 2H), 3,74 (m, 4H), 3,53 (m, 6H), 3,44 (m, 1H), 3,27 (m, 5H), 2,73 (m, 2H), 1,96 (m, 1H), 1,78 (m, 2H), 1,46 (s, 9H), 1,26 (m, 2H), ESIMS *m/z* correspondiente a $(M+H–CO_2{}^tBu)^+$ $C_{18}H_{31}N_6O_4S$ calc.,: 427,2, resultó: 427,2.

Ejemplo M61: 1–Metilciclopropil 4–((6–(4–(etilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato





B2b **M61a**

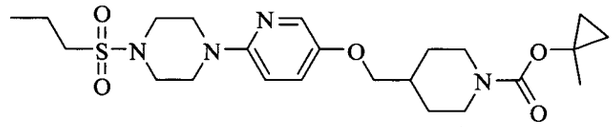


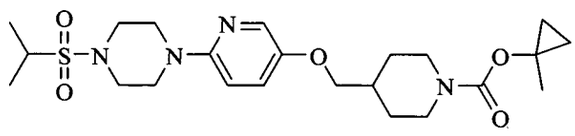
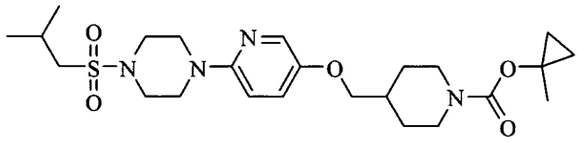
M61

Paso A: Siguiendo un procedimiento similar al empleado para la preparación de **M1c** a partir de **B12a** excepto que se sustituye **B12a** por **B2b**, se prepara **M61a**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{20}H_{31}N_4O_3$ calc.: 375.2, resultó: 375.2.

Paso A: Siguiendo un procedimiento similar al utilizado para la preparación de **M1** a partir de **M1c** excepto que se sustituye **M1c** por **M61a** y el metil 3–(clorosulfonil)propanoato por cloruro de etansulfonilo, se prepara **M61**; ^{1}H NMR (400 MHz, CD_3CN) δ 7,80 (m, 1H), 7,26 (m, 1H), 6,65 (m, 1H), 4,05 (m, 2H), 3,70 (d, J = 6,3 Hz, 2H), 3,52 (m, 3H), 3,37 (m, 4H), 3,21 (m, 1H), 2,92 (m, 2H), 2,67 (dd, J = 12,4, 12,4 Hz, 2H), 1,86 (m, 1H), 1,72 (m, 2H), 1,47 (s, 3H), 1,31 (t, J = 7,3 Hz, 3H), 1,17 (m, 2H), 0,79 (m, 2H), 0,55 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{22}H_{35}N_4O_5S$ calc.: 467,2 , resultó: 467,2.

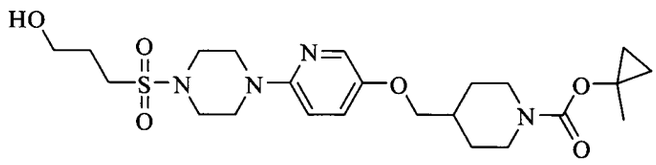
Siguiendo un procedimiento similar al utilizado para la preparación de **M61** a partir de **M61a** excepto que se sustituye **M61a** por los cloruros de sulfonilo existentes en el comercio, se obtienen los siguientes ejemplos:

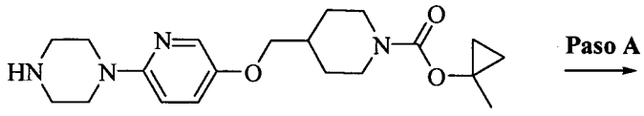
Ejemplo	Estructura	Datos analíticos
M62		^{1}H NMR (400 MHz, CD_3CN) δ 7,88 (m, 1H), 7,24 (m, 1H), 6,71 (m, 1H), 4,13 (m, 2H), 3,78 (d, J = 6,3 Hz, 2H), 3,59 (m, 3H), 3,43 (m, 4H), 3,28 (m, 1H), 2,91 (m, 2H), 2,74 (dd, J = 12,2, 12,1 Hz, 2H),

		1,89 (m, 3H), 1,80 (m, 2H), 1,55 (s, 3H), 1,24 (m, 2H), 1,07 (t, J = 7,4 Hz, 3H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{23}H_{37}N_4O_5S$ calc.: 481,2 , resultó: 481,2.
M63		^{1}H NMR (400 MHz, CD_3CN) δ 7,89 (d, J = 2,8 Hz, 1H), 7,24 (m, 1H), 6,67 (d, J = 8,9 Hz, 1H), 4,12 (m, 2H), 3,77 (d, J = 6,3 Hz, 2H), 3,50 (m, 8H), 3,22 (sept,, J = 6,8 Hz, 1H), 2,74 (dd, J = 12,4, 12,3 Hz, 2H), 1,93 (m, 1H), 1,80 (m, 2H), 1,55 (s, 3H), 1,36 (d, J = 6,9 Hz, 6H), 1,23 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{23}H_{37}N_4O_5S$ calc.: 481,2 , resultó: 481,2...
M64		^{1}H NMR (400 MHz, CD_3CN) δ 7,88 (m, 1H), 7,24 (m, 1H), 6,71 (m, 1H), 4,13 (m, 2H), 3,78 (d, J = 6,3 Hz, 2H), 3,59 (m, 3H), 3,40 (m, 4H), 3,29 (m, 1H), 2,77 (d, J = 6,6 Hz, 2H), 2,74 (dd, J = 12,6, 12,6 Hz, 2H), 2,31 (m, 1H), 1,94 (m, 1H), 1,80 (m, 2H), 1,55 (s, 3H), 1,24 (m, 2H), 1,12 (d, J = 6,7 Hz, 6H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS

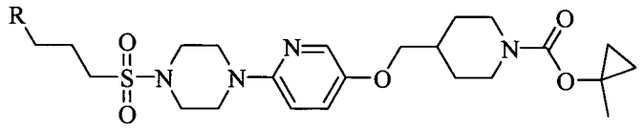
		m/z correspondiente a $(M+H)^+$ $C_{24}H_{39}N_4O_5S$ calc.: 495,3 , resultó: 495,3.

Ejemplo M65: 1–Metilciclopropil 4–((6–(4–(3–hidroxipropilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato





M61a



Paso B: **M65a**: R =Cl

Paso C: **M65b**: R =OAc

Ejemplo 65: R =OH

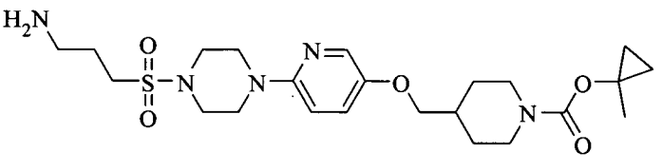
Paso A: Siguiendo un procedimiento similar al utilizado para la preparación de **M6** a partir de **M1c** excepto que se sustituye **M1c** por **M61a**, se prepara **M65a**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{23}H_{36}ClN_4O_5S$ calc.: 515.2, resultó: 515.2.

Paso B: Siguiendo un procedimiento similar al utilizado para la preparación de **M19** a partir de **M5** excepto que se sustituye **M5** por **M65a**, se prepara **M65b**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{25}H_{39}N_4O_7S$ calc: 539,3, resultó: 539,2.

Paso C: Siguiendo un procedimiento similar al utilizado para la preparación de **M43** a partir de **M42** excepto que se sustituye **M42** por **M65b**, se prepara **Ejemplo 65**; ^{1}H NMR (400 MHz, CD_3CN) δ 7,88 (d, J = 3,0 Hz, 1H), 7,19 (dd, J = 9,2, 2,8 Hz, 1H), 6,68 (d, J = 9,1 Hz, 1H), 4,11 (m, 2H), 3,77 (m, 4H), 3,55 (m, 4H), 3,41 (m, 4H), 3,08 (m, 2H), 2,74 (dd, J = 12,3, 12,3 Hz, 2H), 2,08 (m, 2H), 1,92 (m,

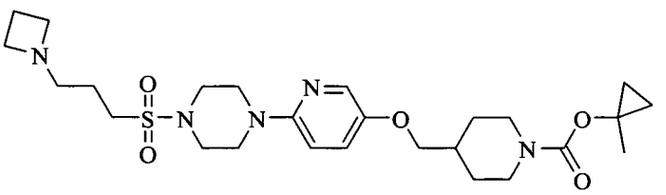
2H), 1,80 (m, 2H), 1,54 (s, 3H), 1,24 (m, 2H), 0,85 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{23}H_{37}N_4O_6S$ calc: 497,2 , resultó: 497,3.

Ejemplo M66: 1–Metilciclopropil 4–((6–(4–(3–aminopropilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato



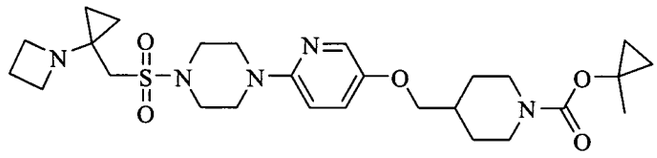
Siguiendo un procedimiento similar al utilizado para la preparación de **M18** a partir de **M16** excepto que se sustituye **M16** por **M65a**, se prepara **M66**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{23}H_{38}N_5O_5S$ calc: 496.3 , resultó: 496,3.

Ejemplo M67: 1–Metilciclopropil 4–((6–(4–(3–(azetidin–1–il)propilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato.



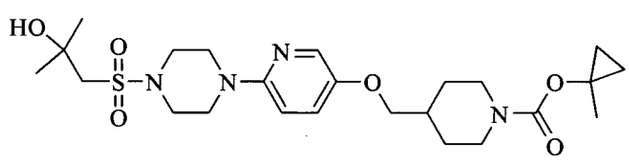
Siguiendo un procedimiento similar al utilizado para la preparación de **M21** a partir de **M6** excepto que se sustituye **M21** por **M65a** y 2–metilimidazol por azetidina, se prepara **M67**; ^1H NMR (400 MHz, Acetona–d_6) δ 7,91 (d, J = 3,2 Hz, 1H), 7,27 (dd, J = 3,2, 9,2 Hz, 1H), 6,84 (d, J = 8,8 Hz, 1H), 4,06 (m, 2H), 3,85 (d, J = 6,4 Hz, 2H), 3,52 (m, 4H), 3,34 (m, 4H), 3,09 (t, J = 6,8 Hz, 4H), 3,05 (m, 2H), 2,80 (m, 2H), 2,44 (d, J = 6,8 Hz, 2H), 1,96 (m, 3H), 1,78 (m, 4H), 1,50 (s, 3H), 1,23 (m, 2H), 0,79 (m, 2H), 0,58 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{26}H_{41}N_5O_5S$ calc: 535,3, resultó: 536,3.

Ejemplo M68: 1–Metilciclopropil 4–((6–(4–((1–(azetidin–1–il)ciclopropil)metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato.



Siguiendo un procedimiento similar al empleado para la preparación de **M35** a partir de **M1c** excepto que se sustituye **M1c** por **M61a**, se prepara **M68**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 7,92 (d, *J* = 2,9 Hz, 1H), 7,14 (dd, *J* = 9,1, 3,0 Hz, 1H), 6,64 (d, *J* = 9,1 Hz, 1H), 4,13 (m, 2H), 3,77 (d, *J* = 6,3 Hz, 2H), 3,54 (m, 4H), 3,49 (m, 4H), 3,06 (m, 4H), 3,01 (s, 2H), 2,74 (m, 2H), 1,91 (m, 2H), 1,85 (m, 2H), 1,80 (m, 2H), 1,55 (s, 3H), 1,25 (m, 2H), 0,86 (m, 4H), 0,70 (m, 2H), 0,62 (m, 2H); ESIMS calc, para $C_{27}H_{42}N_5O_5S$ $[M+H]^+$ 548,3, resultó 548,4.

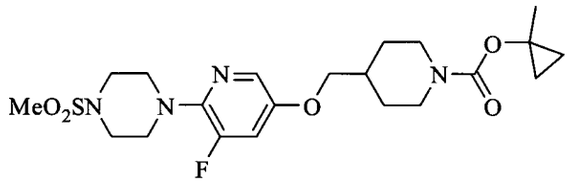
Ejemplo M69: 1–Metilciclopropil 4–((6–(4–(2–hidroxi–2–metilpropilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato

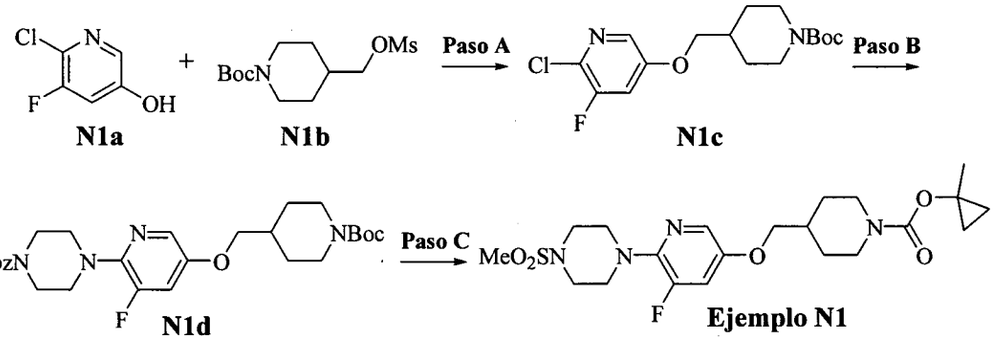


Una solución de **E10** (50 mg, 0,11 mmol) en tetrahidrofurano (3 ml) se enfría a –78 °C y se la trata con exceso de butil litio en hexano (2M, 250 µl). Después de agitar por espacio de 15 minutos, se agrega un exceso de acetona seca y se agita la reacción durante 30 minutos más. Se inactiva la reacción con una solución acuosa saturada de cloruro de amonio, se la calienta a temperatura ambiente y se la reparte entre acetato de etilo y agua. Se aísla la fase orgánica, se la seca sobre $MgSO_4$, filtra y evapora y purifica en gel de sílice empleando un gradiente lineal de

0–100% de acetato de etilo en hexano para producir **M69**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7,90 (d, J = 2,8 Hz, 1H), 7,15 (dd, J = 3,0, 9,1 Hz, 1H), 6,64 (d, J = 9,1 Hz, 1H), 4,13 (m, 2H), 3,77 (d, J = 6,3 Hz, 2H), 3,52 (m, 5H), 3,36 (m, 4H), 3,04 (s, 2H), 2,73 (m, 2H), 1,93 (m, 1H), 1,80 (m, 2H), 1,54 (s, 3H), 1,44 (s, 6H), 1,25 (m, 2H), 0,87 (m, 2H), 0,61 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{24}H_{39}N_4O_6S$ calc: 511,3, resultó: 511,5.

Ejemplo N1: 1–Metilciclopropil 4–((5–fluoro–6–(4–(metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato



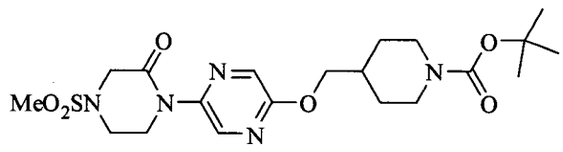


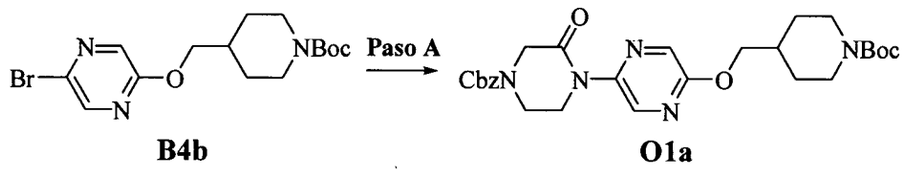
Paso A: Se trata una solución de **N1a** (100 mg, 0,678 mmol) y **N1b** (219 mg, 0,746 mmol) en N–metilpirrolidinona (2 ml) con Cs_2CO_3 (331 mg, 1,01 mmol) y se la calienta a 80 °C por espacio de 2 horas. Se enfría la reacción a temperatura ambiente, se la diluye con acetato de etilo y extrae con agua dos veces. Se secan los extractos orgánicos sobre $MgSO_4$, se la filtra, evapora y purifica en sílice empleando un gradiente lineal de 0 a 50% de acetato de etilo en hexanos para producir **N1c**. ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{16}H_{23}Cl\,FN_2O_3$ calc: 345,1, resultó: 289,0 (M–*t*Bu+H^+).

Paso B: Siguiendo un procedimiento similar al utilizado para la preparación de **B1** a partir de isopropil 4–((6–cloropiridin–3–iloxi)metil)piperidin–1–carboxilato excepto que se sustituye isopropil 4–((6–cloropiridin–3–iloxi)metil)piperidin–1–carboxilato por **N1c** y 1–(metilsulfonil)piperazina por bencil piperazin–1–carboxilato, se prepara **N1d**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{28}H_{38}FN_4O_5$ calc: 529,3, resultó: 529,2.

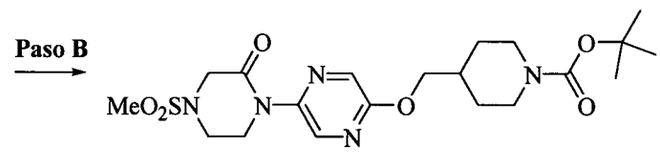
Paso C: Se trata una solución de **N1d** (132 mg, 0,25 mmol) en una mezcla de metanol y dioxano (2 ml, 1:1) con 10 mg de Pd/C al 5% y se la hidrogena de un día para otro a la presión de balón. A continuación se vuelve a cambiar la atmósfera por N_2 y se filtra la reacción a través de Celite® y se separa el solvente. Se coevapora el aceite así obtenido dos veces con tolueno, se lo disuelve en diclorometano (2 ml) con contenido de trietilamina (51 mg, 0,50 mmol) y se lo trata con cloruro de metansulfonilo (43 mg, 0,38 mmol) en forma de solución en diclorometano (1 ml) y se lo agita por espacio de 1 hora. Se separa el solvente y se trata la reacción con ácido trifluoracético puro (3 ml). Al cabo de 20 minutos de agitación, se retira el solvente y se coevapora la reacción dos veces con tolueno y se la trata con diclorometano (2 ml), **E3b** (71 mg, 0,30 mmol) y exceso de trietilamina. Después de 2 h de agitación, se diluye la reacción con acetato de etilo, se la extrae dos veces con NaOH 1 M, una vez con hidrogenocarbonato de sodio saturado, se la seca sobre $MgSO_4$, se la filtra, evapora y purifica en gel de sílice empleando un gradiente lineal de 0 a 100% de acetato de etilo en hexano; ^1H NMR (400 MHz, $CDCl_3$) δ 7,73 (d, J = 2,5 Hz, 1H), 7,07 (dd, J = 2,5, 13,0 Hz, 1H), 4,14 (m, 2H), 3,80 (d, J = 6,3 Hz, 2H), 3,53 (m, 4H), 3,40 (m, 4H), 2,82 (s, 3H), 2,74 (m, 2H), 1,95 (m, 1H), 1,80 (m, 2H), 1,55 (s, 3H), 1,26 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{32}FN_4O_5S$ calc: 471,2, resultó: 471,2.

Ejemplo O1: terc–Butil 4–((5–(4–(metilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.





B4b **O1a**



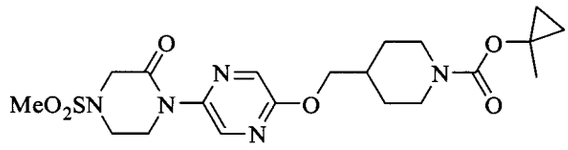
Ejemplo O1

Paso A: Se carga un matraz hermético con **B4b** (4,00 g, 11 mmol) y bencil 3–oxopiperazin–1–carboxilato (3,02 g, 13 mmol), Pd_2dba_3 (295 mg, 0,32 mmol), Xantfos (560 mg, 0,97 mmol) y Cs_2CO_3 (10,5 g, 32 mmol). Se evacua el matraz y se lo recarga con nitrógeno, se lo cierra herméticamente, se lo trata con dioxano (60 ml) y se lo sumerge en un baño precalentado a 120 °C. Al cabo de 2 horas, se enfría la reacción a temperatura ambiente, se la diluye con acetato de etilo y se la extrae dos veces con agua. Se secan los extractos orgánicos sobre $MgSO_4$, se los filtra, evapora y purifica en sílice utilizando un gradiente escalonado de 25, 50 y 75% de acetato de etilo en hexanos para producir **O1a**; ESIMS *m/z* correspondiente a $(M–Boc+H)^+$ $C_{22}H_{28}N_5O_4$ calc: 426.2, resultó: 426.1.

Paso B: Se trata una solución de **O1a** (80 mg, 0,15 mmol) en MeOH (2 ml) con 10 mg de Pd/C al 5% y se la hidrogena a presión de balón de un día para otro. Se retira el catalizador mediante filtración a través de Celite® y se separa el solvente. Se coevapora el residuo con tolueno dos veces, se lo disuelve en diclorometano (2 ml) y se lo trata con exceso de trietilamina seguida por cloruro de metansulfonilo (21 mg, 0,18 mmol) disuelto en diclorometano (1 ml). Al cabo de 1 hora de agitación, se diluye la reacción con acetato de etilo y se la extrae con agua dos veces. Se secan los extractos orgánicos sobre $MgSO_4$, se los filtra,

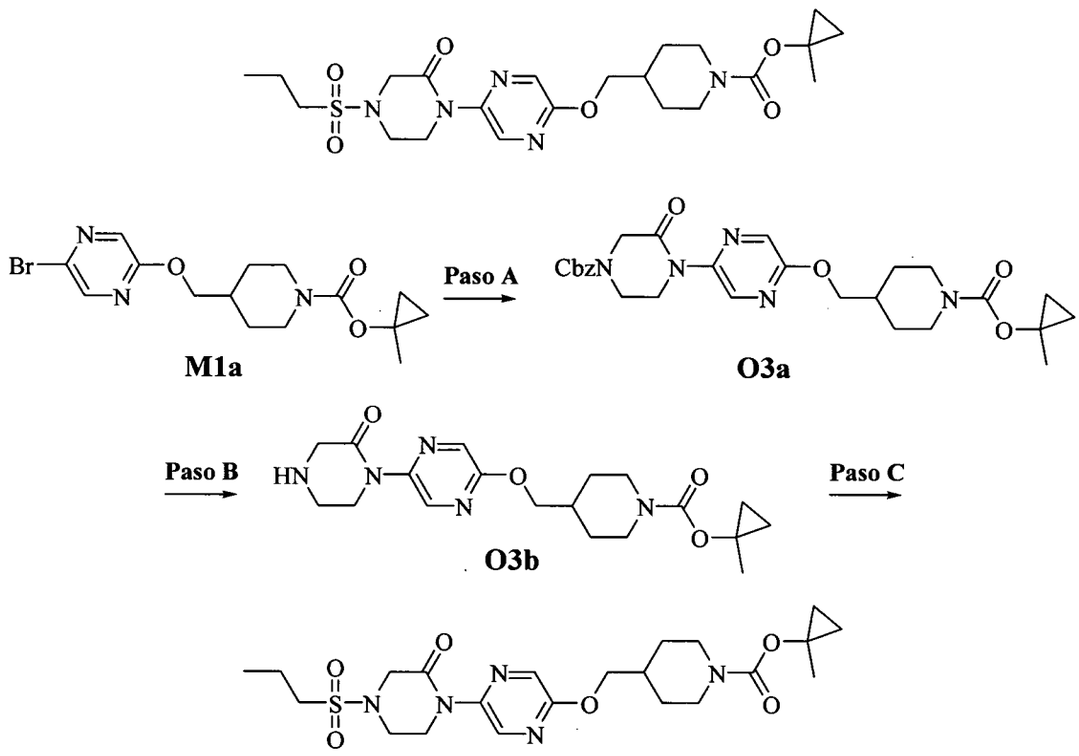
evapora y purifica en sílice empleando un gradiente lineal de 30 a 100% de acetato de etilo en hexanos para producir **O1**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,66 (d, *J* = 1,4 Hz, 1H), 8,02 (d, *J* = 1,4 Hz, 1H), 4,19 (d, *J* = 6,5 Hz, 2H), 4,15 (m, 2H), 4,13 (s, 2H), 4,08 (m, 2H), 3,68 (m, 2H), 2,92 (s, 3H), 2,74 (m, 2H), 1,98 (m, 1H), 1,79 (m, 2H), 1,46 (s, 9H), 1,27 (m, 2H); ESIMS *m/z* correspondiente a $(M+Na)^+$ $C_{20}H_{31}N_5NaO_6S$ calc: 492,2, resultó: 492,2.

Ejemplo O2: 1–Metilciclopropil 4–((5–(4–(metilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



Se trata una muestra de **O1** (50 mg, 0,11 mmol) con ácido trifluoracético (1 ml) y se la hace madurar durante un lapso de 20 minutos. Se retira el solvente y se trata el residuo con diclorometano (2 ml), exceso de trietilamina y **E3b** (30,3 mg, 0,13 mmol). Después de agitar por espacio de 3 horas, se diluye la reacción con acetato de etilo, se la extrae con 1 M NaOH dos veces, una vez con hidrogenocarbonato de sodio saturado, se la seca sobre $MgSO_4$, filtra y evapora y purifica en gel de sílice empleando un gradiente lineal de 0 a 100% de acetato de etilo en hexano; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,65 (d, *J* = 1,4 Hz, 1H), 8,02 (d, *J* = 1,4 Hz, 1H), 4,18 (d, *J* = 6,5 Hz, 2H), 4,12 (s, 2H), 4,12 (m, 2H), 4,07 (m, 2H), 3,67 (m, 2H), 2,93 (s, 3H), 2,72 (m, 2H), 1,98 (m, 1H), 1,79 (m, 2H), 1,54 (s, 3H), 1,25 (m, 2H), 0,87 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{20}H_{30}N_5O_6S$ calc: 468,2, resultó: 468,1.

Ejemplo O3: 1–Metilciclopropil 4–((5–(2–oxo–4–(propilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



Ejemplo O3

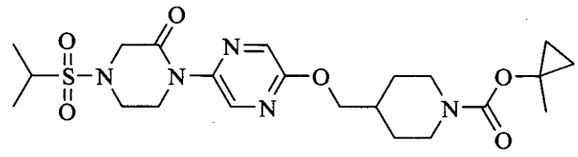
Paso A: Siguiendo un procedimiento similar al utilizado para la preparación de **O1a** a partir de **B4b** excepto que se sustituye **B4b** por **M1a**, se prepara **O3a**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{27}H_{34}N_5O_6$ calc: 524,2, resultó: 524,2.

Paso B: Se trata una solución de **O3a** (3,01 g, 0,15 mmol) en MeOH (30 ml) con 101 mg de $Pd(OH)_2/C$ al 20% y se la hidrogena a presión de balón por espacio de 5 horas. Se separa el catalizador por filtración a través de Celite® y se elimina el solvente para producir **O3b**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{19}H_{28}N_5O_4$ calc: 390,2, resultó: 390,1.

Paso C: Se trata una solución de **O3b** (203 mg, 0,52 mmol) en diclorometano (1,5 ml) con trietilamina (55 mg, 0,54 mmol) y cloruro de *n*–propansulfonilo (77 mg, 0,54 mmol) y se la agita por espacio de 4 horas. A continuación, se agrega otra porción idéntica de trietilamina y cloruro de *n*–propilsulfonilo y se agita la reacción de un día para otro. Seguidamente se carga la mezcla de reacción directamente en una columna de gel de sílice y se la eluye con un gradiente lineal de 0 a 100% de acetato de etilo en hexano para producir

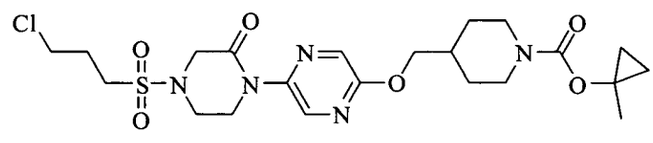
O3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,65 (d, J = 1,4 Hz, 1H), 8,02 (d, J = 1,4 Hz, 1H), 4,18 (d, J = 6,5 Hz, 1H), 4,17 (m, 2H), 4,15 (s, 2H), 4,05 (m, 2H), 3,70 (m, 2H), 3,01 (m, 2H), 2,75 (dd, J = 12,3, 12,2 Hz, 2H), 1,98 (m, 1H), 1,89 (m, 2H), 1,79 (m, 2H), 1,55 (s, 3H), 1,26 (m, 2H), 1,09 (t, J = 7,4 Hz, 3H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{22}H_{34}N_5O_6S$ calc: 496,2, resultó: 496,2.

Ejemplo O4: 1–Metilciclopropil 4–((5–(4–(isopropilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato



Siguiendo un procedimiento similar al utilizado para la preparación de **O3** a partir de **O3b** excepto que se sustituye el cloruro de *n*–propansulfonilo por cloruro de 3–cloropropansulfonilo, se prepara **O4**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,65 (d, J = 1,4 Hz, 1H), 8,02 (d, J = 1,4 Hz, 1H), 4,21 (s, 2H), 4,19 (m, 2H), 4,19 (d, J = 6,5 Hz, 2H), 4,04 (m, 2H), 3,75 (m, 2H), 3,28 (sept,, J = 6,8 Hz, 1H), 2,75 (dd, J = 12,3, 12,3 Hz, 2H), 1,98 (m, 1H), 1,78 (m, 2H), 1,55 (s, 3H), 1,40 (d, J = 6,8 Hz, 6H), 1,26 (m, 2H), 0,87 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{22}H_{34}N_5O_6S$ calc: 496,2, resultó: 496,2.

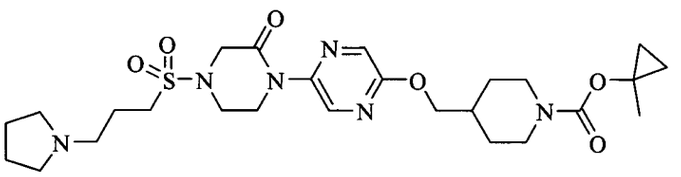
Ejemplo O5: 1–Metilciclopropil 4–((5–(4–(3–cloropropilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato



Siguiendo un procedimiento similar al utilizado para la preparación de **O3** a partir de **O3b** excepto que se sustituye el cloruro *n*–propilsulfonilo por cloruro de *iso*–propilsulfonilo, se prepara **O5**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 8,65 (d, *J* = 1,4 Hz,

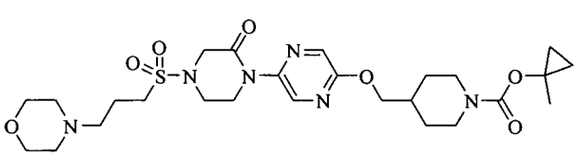
1H), 8,02 (d, *J* = 1,4Hz, 1H), 4,21 (m, 2H), 4,18 (d, *J* = 6,6 Hz, 2 H), 4,17 (s, 2H), 4,07 (m, 2H), 3,71 (m, 4H), 3,21 (m, 2H), 2,75 (dd, *J* = 12,4, 12,3 Hz, 2H), 2,33 (m, 2H), 1,97 (m, 1H), 1,79 (m, 2H), 1,55 (s, 3H), 1,26 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS calc, para $C_{22}H_{33}ClN_5O_6S$ $[M+H]^+$ 530,2, resultó 530,3.

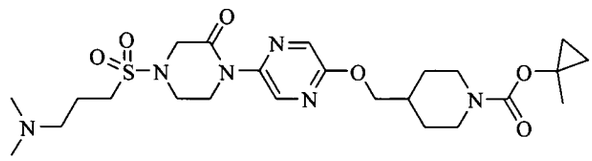
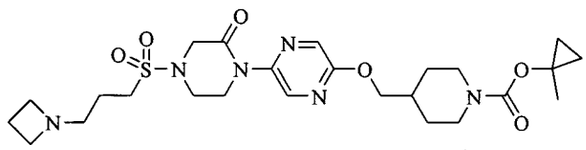
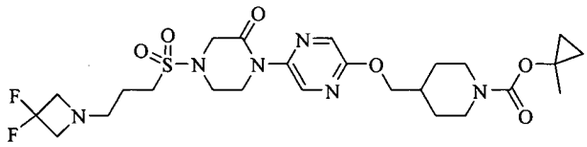
Ejemplo O6: 1–Metilciclopropil 4–((5–(2–oxo–4–(3–(pirrolidin–1–il)propilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato

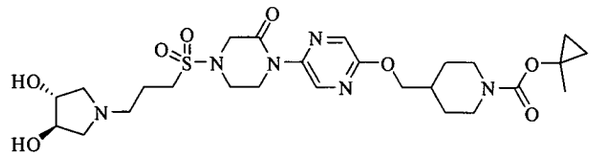
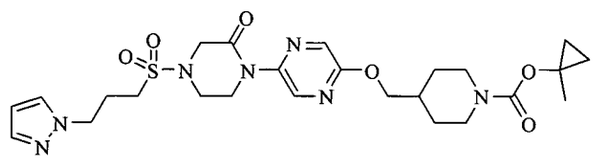


Se trata una solución de **O5** (15 mg, 0,03 mmol) en N,N–dimetilformamida (700 µl) con pirrolidina (23 µl, 0,28 mmol) y se la somete a irradiación por microondas (200 °C, 5 min). Se purifica la solución empleando HPLC de fase inversa dirigida a la masa para producir **O6**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,67 (d, J = 1,2 Hz, 1H), 8,04 (d, J = 1,2 Hz, 1H), 4,20 (d, J = 6,8 Hz, 2H), 4,18 (s, 2H), 4,07 (m, 2H), 3,72 (m, 2H), 3,18 (m, 2H), 2,77 (m, 2H), 2,66 (m, 2H), 2,59 (br s, 3H), 2,07 (m, 3H),1,83 (m, 5H), 1,57 (s, 3H), 1,28 (m, 2H), 0,89 (m, 2H), 0,65 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{26}H_{41}N_6O_6S$ calc: 565,3, resultó: 565,2.

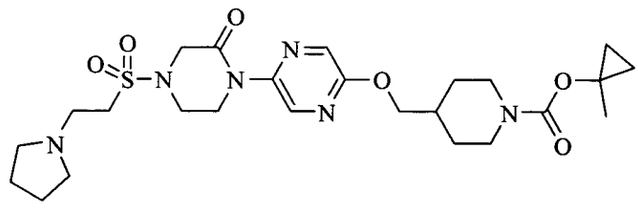
Siguiendo un procedimiento similar al utilizado para la preparación de **O6** a partir de **O5** excepto que se sustituye la pirrolidina por las aminas apropiadas, se obtienen los siguientes ejemplos:

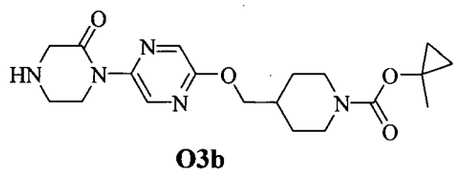
O7		^{1}H NMR (400 MHz, $CDCl_3$) δ 8,64 d, J = 1,6 Hz, 1H), 8,04 (d, J = 1,6 Hz, 1H), 4,20 (d, J = 6,4 Hz, 2H), 4,18 (s, 2H), 4,07 (m, 2H), 3,72 (m, 4H), 3,32 (m, 8H), 3,15 (m, 2H), 2,77 (m, 2H), 2,46 (m, 4H), 2,02 (m, 4H),

		1,80 (m, 2H), 1,56 (s, 3H), 1,29 (m, 2H), 0,87 (m, 2H), 0,64 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{26}H_{41}N_6O_7S$ calc: 581,3, resultó: 581,2,
O8		^1H NMR (400 MHz, $CDCl_3$) δ 8,49 d, J = 1,4 Hz, 1H), 7,86 (d, J = 1,4 Hz, 1H), 4,03 (d, J = 6,4 Hz, 2H), 4,00 (s, 2H), 3,89 (m, 2H), 3,54 (m, 2H), 2,97 (m, 2H), 2,59 (m, 2H), 2,33 (m, 2H), 2,12 (s, 6H), 1,87 (m, 4H), 1,64 (m, 2H), 1,39 (s, 3H), 1,10 (m, 2H), 0,71 (m, 2H), 0,46 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{24}H_{39}N_6O_6S$ calc: 539,3, resultó: 539,2,
O9		^1H NMR (400 MHz, $CDCl_3$) δ 8,44 (d, J = 1,6 Hz, 1H), 7,81 (d, J = 1,6 Hz, 1H), 3,98 (d, J = 6,8 Hz, 2H), 3,94 (s, 2H), 3,84 (m, 2H), 3,48 (m, 2H), 2,98 (m, 3H), 2,89 (m, 2H), 2,54 (m, 2H), 2,31 (m, 2H), 1,86 (m, 2H), 1,78 (m, 1H), 1,65 (m, 4H), 1,34 (s, 3H), 1,05 (m, 2H), 0,66 (m, 2H), 0,41 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{25}H_{39}N_6O_6S$ calc: 551,3, resultó: 551,3,
O10		^1H NMR (400 MHz, $CDCl_3$) δ 8,51 (d, J = 1,2 Hz, 1H), 7,88 (d, J = 1,2 Hz, 1H), 4,04 (d, J = 6,4 Hz, 2H), 4,01 (s, 2H), 3,91 (m, 3H), 3,56 (m, 2H), 3,43 (t, J = 12,0 Hz, 4H), 2,97 (m, 2H), 2,56 (m, 4H), 1,84 (m, 1H), 1,78 (m, 2H), 1,66 (m, 2H), 1,41 (s, 3H), 1,13 (m, 2H),

		0,73 (m, 2H), 0,48 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{25}H_{37}F_2N_6O_6S$ calc: 587,3, resultó: 587,2,
O11		^1H NMR (400 MHz, $CDCl_3$) δ 8,57 (d, J = 1,4 Hz, 1H), 7,95 (d, J = 1,4 Hz, 1H), 4,12 (d, J = 6,4 Hz, 2H), 4,10 (s, 2H), 4,06 (m, 2H), 3,98 (m, 3H), 3,64 (m, 2H), 3,07 (m, 2H), 2,94 (m, 2H), 2,68 (m, 2H), 2,58 (m, 2H), 2,43 (dd, J = 3,6, 10,4 Hz, 2H), 1,95 (m, 4H), 1,72 (m, 2H), 1,48 (s, 3H), 1,18 (m, 2H), 0,80 (m, 2H), 0,56 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{26}H_{41}N_6O_8S$ calc: 597,3, resultó: 597,3,
O12		^1H NMR (400 MHz, $CDCl_3$) δ 8,67 (d, J = 1,2 Hz, 1H), 8,04 (d, J = 1,2 Hz, 1H), 7,54 (d, J = 1,6 Hz, 1H), 7,46 (d, J = 1,6 Hz, 1H), 6,29 (m, 1H), 4,35 (m, 2H), 4,20 (d, J = 6,4 Hz, 2H), 4,12 (s, 2H), 4,05 (m, 3H), 3,68 (m, 2H), 2,99 (m, 2H), 2,77 (m, 2H), 2,45 (m, 2H), 2,00 (m, 1H), 1,82 (m, 2H), 1,57 (s, 3H), 1,28 (m, 2H), 0,89 (m, 2H), 0,64 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{25}H_{36}N_7O_6S$ calc: 562,2, resultó: 562,3,

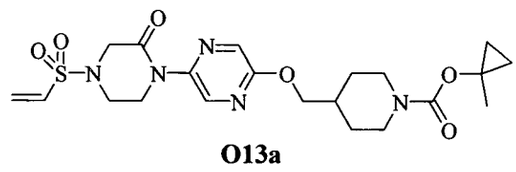
Ejemplo O13: 1–Metilciclopropil 4–((5–(2–oxo–4–(2–(pirrolidin–1–il)etilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato





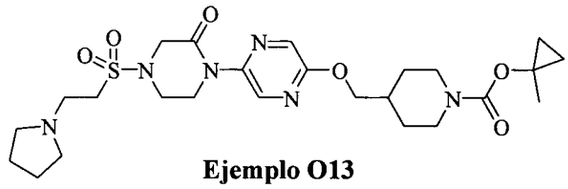
O3b

Paso A



O13a

Paso B

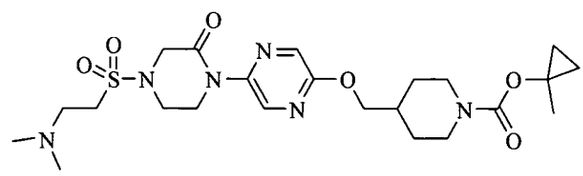
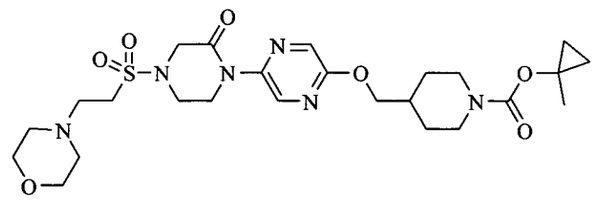
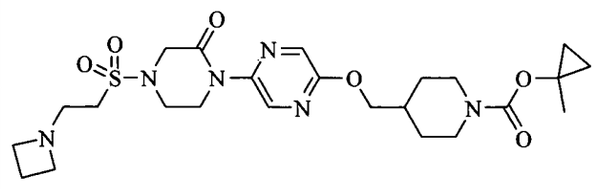


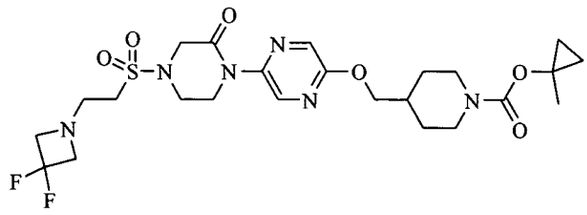
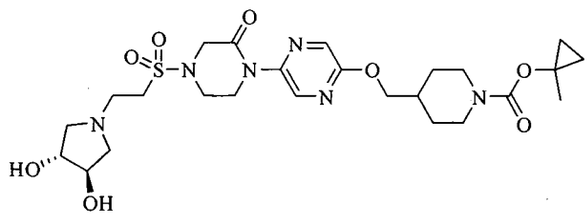
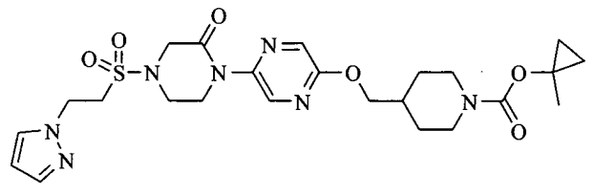
Ejemplo O13

Paso A: Se trata una solución de **O3b** (600 mg, 1,51 mmol) en diclorometano (10 ml) con N,N–diisopropiletilamina (521 µl, 3,02 mmol) y cloruro de 2–cloroetansulfonilo (173 µl, 1,66 mmol) y se la agita por espacio de 2 horas. A continuación se carga la mezcla de reacción directamente en una columna de gel de sílice y se la eluye con un gradiente lineal de 0 a 100% de acetato de etilo en hexano para producir **O13a**. ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{21}H_{30}N_5O_6S$ calc: 480,2, resultó: 480,2.

Paso B: Se trata una solución de **O13a** (15 mg, 0,03 mmol) en N,N–dimetilformamida (1 ml) con pirrolidina (26 µl, 0,31 mmol) y se la agita por espacio de 16 horas a temperatura ambiente. Se purifica la solución empleando una HPLC de fase inversa iniciada por la masa para producir **O13.** ^1H NMR (400 MHz, $CDCl_3$) δ 8,68 (d, J = 1,4 Hz, 1H), 8,04 (d, J = 1,4 Hz, 1H), 4,20 (m, 4H), 4,06 (m, 3H), 3,72 (m, 2H), 3,34 (m, 2H), 3,04 (m, 2H), 2,75 (m, 6H), 2,00 (m, 1H), 1,83 (m, 6H), 1,57 (s, 3H), 1,28 (m, 2H), 0,89 (m, 2H), 0,64 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{25}H_{39}N_6O_6S$ calc: 551,3, resultó: 551,2.

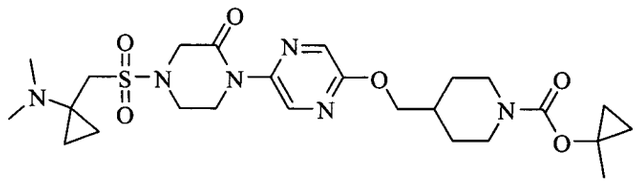
Siguiendo un procedimiento similar al utilizado para la preparación de **O13** a partir de **O13a** excepto que se sustituye la pirrolidina por las aminas apropiadas, se obtienen los siguientes ejemplos:

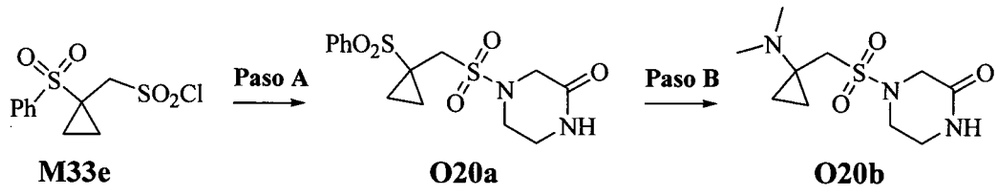
Ex.	Estructura	Datos analíticos
O14		^{1}H NMR (400 MHz, $CDCl_3$) δ 8,67 (d, J = 1,4 Hz, 1H), 8,04 (d, J = 1,4 Hz, 1H), 4,20 (m, 4H), 4,06 (m, 3H), 3,73 (m, 2H), 3,26 (m, 2H), 2,84 (m, 2H), 2,77 (m, 2H), 2,33 (s, 6H), 2,00 (m, 1H), 1,82 (m, 2H), 1,57 (s, 3H), 1,28 (m, 2H), 0,89 (m, 2H), 0,64 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{23}H_{37}N_6O_6S$ calc: 525,3, resultó: 525,2.
O15		^{1}H NMR (400 MHz, $CDCl_3$) δ 8,68 (d, J = 1,2 Hz, 1H), 8,04 (d, J = 1,2 Hz, 1H), 4,21 (m, 4H), 4,08 (m, 2H), 3,72 (m, 6H), 3,25 (m, 2H), 2,88 (m, 2H), 2,77 (m, 2H), 2,53 (m, 4H), 2,00 (m, 1H), 1,81 (m, 2H), 1,57 (s, 3H), 1,28 (m, 2H), 0,89 (m, 2H), 0,64 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{25}H_{39}N_6O_7S$ calc: 567,3, resultó: 567,2.
O16		^{1}H NMR (400 MHz, $CDCl_3$) δ 8,60 (d, J = 1,2 Hz, 1H), 7,95 (d, J = 1,2 Hz, 1H), 4,15 (s, 2H), 4,12 (d, J = 6,4 Hz, 2H), 3,97 (m, 2H), 3,65 (m, 3H), 3,15 (m, 3H), 2,98 (m, 2H), 2,77 (m, 2H), 2,68 (m, 2H), 1,98 (m, 2H), 1,94 (m, 1H), 1,73 (m, 2H), 1,48 (s, 3H), 1,19 (m, 2H), 0,80 (m, 2H), 0,55 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{24}H_{37}N_6O_6S$ calc: 537,3,

		resultó: 567,3.
O17		^{1}H NMR (400 MHz, $CDCl_3$) δ 8,68 (d, J = 1,6 Hz, 1H), 8,04 (d, J = 1,6 Hz, 1H), 4,20 (m, 5H), 4,07 (m, 3H), 3,74 (m, 2H), 3,66 (t, J = 11,6 Hz, 4H), 3,09 (m, 4H), 2,77 (m, 2H), 2,00 (m, 1H), 1,81 (m, 2H), 1,57 (s, 3H), 1,29 (m, 2H), 0,89 (m, 2H), 0,64 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{24}H_{35}F_2N_6O_6S$ calc: 573,2, resultó: 573,2.
O18		^{1}H NMR (400 MHz, $CDCl_3$) δ 8,56 (d, J = 1,4 Hz, 1H), 7,95 (d, J = 1,4 Hz, 1H), 4,15 (s, 2H), 4,12 (d, J = 6,4 Hz, 2H), 4,03 (m, 2H), 3,98 (m, 2H), 3,66 (m, 2H), 3,26 (m, 2H), 2,95 (m, 4H), 2,68 (m, 2H), 2,48 (dd, J = 3,2, 10 Hz, 2H), 1,91 (m, 1H), 1,72 (m, 2H), 1,48 (s, 3H), 1,20 (m, 2H), 0,80 (m, 2H), 0,56 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{25}H_{39}N_6O_8S$ calc: 583,3, resultó: 583,3.
O19		^{1}H NMR (400 MHz, $CDCl_3$) δ 8,55 (d, J = 1,2 Hz, 1H), 7,94 (d, J = 1,2 Hz, 1H), 7,48 (d, J = 2,0 Hz, 1H), 7,41 (d, J = 2,0 Hz, 1H), 6,19 (m, 1H), 4,52 (m, 2H), 4,11 (d, J = 6,4 Hz, 2H), 3,87 (s, 2H), 3,85 (m, 2H), 3,65 (m, 2H), 3,40 (m, 2H) 2,68 (m, 2H), 1,91 (m, 1H), 1,72 (m, 2H), 1,48 (s, 3H), 1,18 (m, 2H), 0,80 (m, 2H), 0,56 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{24}H_{34}N_7O_6S$ calc: 548,2, resultó: 548,2.

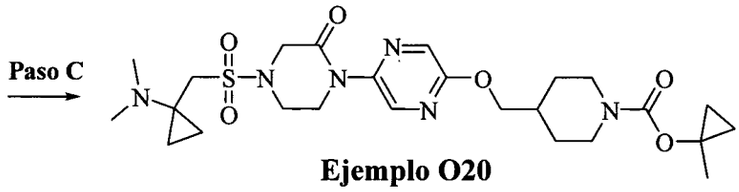
Ejemplo O20: 1–metilciclopropil 4–((5–(4–((1–

(dimetilamino)ciclopropil)metilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.





M33e **O20a** **O20b**



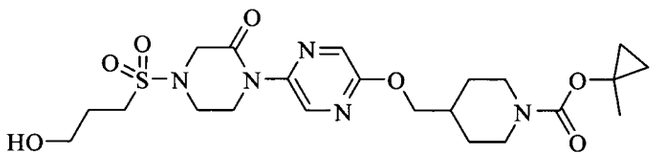
Ejemplo O20

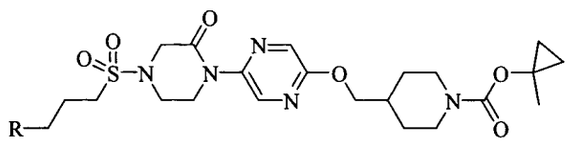
Paso A: Se trata una solución de piperazin–2–ona (36,5 mg, 3,7 mmol) en diclorometano (10 ml) con trietilamina (74 mg, 0,73 mmol seguida por **M33e** (108 mg, 3,7 mmol) y se la agita de un día para otro. Se separa el solvente y se disuelve el residuo en dimetilformamida, se lo filtra y purifica por HPLC de fase inversa iniciada por la masa para producir **O20a**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{14}H_{19}N_2O_5S_2$ calc: 359,1, resultó: 359,0,

Paso B: Se trata una solución de **O20a** (71,7 mg, 0,20 mmol) en dimetilamina 2 M en una solución en tetrahidrofurano (6 ml, 12 mmol) con *terc*–butóxido de potasio (34 mg, 0,30 mmol) y se la agita por espacio de 1 hora a temperatura ambiente. Se retira el solvente y se disuelve el residuo en dimetilformamida, se lo filtra y purifica por HPLC de fase inversa iniciada por la masa para producir **O20a**; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{10}H_{20}N_3O_3S$ calc: 262,1, resultó: 262,1.

Paso C: Siguiendo un procedimiento similar al utilizado para la preparación de **O3a** a partir de **M1a** excepto que se sustituye el bencil 3–oxopiperazin–1–carboxilato por **O20b**, se prepara **O20**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 8,65 (d, *J* = 1,4 Hz, 1H), 8,02 (d, *J* = 1,4Hz, 1H), 4,25 (m, 2H), 4,19 (d, *J* = 6,5 Hz, 2H), 4,17 (s, 2H), 4,04 (m, 2H), 3,70 (m, 2H), 3,16 (s, 2H), 2,75 (dd, *J* = 15,2, 13,8 Hz, 2H), 2,29 (s, 6H), 1,98 (m, 1H), 1,80 (m, 2H), 1,55 (s, 3H), 1,27 (m, 2H), 0,88 (m, 6H), 0,62 (m, 2H); ESIMS calc, para $C_{25}H_{39}N_6O_6S$ $[M+H]^+$ 551,3, resultó 551,4.

Ejemplo O21: 1–Metilciclopropil 4–((5–(4–(3–hidroxipropilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.





Paso A → **O5**: R=Cl

Paso B → **O21a**: R=OCHO

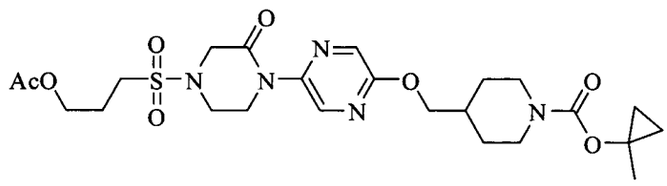
Ejemplo O21: R=OH

Paso A: Se calienta una solución de **O5** (2,76 g; 5,2 mmol), NaI (790 mg, 5,3 mmol) y formiato de sodio (1,06 g, 15,6 mmol) en dimetilformamida (30 ml) a 120 °C por espacio de 2 horas. Se diluye la mezcla con agua, se la extrae con acetato de etilo (2x) y se lava la capa orgánica con agua & solución salina, se la seca ($MgSO_4$), filtra y concentra para producir **O21a** crudo, que es utilizado en el siguiente Paso sin más purificación; ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{23}H_{34}N_5O_8S$ calc: 540,2, resultó: 540,2.

Paso B: Se trata una solución de **O21a** (crudo, obtenido en el paso anterior) en una mezcla 1:1 de metanol y agua (40 ml) con hidrogenocarbonato de

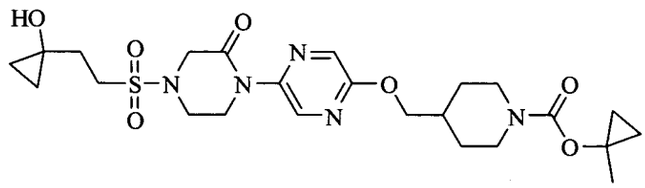
sodio (2,2 g, 26,0 mmol) y se la agita a temperatura ambiente por espacio de 1 hora. Se extrae la mezcla con acetato de etilo y se lava la capa orgánica con solución salina, se la seca ($MgSO_4$), filtra y concentra. Se purifica el residuo en gel de sílice utilizando 0–10% de metanol en diclorometano para producir **O21**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,66 (d, J = 1,4 Hz, 1H), 8,04 (d, J = 1,4 Hz, 1H), 4,20 (m, 4H), 4,08 (m, 2H), 3,82 (m, 2H), 3,74 (m, 2H), 3,22 (m, 2H), 2,77 (m, 2H), 2,12 (m, 2H), 2,00 (m, 1H), 1,83 (m, 2H), 1,74 (t, J = 4,8 Hz, 1H), 1,60 (s, 2H), 1,57 (s, 3H), 1,28 (m, 2H), 0,89 (m, 2H), 0,65 (m, 2H); ESIMS *m/z* correspondiente a $(M+H)^+$ $C_{22}H_{34}N_5O_7S$ calc: 512,2, resultó: 512,2.

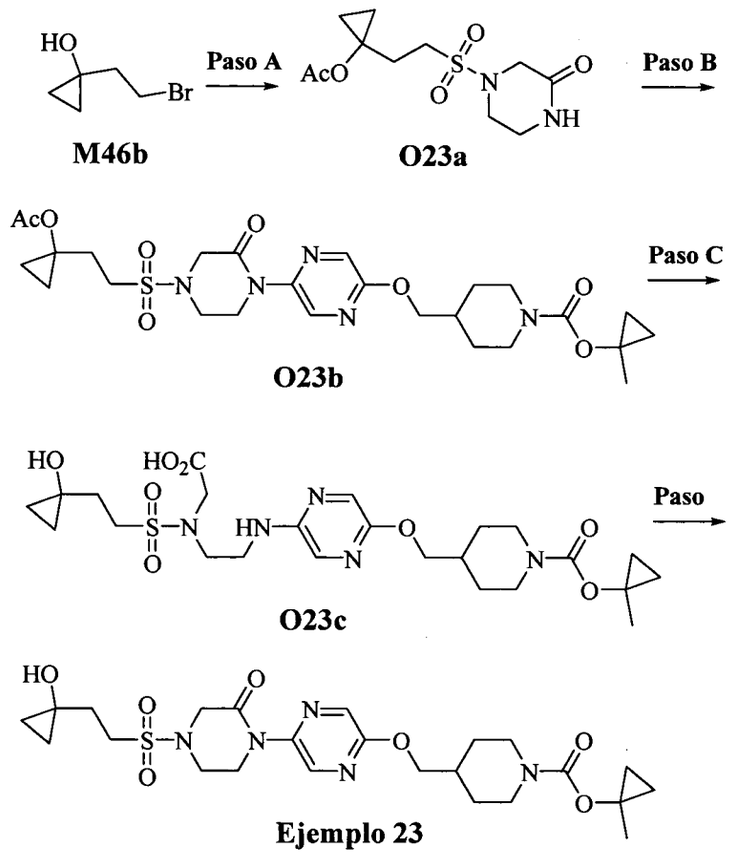
Ejemplo O22: 1–Metilciclopropil 4–((5–(4–(3–acetoxipropilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



Siguiendo un procedimiento similar al utilizado para la preparación de **M19** a partir de **M5** excepto que se sustituye **M5** por **O5**, se prepara **O22**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 8,65 (d, *J* = 1,4 Hz, 1H), 8,02 (d, *J* = 1,4 Hz, 1H), 4,19 (m, 8H), 4,06 (m, 2H), 3,72 (m, 2H), 3,12 (m, 2H), 2,75 (dd, *J* = 12,4, 12,4 Hz, 2H), 2,15–2,22 (m, 2H), 2,08 (s, 3H), 1,98 (m, 1H), 1,79 (m, 2H), 1,55 (s, 3H), 1,27 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS calc, para $C_{24}H_{36}N_5O_8S$ $[M+H]^+$ 554,2, resultó 554,2.

Ejemplo O23: 1–Metilciclopropil 4–((5–(4–(2–(1–hidroxiciclopropil)etilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.





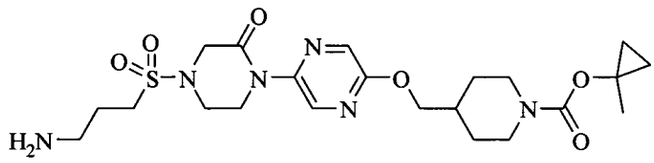
Paso A: Siguiendo un procedimiento similar al utilizado para la preparación de **M46** a partir de **M46b** excepto que se sustituye **M1c** por piperazin–2–ona y purificando por HPLC, se prepara **O23a**; ESIMS calc. para $C_{11}H_{19}N_2O_5S$ $[M+H]^+$ 291.1, resultó 291,1.

Paso B: Siguiendo un procedimiento similar al utilizado para la preparación de **O3a** a partir de **M1a** excepto que se sustituye el bencil 3–oxopiperazin–1–carboxilato por **O23b**, se prepara **O23b**; ESIMS calc. para $C_{26}H_{38}N_5O_8S$ $[M+H]^+$ 580,2, resultó 580,3.

Paso C: Se trata una solución de **O23b** (37,4 mg, 0,65 mmol) en metanol (1 ml) y agua (0,1 ml) con LiOH (5,7 mg, 0,1 mmol) y se la agita de un día para otro. A continuación se purifica directamente la reacción por HPLC de fase inversa iniciada por la masa para producir **O23c**. ESIMS calc. para $C_{24}H_{38}N_5O_8S$ $[M+H]^+$ 556,2, resultó 556,2.

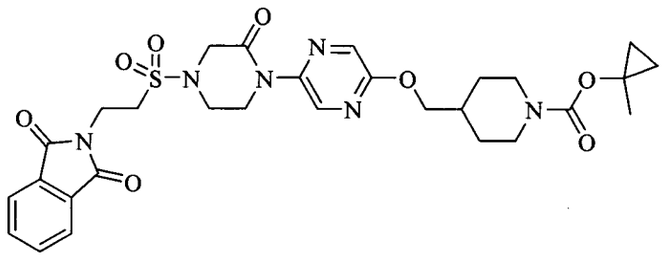
Paso D: Se trata una solución de **O23c** (20 mg, 0,036 mmol) en diclorometano (1 ml) con HATU (13,7 mg, 0,036 mmol) y N,N–diisopropiletilamina (4,6 mg, 0,036 mmol) y se la agita de un día para otro. Se retira el solvente y se disuelve el residuo en metanol y se lo purifica directamente por HPLC de fase inversa iniciada por la masa. ^{1}H–NMR (400MHz, $CDCl_3$) δ 8,64 (d, *J* = 1,4 Hz, 1H), 8,02 (d, *J* = 1,4 Hz, 1H), 4,25 (m, 2H), 4,20 (s, 2H), 4,18 (s, 2H), 4,06 (m, 2H), 3,73 (m, 2H), 3,33 (ddd, *J* = 7,7, 5,3, 5,3 Hz, 2H), 2,74 (dd, *J* = 12,3, 12,1 Hz, 2H), 2,27 (s, 1H), 2,07 (ddd, *J* = 7,7, 5,2, 5,2 Hz, 2H), 1,98 (m, 1H), 1,80 (m, 2H), 1,55 (s, 3H), 1,26 (m, 2H), 0,86 (m, 4H), 0,62 (m, 2H), 0,57 (m, 2H); ESIMS calc, para $C_{24}H_{36}N_5O_7S$ $[M+H]^+$ 538,2, resultó 538,8.

Ejemplo O24: 1–Metilciclopropil 4–((5–(4–(3–aminopropilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



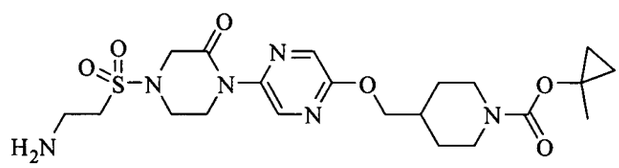
Siguiendo un procedimiento similar al utilizado para la preparación de **M18** a partir de **M6** excepto que se sustituye **M6** por **O5**, se prepara **O23b**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,45 (d, J = 1,4 Hz, 1H), 7,82 (d, J = 1,4 Hz, 1H), 3,99 (d, J = 6,8 Hz, 2H), 3,97 (s, 2H), 3,86 (m, 2H), 3,51 (m, 2H), 2,96 (m, 2H), 2,68 (t, J = 6,8 Hz, 2H), 2,55 (m, 2H), 1,78 (m, 3H), 1,60 (m, 2H), 1,35 (s, 3H), 1,18 (br s, 2H), 1,06 (m, 2H), 0,67 (m, 2H), 0,42 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{22}H_{35}N_6O_6S$ calc.: 511,2, resultó: 511,2.

Ejemplo O25: 1–Metilciclopropil 4–((5–(4–(2–(1,3–dioxoisoindolin–2–il)etilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



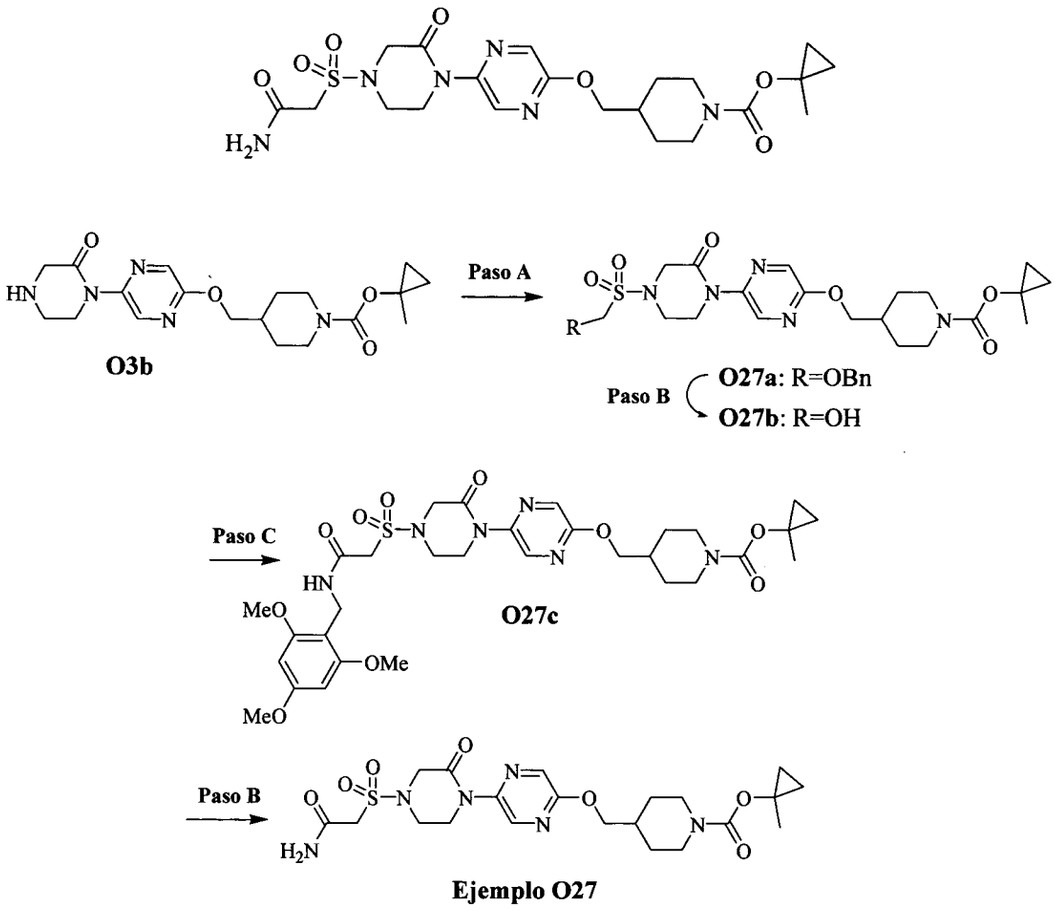
Siguiendo un procedimiento similar al utilizado para la preparación de **O3** a partir de **O3b** excepto que se sustituye cloruro de *n*–propansulfonilo por cloruro de 2–(1,3–dioxoisoindolin–2–il)etansulfonilo, se prepara **O25**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,58 (d, J = 1,4 Hz, 1H), 7,94 (d, J = 1,4 Hz, 1H), 7,80 (m, 2H), 7,67 (m, 2H), 4,10 (s, 7H), 3,99 (m, 2H), 3,67 (m, 2H), 3,40 (t, J = 6,8 Hz, 2H), 2,68 (m, 2H), 1,94 (m, 1H), 1,73 (m, 2H), 1,50 (s, 3H), 1,20 (m, 2H), 0,80 (m, 2H), 0,55 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{29}H_{35}N_6O_8S$ calc.: 627,2, resultó: 627,2.

Ejemplo O26: 1–Metilciclopropil 4–((5–(4–(2–aminoetilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



Se trata una solución de **O25** (15 mg, 0,02 mmol) en etanol (2 ml) con hidrazina (8 µl, 0,24 mmol) y se la agita por espacio de de 1 hora. Se concentra la solución y se la purifica empleando HPLC de fase inversa iniciada por la masa para producir **O26**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,51 (d, J = 1,4 Hz, 1H), 7,88 (d, J = 1,4 Hz, 1H), 4,05 (m, 4H), 3,92 (m, 2H), 3,58 (m, 2H), 3,10 (m, 2H), 3,03 (m, 2H), 2,61 (m, 2H), 1,85 (m, 1H), 1,66 (m, 2H), 1,41 (s, 3H), 1,13 (m, 2H), 0,73 (m, 2H), 0,49 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{21}H_{33}N_6O_6S$ calc.: 497,2, resultó: 497,2.

Ejemplo O27: 1–Metilciclopropil 4–((5–(4–(2–amino–2–oxoetilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



Ejemplo O27

Paso A: Siguiendo un procedimiento similar al utilizado para la preparación de **O3** a partir de **O3b** excepto que se sustituye el cloruro *n*–propansulfonilo por bencil 2–(clorosulfonil)acetato, se prepara **O27a**; ESIMS *m/z* por $(M+H)^+$ $C_{28}H_{36}N_5O_8S$ calc.: 602,2, resultó: 602,1.

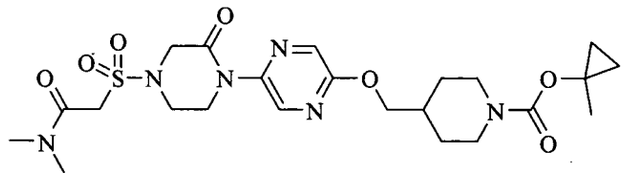
Paso B: Siguiendo un procedimiento similar al utilizado para la preparación de **M48** a partir de **M48e**, se prepara **O27b**; ^1H NMR (400 MHz, $CDCl_3$) δ 8,37 (d, J = 1,2 Hz, 1H), 7,80 (d, J = 1,2 Hz, 1H), 4,11 (s, 2H), 3,96 (m, 3H), 3,84 (m, 5H), 3,59 (m, 2H), 2,53 (m, 2H), 1,76 (m, 1H), 1,57 (m, 2H), 1,32 (s, 3H), 1,05 (m, 2H), 0,64 (m, 2H), 0,40 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{21}H_{30}N_5O_8S$ calc,: 512,2, resultó: 512,1.

Paso C: Se trata una solución de **O27b** (60 mg, 0,12 mmol), HATU (89 mg, 0,23 mmol) y 2,4,6–trimetoxibencilamina–HCl (33 mg, 0,14 mmol) en diclorometano (10 ml) con diisopropiletilamina (61 µl, 0,35 mmol) y se agita la mezcla a temperatura

ambiente por espacio de 14 horas. Se diluye la mezcla con agua y se la extrae diclorometano. Se secan los extractos orgánicos, se los filtra y concentra para dar **O27c**, que fue utilizado sin más purificación. ESIMS *m/z* por $(M+H)^+$ $C_{31}H_{43}N_6O_{10}S$ calc.: 691,3, resultó: 691,2.

Paso B: Se trata una solución de **O27c** (0,12 mmol) en diclorometano (2 ml) con TFA (1 ml) y se la deja madurar por espacio de 1 hora a temperatura ambiente. Se concentra el residuo y se lo purifica utilizando HPLC de fase inversa iniciada por la masa para producir **O27**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,59 (d, J = 1,6 Hz, 1H), 7,95 (d, J = 1,6 Hz, 1H), 4,19 (s, 2H), 4,12 (d, J = 6,4 Hz, 2H), 3,99 (m, 2H), 3,90 (s, 2H), 3,72 (m, 2H), 2,68 (m, 3H), 1,89 (m, 1H), 1,72 (m, 2H), 1,48 (s, 3H), 1,13 (m, 2H), 0,80 (m, 2H), 0,55 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{21}H_{31}N_6O_7S$ calc,: 511,2, resultó: 511,2.

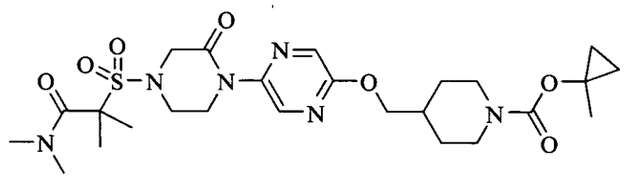
Ejemplo O28: 1–Metilciclopropil 4–((5–(4–(2–(dimetilamino)–2–oxoetilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.

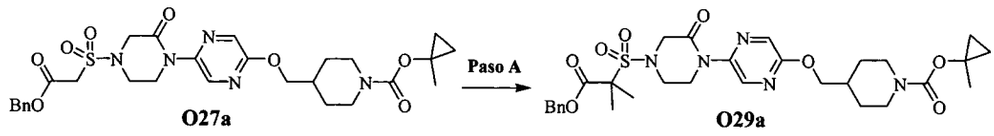


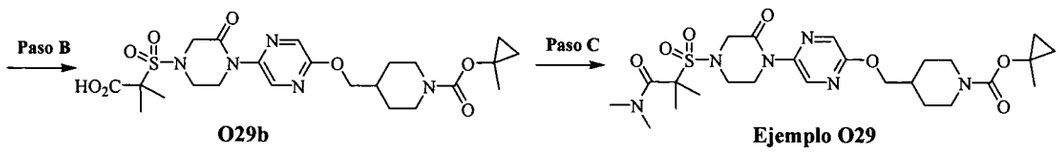
Siguiendo un procedimiento similar al utilizado para la preparación de **O27c** a partir de **O27b** excepto que se sustituye 2,4,6–trimetoxibencilamina–HCl por dimetilamina–HCl, **O28** se prepara; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,67 (d, J = 1,6 Hz, 1H), 8,03 (d, J = 1,6 Hz, 1H), 4,28 (s, 2H), 4,19 (m, 4H), 4,06 (m, 2H), 3,82 (s, 2H), 3,23 (s, 3H), 3,04 (s, 3H), 2,77 (m, 2H), 2,00 (m, 1H), 1,81 (m, 2H), 1,57 (s, 3H), 1,28 (m, 2H), 0,88 (m, 2H), 0,64 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{23}H_{35}N_6O_7S$ calc,: 539,2, resultó: 539,2.

Ejemplo O29: 1–Metilciclopropil 4–((5–(4–(1–(dimetilamino)–2–metil–1–oxopropan–2–ilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–

1–carboxilato.







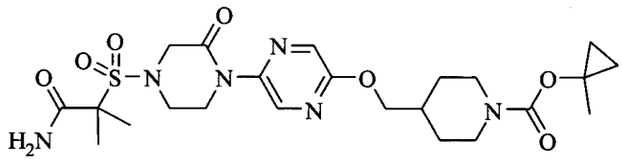
Paso A: Se trata una solución de **O27a** (200 mg, 0,33 mmol) en dimetilformamida (5 ml) con carbonato de potasio (138 mg, 1,0 mmol) y yodometano (63 µl, 1,0 mmol) y se la calienta a 70 °C por espacio de 1 hora. Se diluye la mezcla con agua y se la extrae con acetato de etilo. Se lava la capa orgánica con agua y solución salina, se la seca ($MgSO_4$), filtra y concentra para producir **O29a**; ESIMS *m/z* por $(M+H)^+$ $C_{30}H_{40}N_5O_8S$ calc.: 630,3, resultó: 630,3.

Paso B: Se trata una solución de **O29a** (cruda a partir de **Paso A**) y formiato de amonio (~1 mmol) en metanol (5 ml) con Pd/C (húmedo, al 10%) y se la calienta a 80 °C por espacio de 1 hora. Se enfría la mezcla, se la filtra y se lava el filtrado con agua y acetato de etilo. Se separan las capas y se lava la capa orgánica con HCl 1N y solución salina, luego se la seca sobre $MgSO_4$, filtra y concentra. Se purifica el residuo utilizando HPLC de fase inversa iniciada por la masa para producir **O29b**; ^1H NMR (400 MHz, $CDCl_3$) δ 8,61 (d, J = 1,6 Hz, 1H), 8,05 (d, J = 1,6 Hz, 1H), 4,43 (s, 2H), 4,21 (d, J = 6,4 Hz, 2H), 4,05 (m, 2H), 3,87 (br s, 2H), 2,78 (m, 2H), 2,03 (m, 1H), 1,82 (s, 6H), 1,57 (s, 3H), 1,28 (m, 2H), 0,89 (m, 2H), 0,65 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{23}H_{34}N_5O_8S$ calc,: 540,2, resultó: 540,1.

Paso C: Siguiendo un procedimiento similar al utilizado para la

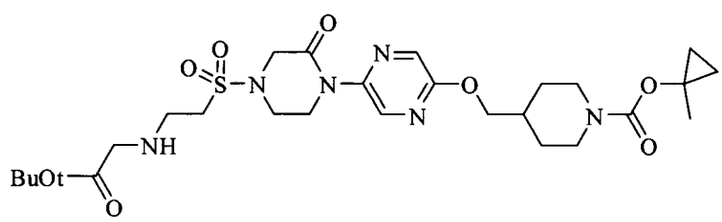
preparación de **O27c** a partir de **O27b** excepto que se sustituye la 2,4,6–trimetoxibencilamina–HCl por dimetilamina–HCl y **O27c** por **O29b**, se prepara **O29**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,51 (d, J = 1,4 Hz, 1H), 7,87 (d, J = 1,4 Hz, 1H), 4,14 (s, 2H), 4,04 (d, J = 6,4 Hz, 2H), 3,88 (m, 2H), 3,66 (s, 2H), 2,60 (m, 2H), 1,84 (m, 1H), 1,65 (m, 2H), 1,54 (s, 6H), 1,41 (s, 6H), 1,11 (m, 2H), 0,73 (m, 2H), 0,48 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{25}H_{39}N_6O_7S$ calc,: 567,3, resultó: 567,2.

Ejemplo O30: 1–Metilciclopropil 4–((5–(4–(1–amino–2–metil–1–oxopropan–2–ilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



Siguiendo un procedimiento similar al utilizado para la preparación de **O27** a partir de **O27b** excepto que se sustituye **O27b** por **O29b**, se prepara **O30**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,66 (d, J = 1,4 Hz, 1H), 8,03 (d, J = 1,4 Hz, 1H), 4,23 (s, 2H), 4,20 (d, J = 6,4 Hz, 2H), 4,02 (m, 2H), 3,78 (s, 2H), 2,77 (m, 2H), 2,00 (m, 1H), 1,81 (s, 6H), 1,57 (s, 3H), 1,27 (m, 2H), 0,89 (m, 2H), 0,64 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{23}H_{35}N_6O_7S$ calc,: 539,2, resultó: 539,2.

Ejemplo O31: 1–Metilciclopropil 4–((5–(4–(2–(2–terc–butoxi–2–oxoetilamino)etilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.

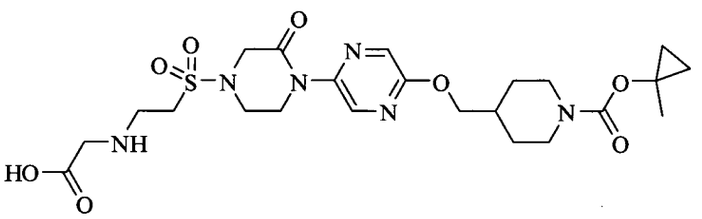


Una solución de **O13a** (50 mg, 0,10 mmol), t–butilglicina–HCl (105 mg, 0,62

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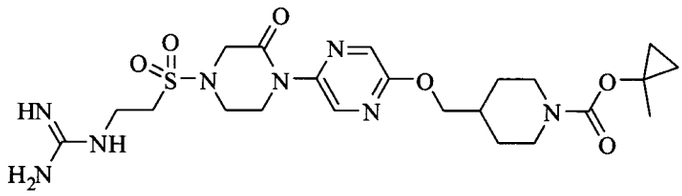
mmol) y diisopropiletilamina (108 µl, 0,62 mmol) en metanol (2 ml) y dimetilformamida (2 ml) y se la agita a temperatura ambiente por espacio de 14 horas. Se diluye la mezcla con agua y se la extrae con acetato de etilo. Se lavan los extractos orgánicos con agua y luego con solución salina, se los seca sobre $MgSO_4$ y filtra. Se concentra el residuo y se lo purifica utilizando HPLC de fase inversa iniciada por la masa para producir **O31**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 1.2 Hz, 1H), 8,04 (d, J = 1.2 Hz, 1H), 4.20 (s, 4H), 4,07 (m, 2H), 3.76 (m, 2H), 3.48 (s, 2H), 3.40 (m, 2H), 3.28 (m, 2H), 2.77 (m, 2H), 2,00 (m, 1H), 1.82 (m, 2H), 1.57 (s, 3H), 1.49 (s, 9H), 1.28 (m, 2H), 0,89 (m, 2H), 0,64 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{27}H_{43}N_6O_8S$ calc.: 611.3, resultó: 611.2.

Ejemplo O32: Ácido 2–(2–(4–(5–((1–((1–Metilciclopropoxi)carbonil)piperidin–4–il)metoxi)pirazin–2–il)–3–oxopiperazin–1–ilsulfonil)etilamino)acético.



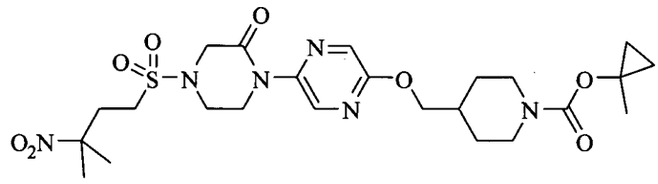
Se trata una solución de **O31** (31 mg, 0,05 mmol) en diclorometano (1 ml) con HCl (1 ml de 4N en dioxano) y se la hace madurar por espacio de 2 horas a temperatura ambiente. Se concentra la mezcla y se la purifica empleando HPLC de fase inversa iniciada por la masa para producir el **O32**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,51 (d, J = 1,4 Hz, 1H), 7,90 (d, J = 1,4 Hz, 1H), 4,01 (m, 4H), 3,88 (m, 2H), 3,46 (m, 8H), 2,69 (m, 2H), 1,88 (m, 1H), 1,69 (m, 2H), 1,47 (s, 3H), 1,18 (m, 2H), 0,80 (m, 2H), 0,55 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{23}H_{35}N_6O_8S$ calc,: 555,2, resultó: 555,1.

Ejemplo O33: 1–Metilciclopropil 4–((5–(4–(2–guanidinoetilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



Se trata una solución de **O26** (22 mg, 0,044 mmol) y nitrato de 3,5–dimetoxipirazol–1–carboxamidina (13 mg, 0,066 mmol) en dimetilformamida (3 ml) con diisopropiletilamina (23 µl, 0,13 mmol) y se la agita a temperatura ambiente por espacio de 14 horas. Se diluye la mezcla con hidrogenocarbonato de sodio y se la extrae con acetato de etilo. Se lava la capa orgánica con solución salina, se la seca sobre $MgSO_4$, filtra, concentra y purifica empleando HPLC de fase inversa iniciada por la masa para producir **O33**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,48 (d, J = 1,4 Hz, 1H), 7,93 (d, J = 1,4 Hz, 1H), 4,11 (m, 4H), 4,06 (m, 2H), 3,92 (m, 2H), 3,62 (m, 3H), 2,68 (m, 2H), 1,80 (m, 1H), 1,72 (m, 2H), 1,18 (m, 3H), 0,80 (m, 2H), 0,56 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{22}H_{35}N_8O_6S$ calc,: 539,2, resultó: 539,2.

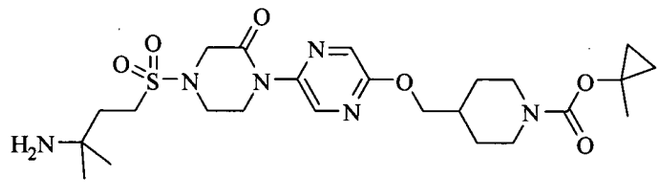
Ejemplo O34: 1–Metilciclopropil 4–((5–(4–(3–metil–3–nitrobutilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



Se trata una solución de **O13a** (62 mg, 0,13 mmol) y 2–nitropropano (116 µl, 1,29 mmol) en metanol (0,5 ml) y tetrahidrofurano (1 ml) con 1,8–diazabiciclo[5.4,0]undec–7–eno (154 µl, 1,03 mmol) y se la agita a temperatura ambiente por espacio de 14 horas. Se diluye la mezcla con agua, se la extrae con acetato de etilo y se la lava con solución salina. Se seca la capa orgánica ($MgSO_4$), se la filtra, concentra y purifica en gel de sílice empleando 0–100% de acetato de etilo en diclorometano para producir **O34**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,59 (d, J = 1,4 Hz, 1H), 7,95 (d, J = 1,4 Hz, 1H), 4,11 (m, 4H), 4,00 (m, 2H), 3,65

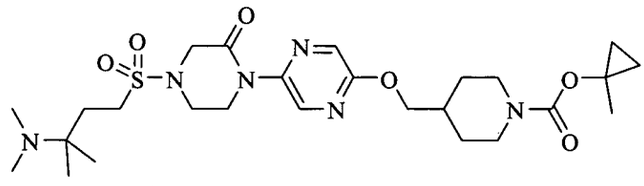
(m, 2H), 2,99 (m, 2H), 2,68 (m, 2H), 2,35 (m, 2H), 1,92 (m, 1H), 1,72 (m, 2H), 1,59 (s, 6H), 1,48 (s, 3H), 1,18 (m, 2H), 0,80 (m, 2H), 0,56 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{24}H_{37}N_6O_8S$ calc,: 569,2, resultó: 569,2.

Ejemplo O35: 1–Metilciclopropil 4–((5–(4–(3–amino–3–metilbutilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



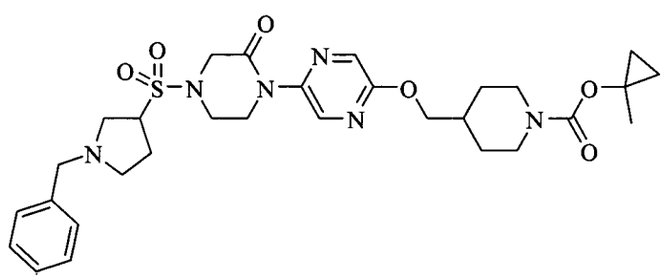
Se trata una solución de **O34** (105 mg, 0,18 mmol) en una mezcla de metanol (5 ml) y tetrahidrofurano (4 ml) con $NiCl_2$ (72 mg, 0,55 mmol) seguido por borohidruro de sodio (21 mg, 0,55 mmol) y se agita la mezcla así obtenida a temperatura ambiente por espacio de 3 horas. Se diluye la mezcla con acetato de etilo y se la filtra, luego se la lava con hidrogenocarbonato de sodio acuoso saturado y solución salina. Se seca la capa orgánica ($MgSO_4$), se la filtra, concentra y purifica utilizando HPLC de fase inversa iniciada por la masa para producir **O35**; ^1H NMR (400 MHz, $CDCl_3$) δ 8,63 (d, J = 1,2 Hz, 1H), 8,04 (d, J = 1,2 Hz, 1H), 4,20 (d, J = 6,4 Hz, 2H), 4,18 (s, 2H), 4,05 (m, 2H), 3,74 (m, 2H), 3,27 (m, 2H), 2,75 (m, 2H), 2,00 (m, 3H), 1,80 (m, 2H), 1,56 (s, 3H), 1,35 (m, 2H), 1,29 (s, 6H), 0,88 (m, 2H), 0,64 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{24}H_{39}N_6O_6S$ calc,: 539,3, resultó: 539,2.

Ejemplo O36: 1–Metilciclopropil 4–((5–(4–(3–(dimetilamino)–3–metilbutilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



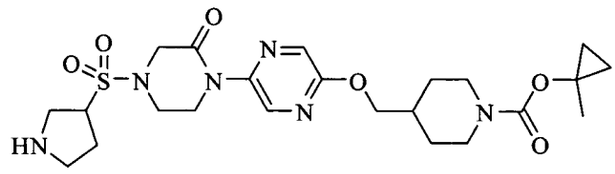
Se trata una solución de **O35** (56 mg, 0,10 mmol) en dimetilformamida (2 ml) con K_2CO_3 (43 mg, 0,31 mmol) y yodometano (13 µl, 0,21 mmol) y se la agita a temperatura ambiente por espacio de 3 horas. Se diluye la mezcla con agua, se la extrae con acetato de etilo, y se la lava con agua y solución salina. Se secan los extractos orgánicos ($MgSO_4$), se los filtra, concentra y purifica utilizando HPLC de fase inversa iniciada por la masa para producir **O36**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,66 (d, J = 1,2 Hz, 1H), 8,04 (d, J = 1,2 Hz, 1H), 4,20 (d, J = 6,4 Hz, 2H), 4,18 (s, 2H), 4,07 (m, 2H), 3,72 (m, 2H), 3,21 (m, 2H), 2,77 (m, 2H), 2,35 (br s, 4H), 2,02 (m, 3H), 1,82 (m, 2H), 1,57 (s, 3H), 1,29 (m, 2H), 1,15 (br s, 6H), 0,88 (m, 2H), 0,64 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{26}H_{43}N_6O_6S$ calc,: 567,3, resultó: 567,2.

Ejemplo O37: 1–Metilciclopropil 4–((5–(4–(1–bencilpirrolidin–3–ilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



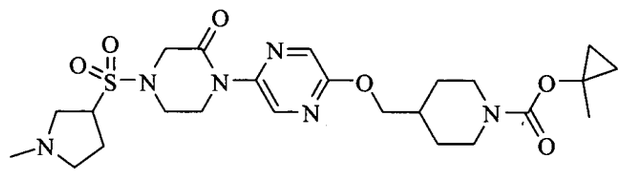
Se trata una solución de **O13a** (96 mg, 0,20 mmol) y N–trimetilsilil–N–cianometilbencilamina (104 µl, 0,42 mmol) en acetonitrilo (5 ml) con AgF (54 mg, 0,42 mmol) y se la calienta a 75 °C por espacio de 4 horas. Se filtra la mezcla, se la lava con acetato de etilo, se la concentra y purifica en gel de sílice utilizando 0–100% de acetato de etilo en hexano para producir **O37**; ESIMS *m/z* por $(M+H)^+$ $C_{30}H_{41}N_6O_6S$ calc.: 613,3, resultó: 613,2.

Ejemplo O38: 1–Metilciclopropil 4–((5–(2–oxo–4–(pirrolidin–3–ilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



Se hidrogena una solución de **O37** (45 mg) en EtOH (5 ml) en un dispositivo H–cube® (Pd/C, 50 bar H_2, 70 °C, 1 ml/min). Se concentra el residuo para producir **O38** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,58 (d, J = 1,4 Hz, 1H), 7,95 (d, J = 1,4 Hz, 1H), 4,11 (m, 4H), 3,98 (m, 2H), 3,68 (m, 2H), 3,50 (m, 1H), 3,40 (dd, J = 4,0, 13,2 Hz, 1H), 3,13 (m, 2H), 2,83 (m, 1H), 2,68 (m, 2H), 2,10 (m, 2H), 1,89 (m, 1H), 1,73 (m, 5H), 1,48 (s, 3H), 1,18 (m, 2H), 0,80 (m, 2H), 0,56 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{23}H_{35}N_6O_6S$ calc,: 523,2, resultó: 523,2.

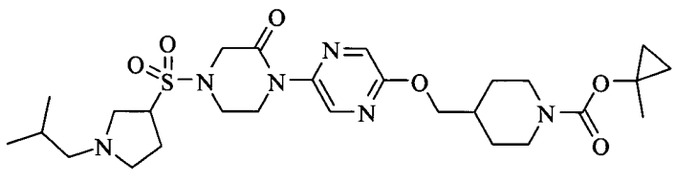
Ejemplo O39: 1–Metilciclopropil 4–((5–(4–(1–metilpirrolidin–3–ilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



Se trató una solución de **O38** (24 mg, 0,05 mmol) y paraformaldehído (~0,25 mmol) en 1,2–dicloroetano (5 ml) con acético ácido (50 µl) y se la calienta a 80 °C por espacio de 1 hora. Se agrega $NaBH(OAc)_3$ (20 mg, 0,09 mmol) y se agita la mezcla a 80 °C durante 2 horas más. SE enfría la mezcla, se la diluye con hidrogenocarbonato de sodio acuoso saturado y se la extrae con diclorometano (2x). Se secan las capas orgánicas sobre $MgSO_4$, se las filtra, concentra y purifica empleando HPLC de fase inversa iniciada por la masa para producir **O39**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,57 (d, J = 1,4 Hz, 1H), 7,95 (d, J = 1,4 Hz, 1H), 4,17 (d, J = 7,2 Hz, 2H), 4,12 (d, J = 6,4 Hz, 2H), 3,71 (m, 3H), 2,86 (m, 1H), 2,66 (m, 3H), 2,33 (s, 3H), 2,18 (m, 2H), 1,91 (m, 1H), 1,73 (m, 2H), 1,48 (s, 3H), 1,20

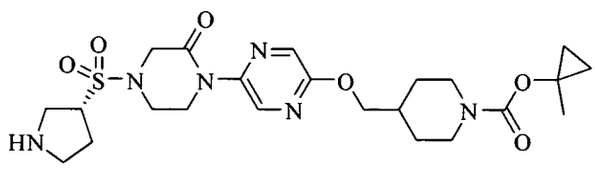
(m, 2H), 0,80 (m, 2H), 0,55 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{24}H_{37}N_6O_6S$ calc,: 537,3, resultó: 537,2.

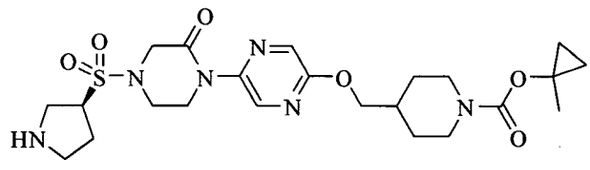
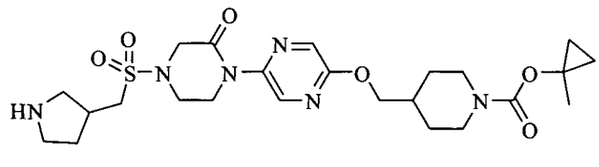
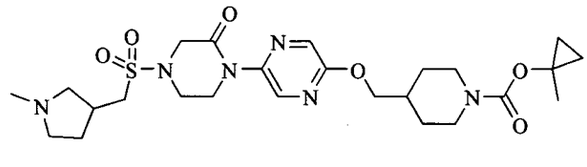
Ejemplo O40: 1–Metilciclopropil 4–((5–(4–(1–isobutilpirrolidin–3–ilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.

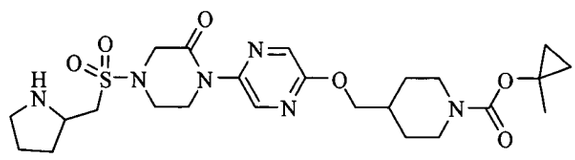
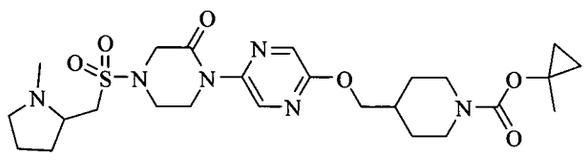
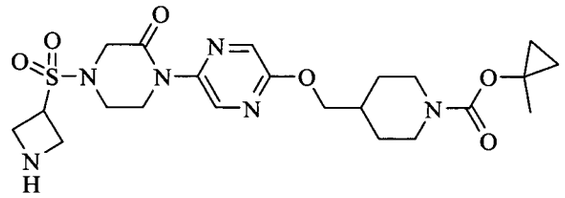


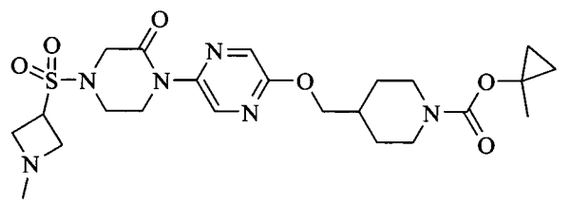
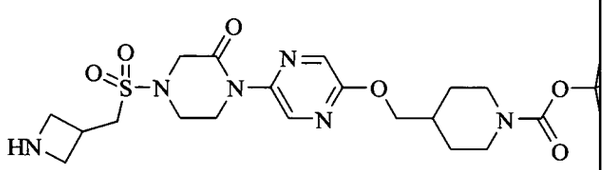
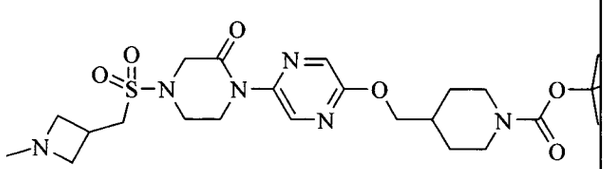
Siguiendo un procedimiento similar al utilizado para la preparación de **O39** a partir de **O38** excepto que se sustituye el paraformaldehído por isobutiraldehído, se prepara **O40**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,58 (d, J = 1,2 Hz, 1H), 7,94 (d, J = 1,2 Hz, 1H), 4,18 (d, J = 6,0 Hz, 2H), 4,12 (d, J = 4,4 Hz, 2H), 3,96 (m, 2H), 3,69 (m, 2H), 2,80 (m, 2H), 2,68 (m, 2H), 2,58 (m, 2H), 2,17 (m, 3H), 1,91 (m, 1H), 1,73 (m, 2H), 1,65 (m, 1H), 1,48 (s, 3H), 1,20 (m, 2H), 0,84 (m, 6H), 0,79 (m, 2H), 0,55 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{27}H_{43}N_6O_6S$ calc,: 579,3, resultó: 579,2

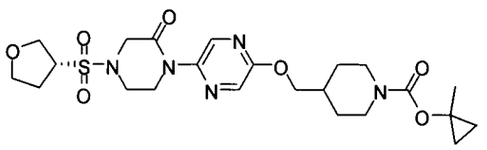
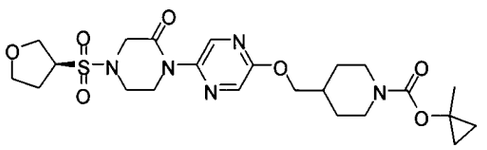
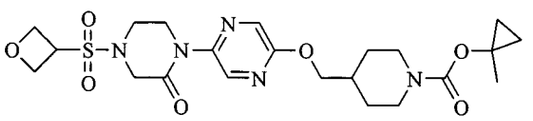
Siguiendo un procedimiento similar al utilizado para la preparación de **M48** a partir de **M48a** excepto que se sustituye **M48a** por el alcohol apropiado y **M1c** por **O3b**, seguido en algunos casos por aminaciones reductivas como en el caso de la preparación de **O39** y **O40**, se preparan los siguientes compuestos;

Ej.	Estructura	Datos analíticos
O41		^{1}H NMR (400 MHz, $CDCl_3$) δ 8,58 (d, J = 1,4 Hz, 1H), 7,95 (d, J = 1,4 Hz, 1H), 4,11 (m, 4H), 3,97 (m, 2H), 3,68 (m, 2H), 3,60 (m, 1H), 3,39 (dd, J = 4,0, 12,8 Hz, 1H), 3,10 (m, 2H), 2,82 (m, 1H), 2,68 (m, 2H), 2,08 (m, 2H), 1,91 (s, 1H), 1,72 (m, 2H), 1,48 (s, 3H), 1,20 (m, 2H), 0,80 (m, 2H),

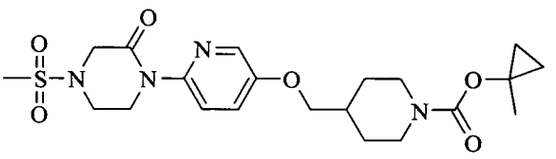
		0,55 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{23}H_{35}N_6O_6S$ calc,: 523,2, resultó: 523,2.
O42		^1H NMR (400 MHz, $CDCl_3$) δ 8,58 (d, J = 1,4 Hz, 1H), 7,95 (d, J = 1,4 Hz, 1H), 4,11 (m, 4H), 3,97 (m, 2H), 3,68 (m, 2H), 3,60 (m, 1H), 3,39 (dd, J = 4,0, 12,8 Hz, 1H), 3,10 (m, 2H), 2,82 (m, 1H), 2,68 (m, 2H), 2,08 (m, 2H), 1,91 (s, 1H), 1,72 (m, 2H), 1,48 (s, 3H), 1,20 (m, 2H), 0,80 (m, 2H), 0,55 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{23}H_{35}N_6O_6S$ calc,: 523,2, resultó: 523,2.
O43		^1H NMR (400 MHz, $CDCl_3$) δ 8,45 (d, J = 1,4 Hz, 1H), 7,82 (d, J = 1,4 Hz, 1H), 3,98 (d, J = 6,4 Hz, 2H), 3,95 (s, 2H), 3,85 (m, 2H), 3,50 (m, 2H), 3,13 (m, 2H), 2,89 (m, 4H), 2,61 (m, 5H), 1,97 (m, 5H), 1,78 (m, 2H), 1,59 (m, 2H), 1,44 (m, 2H), 1,35 (s, 3H), 1,05 (m, 2H), 0,67 (m, 2H), 0,43 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{24}H_{37}N_6O_6S$ calc,: 537,3, resultó: 537,3.
O44		^1H NMR (400 MHz, $CDCl_3$) δ 8,85 (d, J = 1,2 Hz, 1H), 7,95 (d, J = 1,2 Hz, 1H), 4,11 (d, J = 6,4 Hz, 2H), 4,08 (s, 2H), 3,98 (m, 2H), 3,62 (m, 2H), 3,04 (m, 2H), 2,68 (m, 6H), 2,50 (m, 2H), 2,33 (s, 3H), 2,17 (m, 1H), 1,91 (m, 2H), 1,72 (m, 5H), 1,62 (m, 2H), 1,48 (s, 3H), 1,18 (m, 2H), 0,79 (m,

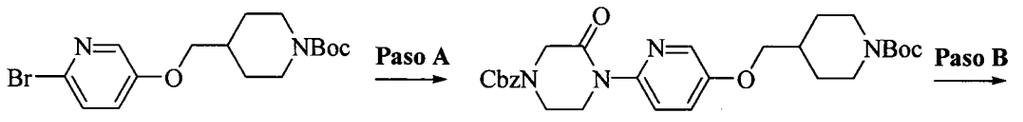
		2H), 0,55 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{25}H_{39}N_6O_6S$ calc,: 551,3, resultó: 551,2.
O45		^1H NMR (400 MHz, $CDCl_3$) δ 8,57 (d, J = 1,2 Hz, 1H), 7,94 (d, J = 1,2 Hz, 1H), 4,15 (m, 5H), 3,99 (m, 2H), 3,65 (m, 3H), 3,24 (m, 1H), 3,12 (dd, J = 4,0, 14,0 Hz, 1H), 2,99 (m, 2H), 2,68 (m, 2H), 2,04 (m, 2H), 1,85 (m, 9H), 1,48 (s, 3H), 1,20 (m, 2H), 0,80 (m, 2H), 0,56 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{24}H_{37}N_6O_6S$ calc,: 537,3, resultó: 537,3.
O46		^1H NMR (400 MHz, $CDCl_3$) δ 8,58 (d, J = 1,2 Hz, 1H), 7,95 (d, J = 1,2 Hz, 1H), 4,11 (d, J = 6,4 Hz, 2H), 4,10 (s, 2H), 3,99 (m, 2H), 3,64 (m, 2H), 2,68 (m, 2H), 2,37 (s, 2H), 2,20 (s, 2H), 1,90 (m, 1H), 1,74 (m, 4H), 1,48 (s, 3H), 1,20 (m, 2H), 0,79 (m, 2H), 0,55 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{25}H_{39}N_6O_6S$ calc,: 551,3, resultó: 551,2.
O47		^1H NMR (400 MHz, $CDCl_3$) δ 8,57 (s, 1H), 7,95 (s, 1H), 4,16 (m, 2H), 4,12 (m, 4H), 4,02 (m, 2H), 3,97 (m, 2H), 3,82 (m, 2H), 3,66 (m, 3H), 2,68 (m, 2H), 2,04 (m, 2H), 1,91 (m, 1H), 1,72 (m, 2H), 1,48 (s, 3H), 1,18 (m, 2H), 0,80 (m, 2H), 0,55 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{22}H_{33}N_6O_6S$ calc,: 509,2, resultó: 509,2.

O48		^{1}H NMR (400 MHz, $CDCl_3$) δ 8,57 (d, J = 1,0 Hz, 1H), 7,95 (d, J = 1,0 Hz, 1H), 4,14 (s, 2H), 4,12 (d, J = 4,4 Hz, 2H), 3,96 (m, 2H), 3,90 (m, 1H), 3,67 (m, 2H), 3,54 (m, 2H), 3,44 (m, 2H), 2,68 (m, 2H), 2,30 (s, 3H), 1,91 (m, 1H), 1,72 (m, 2H), 1,48 (s, 3H), 1,18 (m, 2H), 0,80 (m, 2H), 0,55 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{23}H_{35}N_6O_6S$ calc,: 523,2, resultó: 523,2..
O49		^{1}H NMR (400 MHz, $CDCl_3$) δ 8,59 (d, J = 1,2 Hz, 1H), 7,94 (d, J = 1,4 Hz, 1H), 4,12 (d, J = 6,8 Hz, 2H), 4,06 (s, 2H), 3,98 (m, 2H), 3,77 (m, 2H), 3,72 (m, 1H), 3,62 (m, 2H), 3,44 (m, 2H), 3,26 (m, 2H), 3,18 (m, 1H), 2,68 (m, 2H), 1,90 (m, 1H), 1,73 (m, 2H), 1,48 (s, 3H), 1,20 (m, 3H), 0,80 (m, 2H), 0,55 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{23}H_{35}N_6O_6S$ calc,: 523,2, resultó: 523,2.
O50		^{1}H NMR (400 MHz, $CDCl_3$) δ 8,59 (d, J = 1,6 Hz, 1H), 7,94 (d, J = 1,6 Hz, 1H), 4,12 (d, J = 6,8 Hz, 2H), 3,98 (m, 3H), 3,72 (m, 1H), 3,62 (m, 2H), 3,43 (m, 2H), 3,23 (d, J = 7,2 Hz, 2H), 2,95 (m, 2H), 2,84 (m, 1H), 2,68 (m, 2H), 2,23 (s, 3H), 1,91 (m, 1H), 1,72 (m, 2H), 1,48 (s, 3H), 1,20 (m, 3H), 0,80 (m, 2H), 0,55 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{24}H_{37}N_6O_6S$ calc,: 537,3, resultó:

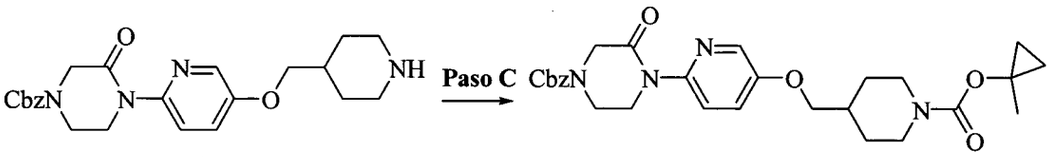
		537,2.
O51		^{1}H–NMR (400MHz, $CDCl_3$) δ 8,64 (d, *J* = 1,4 Hz, 1H), 8,02 (d, *J* = 1,4 Hz, 1H), 4,23 (m, 2H), 4,19 (m, 2H), 4,06–4,06 (m, 5H), 3,84 (m, 2H), 3,76 (m, 2H), 2,74 (m, 2H), 2,33 (m, 2H), 1,98 (m, 1H), 1,80 (m, 2H), 1,55 (s, 3H), 1,26 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS calc, para $C_{23}H_{34}N_5O_7S$ $[M+H]^+$ 524,2, resultó 524,3,.
O52		^{1}H–NMR (400MHz, $CDCl_3$) δ 8,65 (d, *J* = 1,4 Hz, 1H), 8,02 (d, *J* = 1,4 Hz, 1H), 4,21 (m, 2H), 4,18 (d, *J* = 6,5 Hz, 2H), 4,11–4,16 (m, 2H), 3,98–4,06 (m, 5H), 3,84 (m, 2H), 3,76 (m, 2H), 2,75 (dd, *J* = 12,3, 12,3 Hz, 2H), 2,33 (m, 2H), 1,97 (m, 1H), 1,79 (m, 2H), 1,55 (s, 3H), 1,26 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS calc, para $C_{23}H_{34}N_5O_7S$ $[M+H]^+$ 524,2, resultó 524,4.
O53		^{1}H–NMR (400MHz, $CDCl_3$) δ8,65 (d, *J* = 1,4 Hz, 1H), 8,02 (d, *J* = 1,4 Hz, 1H), 4,93 (m, 4H), 4,51 (tt, *J* = 8,0, 6,4 Hz, 1H), 3,95–4,30 (m, 8H), 3,75 (m, 2H), 2,75 (m, 2H), 1,98 (m, 1H), 1,79 (m, 2H), 1,55 (s, 3H), 1,26 (m, 2H), 0,87 (m, 2H), 0,63 (m, 2H); ESIMS calc, para $C_{22}H_{32}N_5O_7S$ $[M+H]^+$ 510,2, resultó 510,2.

Ejemplo O54: 1–Metilciclopropil 4–((5–(4–(isopropilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.

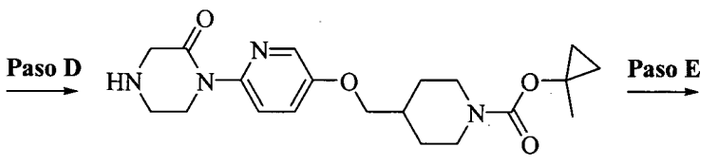




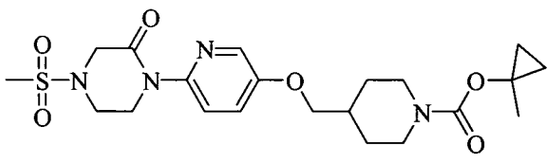
B2b **O54a**



O54b **O54c**



O54d



Ejemplo O54

Paso A: : Siguiendo un procedimiento similar al utilizado para la preparación de **O1a** a partir de **B4b** excepto que se sustituye **B4b** por **B2b**, se prepara **O54a**; ESIMS *m/z* por $(M+H)^+$ $C_{28}H_{37}N_4O_6$ calc.: 525,3, resultó: 525,2.

Paso B: Se trata una muestra de **O54a** (200 mg, 0,38 mmol) con ácido trifluoroacético (3 ml) y se la hace madurar durante 30 minutos. Se separa el solvente y se trata la reacción con acetato de etilo y se la extrae tres veces con HCl 1 M. Se descarta la capa orgánica y se basifica la capa acuosa con Na_2CO_3 sólido y se la extrae tres veces con acetato de etilo. Se secan los extractos

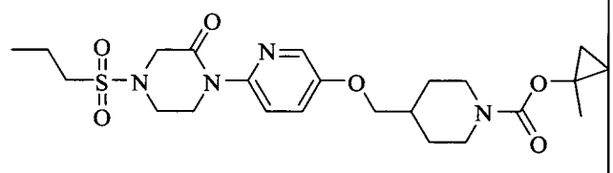
orgánicos combinados sobre $MgSO_4$, se los filtra y evapora para producir **O54b**; ESIMS *m/z* por $(M+H)^+$ $C_{23}H_{29}N_4O_4$ calc.: 425,2, resultó: 425,2.

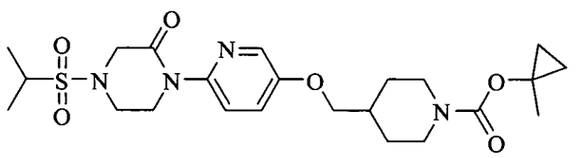
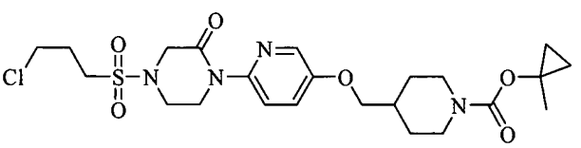
Paso C: Siguiendo un procedimiento similar al utilizado para la preparación de **O2** a partir de **O1** excepto que se sustituye **O1** por **O54b**, se prepara **O54c**; ESIMS *m/z* por $(M+H)^+$ $C_{28}H_{35}N_4O_6$ calc.: 523,3, resultó: 523,2.

Paso D: Siguiendo un procedimiento similar al utilizado para la preparación de **O3b** a partir de **O3a** excepto que se sustituye **O3a** por **O54c**, se prepara **O54d**; ESIMS *m/z* por $(M+H)^+$ $C_{20}H_{29}N_4O_4$ calc.: 389,2, resultó: 389,2.

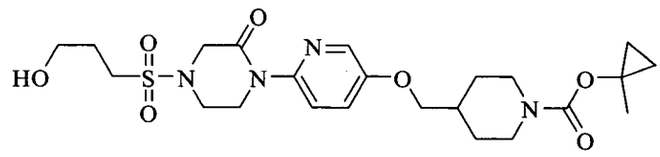
Paso E: Siguiendo un procedimiento similar al utilizado para la preparación de **O3** a partir de **O3b** excepto que se sustituye **O3b** por **O54d** y cloruro de *n*–propanesulfonilo por cloruro de metansulfonilo, se prepara **O54**; ^1H NMR (400 MHz, $CDCl_3$) δ 8,00 (d, J = 2,9 Hz, 1H), 7,66 (d, J = 9,0 Hz, 1H), 7,17 (dd, J = 2,9, 9,0, 1H), 4,10 (m, 2H), 4,05 (m, 2H), 4,03 (s, 2H), 3,77 (d, J = 6,3 Hz, 2H), 3,58 (m, 2H), 2,48 (s, 3H), 2,69 (m, 2H), 1,90 (m, 1H), 1,74 (m, 2H), 1,48 (s, 3H), 1,20 (m, 2H)), 0,79 (m, 2H), 0,57 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{21}H_{31}N_4O_6S$ calc,: 467,2, resultó: 467,2.

Siguiendo un procedimiento similar al utilizado para la preparación de **O54** a partir de **O54d** excepto que se sustituye el cloruro de metansulfonilo por el cloruro de sulfonilo apropiado, se preparan los siguientes compuestos;

Ej.	Estructura	Datos analíticos
O55		^1H NMR (400 MHz, $CDCl_3$) δ 8,07 (d, J = 2,9 Hz, 1H), 7,73 (d, J = 9,0 hz, 1H), 7,24 (dd, J = 9,0, 3,0 Hz, 1H), 4,20 (m, 2H), 4,13 (s, 2H), 4,09 (m, 2H), 3,84 (d, J = 6,3 Hz, 2H), 3,68 (m, 2H), 3,00 (m, 2H), 2,76 (dd, J = 12,4, 12,4 Hz, 2H), 1,98 (m, 1H), 1,89 (m, 2H), 1,82 (m, 2H), 1,55 (s, 3H), 1,27 (m, 2H), 1,08 (t, J = 7,5 Hz, 3H), 0,87 (m, 2H),

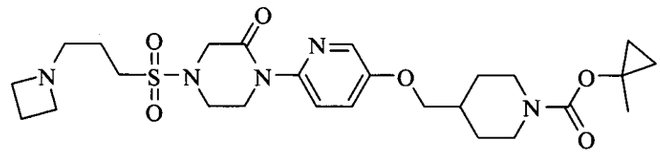
		0,63 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{23}H_{35}N_4O_6S$ calc,,: 495,2, resultó: 495,6.
O56		^{1}H NMR (400 MHz, $CDCl_3$) δ 8,07 (d, J = 2,7 Hz, 1H), 7,73 (d, J = 9,0 Hz, 1H), 7,24 (dd, J = 9,0, 3,0 Hz, 1H), 4,18 (s, 2H), 4,16 (m, 2H), 4,08 (m, 2H), 3,84 (d, J = 6,3 Hz, 2H), 3,73 (m, 2H), 3,27 (sept,, J = 6,8 Hz, 1H), 2,76 (dd, J = 12,3, 12,3 Hz, 2H), 1,97 (m, 1H), 1,82 (m, 2H), 1,55 (s, 3H), 1,40 (d, J = 6,8 Hz, 6H), 1,27 (m, 2H), 0,87 (m, 2H), 0,63 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{23}H_{35}N_4O_6S$ calc,,: 495,2, resultó: 495,6.
O57		^{1}H NMR (400 MHz, $CDCl_3$) δ 8,00 (d, J = 2,8 Hz, 1H), 7,67 (d, J = 9,2 Hz, 1H), 7,17 (dd, J = 9,2, 3,2 Hz, 1H), 4,15 (m, 2H), 4,08 (m, 2H), 4,04 (m, 2H), 3,78 (d, J = 6,4 Hz, 2H), 3,63 (m, 2H), 3,15 (m, 2H), 2,69 (t, J = 12,4 Hz, 2H), 2,26 (m, 2H), 1,91 (m, 1H), 1,75 (d, J = 12,4 Hz, 2H), 1,49 (s, 3H), 1,20 (m, 2H), 0,80 (m, 2H), 0,56 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{23}H_{34}ClN_4O_6S$ calc,,: 529,2, resultó: 529,1.

Ejemplo O58: 1–Metilciclopropil 4–((6–(4–(3–hidroxipropilsulfonil)–2–oxopiperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato.



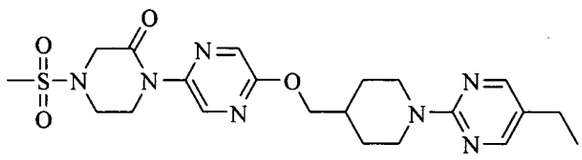
Siguiendo un procedimiento similar al utilizado para la preparación de **O21** a partir de **O5** excepto que se sustituye **O5** por **O57**, se prepara **O58**; ^{1}H NMR (400 MHz, CD_3CN) δ 8,09 (d, J = 2,1 Hz, 1H), 7,65 (d, J = 6,9 Hz, 1H), 7,34 (dd, J = 3,0, 6,6 Hz, 1H), 4,02 (s, 2H), 4,01 (m, 2H), 3,96 (m, 2H), 3,90 (d, J = 4,8 Hz, 2H), 3,63 (m, 2H), 3,59 (dd, J = 4,5, 9,0 Hz, 2H), 3,16 (m, 2H), 2,79 (m, 3H), 1,92 (m, 1H), 1,77 (m, 2H), 1,49 (s, 3H), 1,19 (m, 2H), 0,80 (m, 2H), 0,59 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{23}H_{54}N_4O_7S$ calc,,: 511,2, resultó: 511,1.

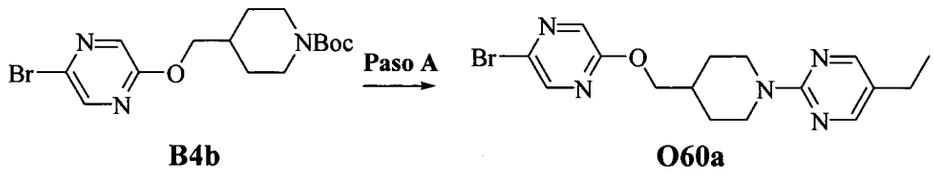
Ejemplo O59: 1–Metilciclopropil 4–((6–(4–(3–(azetidin–1–il)propilsulfonil)–2–oxopiperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato.



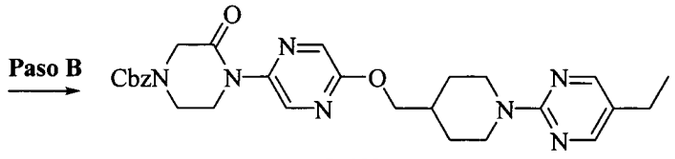
Siguiendo un procedimiento similar al utilizado para la preparación de **O16** a partir de **O5** excepto que se sustituye **O5** por **O57**, se prepara **O59**; ^{1}H NMR (400 MHz, CD_3CN) δ 8,09 (d, J = 3,2 Hz, 1H), 7,66 (d, J = 9,2 Hz, 1H), 7,33 (dd, J = 9,2, 3,2 Hz, 1H), 4,02 (m, 2H), 4,01 (m, 2H), 3,97 (m, 2H), 3,90 (d, J = 6,4 Hz, 2H), 3,63 (m, 2H), 3,41 (m, 2H), 3,19 (m, 2H), 2,70 (m, 4H), 2,10 (m, 4H), 1,80 (m, 4H), 1,49 (s, 3H), 1,20 (m, 2H), 0,80 (m, 2H), 0,59 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{26}H_{40}N_5O_6S$ calc..: 550,3, resultó: 550,1.

Ejemplo O60: 1–(5–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metoxi)pirazin–2–il)–4–(metilsulfonil)piperazin–2–ona.

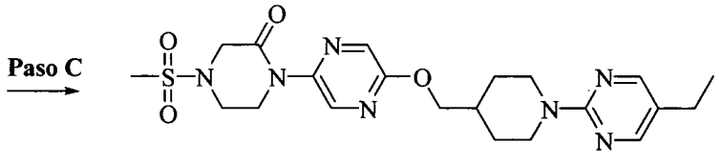




B4b **O60a**



O60b



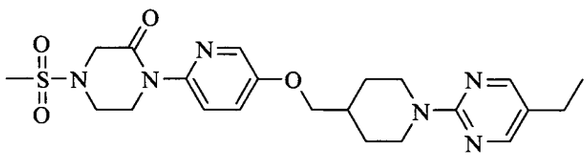
Ejemplo O60

Paso A: Siguiendo un procedimiento similar al empleado para la preparación de **E1** a partir de **E1a**, excepto que se sustituye **E1a** por **B4b**, se prepara **O60a**; ESIMS *m/z* por $(M+H)^+$ $C_{16}H_{21}BrN_5O$ calc.: 378,1, resultó: 378,1.

Paso B: Siguiendo un procedimiento similar al empleado para la preparación de **O1a** a partir de **B4b**, excepto que se sustituye **B4b** por **O60a**, se prepara **O60b**; ESIMS *m/z* por $(M+H)^+$ $C_{28}H_{34}N_7O_4$ calc.: 532,3, resultó: 532,2.

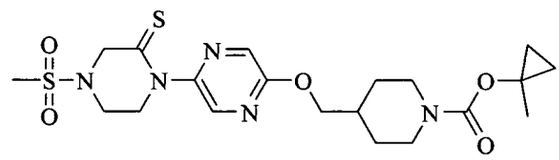
Paso C: Siguiendo un procedimiento similar al empleado para la preparación de **O3** a partir de **O3b**, excepto que se sustituye **O3b** por **O60b**, y cloruro de *n*–propanesulfonilo por cloruro de metansulfonilo, se prepara **O60**; ^1H NMR (400 MHz, $CDCl_3$) δ 8,65 (d, J = 1,4 Hz, 1H), 8,41 (s, 2H), 8,04 (d, J = 1,4 Hz, 1H), 4,72 (m, 2H), 4,25 (d, J = 6,4, 2H), 4,14 (s, 2H), 4,09 (m, 2H), 3,68 (m, 2H), 3,21 (m, 2H), 2,94 (s, 3H), 2,60 (dd, J = 15,2, 7,6, 2H), 2,22 (m, 1H), 2,05 (m, 2H), 1,48 (m, 2H), 1,26 (dd, J = 7,6, 7,6, 3H); ESIMS *m/z* por $(M+H)^+$ $C_{21}H_{29}N_7O_4S$ calc,: 476,2, resultó: 476,3.

Ejemplo O61: 1–(5–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metoxi)piridin–2–il)–4–(metilsulfonil)piperazin–2–ona.



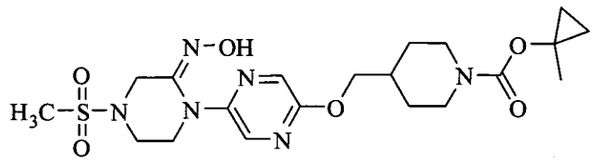
Siguiendo un procedimiento similar al empleado para la preparación de **O60** a partir de **B4b**, excepto que se sustituye **B4b** por **B2b**, se prepara **O61b**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,18 (s, 2H), 8,09 (d, J = 2,9 Hz, 1H), 7,73 (d, J = 9,0 Hz, 1H), 7,25 (dd, J = 9,0, 2,9), 4,79 (m, 2H), 4,12 (m, 2H), 4,10 (s, 2H), 3,87 (d, J = 6,4, 2H), 3,64 (m, 2H), 2,92 (s, 3H), 2,91 (m, 2H), 2,46 (dd, J = 15,2, 7,6, 2H), 2,11 (m, 1H), 1,93 (m, 2H), 1,37 (m, 2H), 1,19 (dd, J = 7,6, 7,6, 3H); ESIMS *m/z* por $(M+H)^+$ $C_{22}H_{31}N_6O_4S$ calc,: 475,2, resultó: 475,2.

Ejemplo O62: 1–Metilciclopropil 4–((5–(4–(metilsulfonil)–2–thioxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



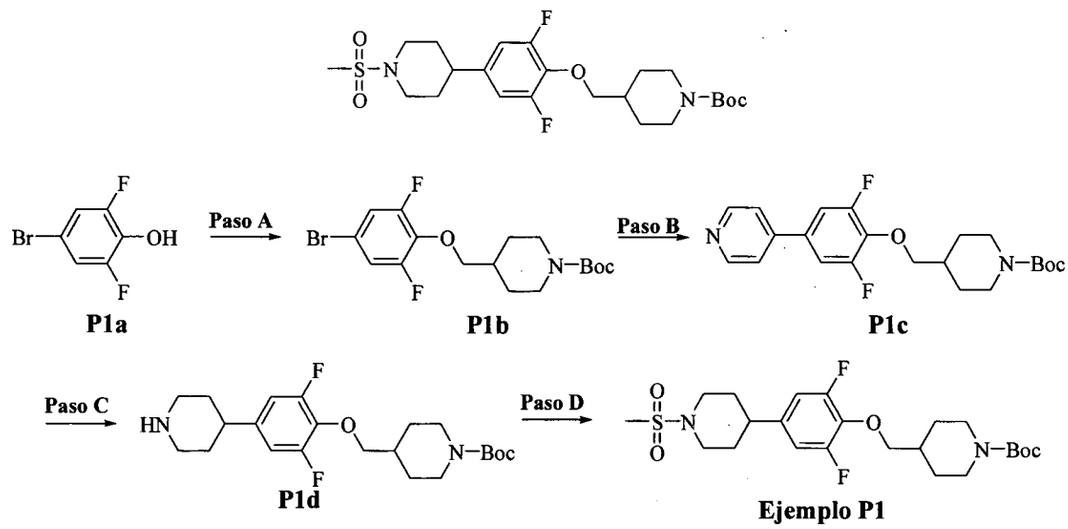
Se trata una solución de **O2** (121 mg, 0,26 mmol) en tetrahidrofurano (3 ml) con reactivo de Lawesson (115 mg, 0,29 mmol), se la sella en un recipiente de reacción y se la agita a 90°C de un día para otro. Se enfría la reacción a temperatura ambiente, se la evapora a sequedad y se la purifica en gel de sílice utilizando un gradiente lineal de 0–100% de acetato de etilo en hexano para producir **O62**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8,39 (d, J = 1,3 Hz, 1H), 8,12 (d, J = 1,4 Hz, 1H), 4,58 (s, 2H), 4,21 (m, 2H), 4,21 (d, J = 6,5 Hz, 2H), 4,03 (m, 2H), 3,78 (m, 2H), 2,98 (s, 3H), 2,77 (m, 2H), 1,99 (m, 1H), 1,81 (m, 2H), 1,55 (s, 3H), 1,29 (m, 2H), 0,87 (m, 2H), 0,62 (m, 2H); ESIMS *m/z* por $(M+Na)^+$ $C_{20}H_{29}N_5O_5S_2Na$ calc,: 506,2, resultó: 506,1 ($M+ Na^+$).

Ejemplo O63: 1–Metilciclopropil 4–((5–(2–(hidroxiimino)–4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



Se trata una solución de **O62** (30 mg, 0,062 mmol) en etanol (1 ml) con hidroxilamina (7 µl de una solución al 50%, 0,12 mmol) se la sella en un recipiente de reacción y se la agita a 80 °C de un día para otro. Se enfría la reacción a temperatura ambiente y se la evapora a sequedad para producir **63**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 8,46 (d, *J* = 1,4 Hz, 1H), 7,96 (d, *J* = 1,4Hz, 1H), 4,47 (s, 2H), 4,21 (m, 2H), 4,14 (d, *J* = 6,5 Hz, 2H), 3,87 (m, 2H), 3,62 (m, 2H), 3,52 (m, 1H), 2,92 (s, 3H), 2,74 (m, 2H), 1,95 (m, 1H), 1,79 (m, 2H), 1,55 (s, 3H), 1,26 (m, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS calc, para $C_{20}H_{31}N_6O_6S$ $[M+H]^+$ 483,2, resultó 483,4.

Ejemplo P1: *terc*–Butil 4–((2,6–difluoro–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato.



Paso A: Se calienta una mezcla de **P1a** (1,67 g, 8 mmol), *terc*–butil 4–((metilsulfoniloxi)metil)piperidin–1–carboxilato (2,35 g, 8 mmol), y Cs_2CO_3 (3,91 g, 12 mmol) en N,N–dimetilformamida (30 ml) a 90°C de un día para otro. Se vierte la mezcla de reacción en agua (200 ml), se la extrae con acetato de etilo (3 x 50 ml), se la lava con agua (2 x 30 ml), seca (Na_2SO_4) y concentra para dar **P1b;** ESIMS calc. para $C_{17}H_{22}BrF_2NNaO_3$ $(M+Na)^+$ 428,1, resultó 428,2. Se utiliza el producto sin purificación.

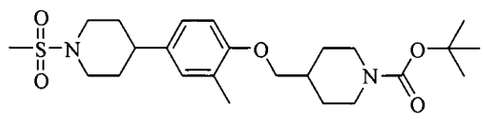
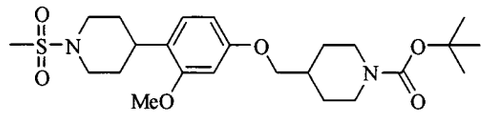
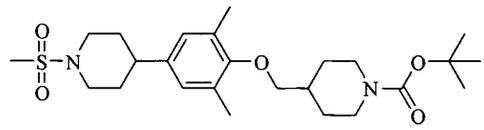
Paso B: Se calienta una mezcla de **P1b** (2,03 g, 5 mmol), ácido piridin–4–ilbórico (0,80 g, 6,5 mmol), Na_2CO_3 (2,65, 25 mmol), y $Pd(PPh_3)_4$ (289 mg, 0,25 mmol) en agua (13 ml) y DME (52 ml)) a 80°C de un día para otro bajo atmósfera de nitrógeno. Se concentra la mezcla de reacción, se le agrega agua (200 ml), se la extrae con acetato de etilo (3 x 100 ml), se la lava con agua (2 x 30 ml), se la seca (Na_2SO_4) y concentra. La cromatografía en gel de sílice (gradiente de 0% a 5% de MeOH en diclorometano) dio **P1c**; ESIMS calc. para $C_{22}H_{27}F_2N_2O_3$ $(M+H)^+$ 405,2, resultó 405,2.

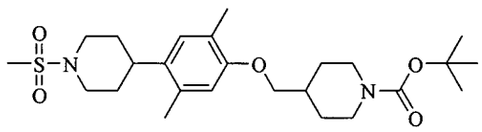
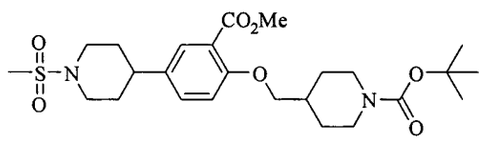
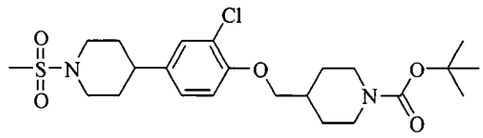
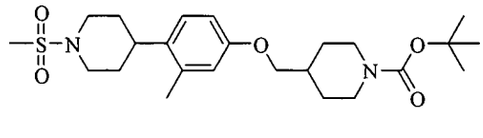
Paso C: Se hidrogena una solución de **P1c** (654 mg, 1.59 mmol) y TFA (118 µl, 1.59 mmol) en EtOH (100ml) empleando un cartucho de Pd/C al 10% en un H–Cube (caudal de 1ml/min) a 70 atm y 90°C. A la solución así obtenida se agrega una solución saturada de hidrogenocarbonato de sodio (1 ml) y se evapora el EtOH. Se agrega agua (50 ml) y diclorometano (30 ml) al residuo. Se extrae además la fase acuosa con diclorometano (2 x 30 ml) y se la descarta. Se secan los extractos orgánicos combinados sobre Na_2SO_4 y se los concentra para producir **P1d**; ESIMS calc. para $C_{22}H_{33}F_2N_2O_3$ $(M+H)^+$ 411,2, resultó 411,2.

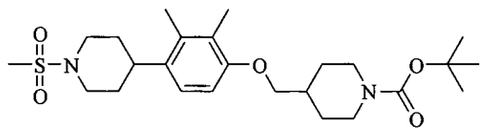
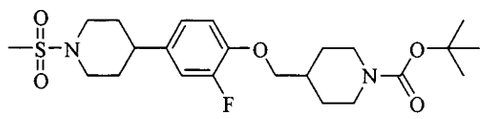
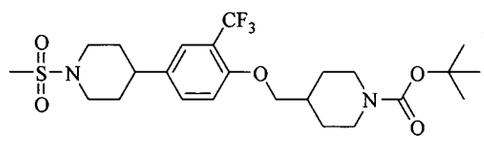
Paso D: Se agrega por goteo cloruro de metansulfonilo (117 µl, 1,5 mmol) a una solución fría (baño hielo/agua) de **P1d** (411 mg, 1 mmol) y Et_3N (418 µl, 3 mmol) en diclorometano seco (6 ml). Se agita la solución así obtenida a temperatura ambiente por espacio de 2 horas. Se agrega la mezcla de reacción al agua (40 ml) y se la extrae con diclorometano (3 x 40 ml). Se secan las capas orgánicas combinadas (Na_2SO_4) y se las concentra para dar **P1**; ^{1}H–NMR (600MHz, $CDCl_3$) δ 6,74 (m, 2H), 4,14 (m, 2H), 3,94 (m, 4H), 2,82 (s, 3H), 2,75 (td, J = 12,1, 2,5 Hz, 4H), 2,53 (tt, J = 12,1, 3,6 Hz, 1H), 1,93 (m, 3H), 1,84 (m, 2H), 1,74 (m, 2H), 1,46

(s, 9H), 1,25 (qd, J = 12,4, 4,2 Hz, 2H), ESIMS calc, para $C_{18}H_{27}F_2N_2O_3S$ $(M–Boc+H)^+$ 389,2, resultó 389,2.

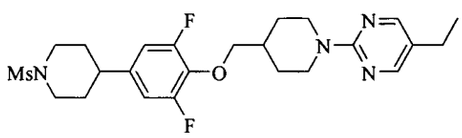
Siguiendo un procedimiento similar al empleado para la preparación de **P1** a partir de **P1a**, excepto que se sustituye **P1a** por el halofenol apropiado existente en el comercio, se preparan los siguientes ejemplos:;

P2		^{1}H–NMR (600MHz, $CDCl_3$) δ 6,97 (m, 2H), 6,73 (d, J = 8,2 Hz, 1H), 4,15 (m, 2H), 3,92 (dt, J = 11,7, 2,1 Hz, 2H), 3,79 (d, J = 6,2 Hz, 2H), 2,81 (s, 3H), 2,75 (m, 4H), 2,52 (tt, J = 12,1, 3,6 Hz, 1H), 2,21 (s, 3H), 1,98 (m, 1H), 1,92 (m, 2H), 1,80 (m, 4H), 1,47 (s, 9H), 1,30 (qd, J = 12,4, 4,2 Hz, 2H), ESIMS calc, para $C_{19}H_{31}N_2O_3S$ $(M–Boc+H)^+$ 367,2, resultó 367,2.
P3		^{1}H–NMR (600MHz, $CDCl_3$) δ 7,02 (d, J = 8,1 Hz, 1H), 6,43 (m, 2H), 4,15 (m, 2H), 3,91 (m, 2H), 3,79 (m, 5H), 2,94 (tt, J = 12,2, 3,4 Hz, 1H), 2,91 (s, 3H), 2,77 (m, 4H), 1,95 (m, 1H), 1,89 (m, 2H), 1,83 (m, 2H), 1,77 (m, 2H), 1,47 (s, 9H), 1,28 (qd, J = 12,4, 4,2 Hz, 2H), ESIMS calc, para $C_{19}H_{31}N_2O_4S$ $(M–Boc+H)^+$ 383,2, resultó 383,2.
P4		^{1}H–NMR (600MHz, $CDCl_3$) δ 7,26 (s, 2H), 4,17 (m, 2H), 3,92 (m, 2H), 3,58 (d, J = 6,3 Hz, 2H), 2,81 (s, 3H), 2,75 (m, 4H), 2,48 (tt, J = 12,2, 3,6 Hz, 1H), 2,24 (s, 6H), 1,98 (m, 1H), 1,90 (m, 4H), 1,79 (m, 2H), 1,47 (s, 9H), 1,33 (qd, J = 12,4, 4,1 Hz, 2H), ESIMS calc, para $C_{20}H_{33}N_2O_3S$ $(M–Boc+H)^+$

		381,2, resultó 381,2.
P5		^{1}H–NMR (600MHz, $CDCl_3$) δ 6,94 (s, 1H), 6,58 (s, 1H), 4,15 (m, 2H), 3,94 (m, 2H), 3,77 (d, J = 6,2 Hz, 2H), 2,82 (s, 3H), 2,75 (m, 5H), 2,29 (s, 3H), 2,17 (s, 3H), 1,97 (m, 1H), 1,81 (m, 6H), 1,47 (s, 9H), 1,29 (m, 2H), ESIMS calc, para $C_{20}H_{33}N_2O_3S$ (M–Boc+H)$^+$ 381,2, resultó 381,2,
P6		^{1}H–NMR (400MHz, $CDCl_3$) δ 7,63 (d, J = 2,4 Hz, 1H), 7,28 (dd, J = 8,7, 2,5 Hz, 1H), 6,89 (d, J = 8,6 Hz, 1H), 4,16 (m, 2H), 3,93 (m, 2H), 3,88 (s, 3H), 3,85 (d, J = 6,2 Hz, 2H), 2,82 (s, 3H), 2,75 (m, 4H), 2,58 (tt, J = 12,1, 3,6 Hz, 1H), 1,74–2,07 (m, 7H), 1,46 (s, 9H), 1,29 (m, 2H), ESIMS calc, para $C_{20}H_{31}N_2O_5S$ (M–Boc+H)$^+$ 411,2, resultó 410,8.
P7		^{1}H–NMR (400MHz, $CDCl_3$) δ 7,20 (d, J = 2,2 Hz, 1H), 7,03 (dd, J = 8,4, 2,2 Hz, 1H), 6,85 (d, J = 8,5 Hz, 1H), 4,16 (m, 2H), 3,93 (m, 2H), 3,84 (d, J = 6,4 Hz, 2H), 2,82 (s, 3H), 2,75 (m, 4H), 2,53 (tt, J = 12,1, 3,6 Hz, 1H), 2,02 (m, 1H), 1,92 (m, 2H), 1,71 (m,4H), 1,46 (s, 9H), 1,29 (m, 2H), ESIMS calc, para $C_{18}H_{28}ClN_2O_3S$ (M–Boc+H)$^+$ 387,2, resultó 386,8.
P8		^{1}H–NMR (400MHz, $CDCl_3$) δ 7,08 (d, J = 8,2 Hz, 1H), 6,71 (m, 2H), 4,14 (m, 2H), 3,94 (m, 2H), 3,77 (d, J = 6,4 Hz, 2H), 2,82 (s, 3H), 2,76 (m, 5H), 2,31 (s, 3H), 1,93 (m, 1H), 1,81 (m, 6H), 1,46 (s, 9H), 1,25 (m, 2H), ESIMS calc, para $C_{19}H_{31}N_2O_3S$ (M–Boc+H)$^+$ 367,2, resultó 367,2.

P9		^{1}H–NMR (400MHz, $CDCl_3$) δ 6,99 (d, J =8,8 Hz, 1H), 6,69 (d, J = 8,7 Hz, 1H), 4,16 (m, 2H), 3,95 (m, 2H), 3,78 (d, J = 6,2 Hz, 2H), 2,72–2,84 (m, 8H), 2,24 (s, 3H), 2,18 (s, 3H), 1,83 (m, 7H), 1,47 (s, 9H), 1,30 (m, 2H), ESIMS calc, para $C_{20}H_{33}N_2O_3S$ (M–Boc+H)$^+$ 381,2, resultó 381,2.
P10		^{1}H–NMR (400MHz, $CDCl_3$) δ 6,90 (m, 3H), 4,15 (m, 2H), 3,93 (m, 2H), 3,84 (d, J = 6,5 Hz, 2H), 2,82 (s, 3H), 2,75 (m, 4H), 2,54 (tt, J = 12,1, 3,6 Hz, 1H), 1,99 (m, 1H), 1,93 (m, 1H), 1,84 (m, 2H), 1,77 (m, 2H), 1,46 (s, 9H), 1,26 (m, 2H), ESIMS calc, para $C_{18}H_{28}FN_2O_3S$ (M–Boc+H)$^+$ 371,2, resultó 371,2.
P11		^{1}H–NMR (400MHz, $CDCl_3$) δ 7,39 (d, J = 2,1 Hz, 1H), 7,30 (dd, J = 8,6, 2,1 Hz, 1H), 6,92 (d, J = 8,6 Hz, 1H), 4,16 (m, 2H), 3,94 (m, 2H), 3,85 (d, J = 6,1 Hz, 2H), 2,82 (s, 3H), 2,76 (m, 4H), 2,60 (tt, J = 12,1, 3,6 Hz, 1H), 2,00(m, 1H), 1,94 (m, 2H), 1,82 (m, 4H), 1,46 (s, 9H), 1,27 (m, 2H), ESIMS calc, para $C_{19}H_{28}F_3N_2O_3S$ (M–Boc+H)$^+$ 421,2, resultó 421,1.

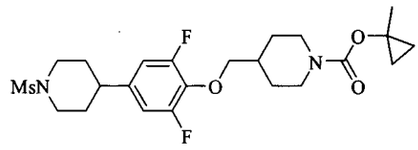
Ejemplo P12: 2–(4–((2,6–Difluoro–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)–5–etilpirimidina.



Siguiendo un procedimiento similar al empleado para la preparación de **E1** a partir de **B2**, excepto que se sustituye **B2** por **P1**, se prepara **P12**; ^{1}H–NMR

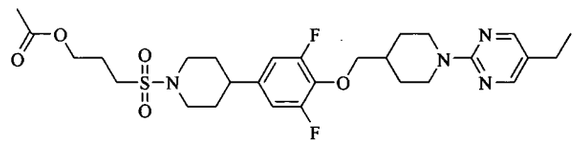
(400MHz, $CDCl_3$) δ 8,18 (s, 2H), 6,67 (d, J = 9,2 Hz, 2H), 4,70 (m, 2H), 2,91 (dt, J = 2,0, 12,4 Hz, 2H), 2,75 (s, 3H), 2,68 (dt, J = 2,4, 12,4 Hz, 2H), 2,43 (m, 3H), 2,01 (m, 3H), 1,70 (m, 2H), 1,31 (m, 2H), 1,13 (t, J = 7,6 Hz, 3H); ESIMS calc, para $C_{24}H_{33}F_2N_4O_3S$ $[M+H]^+$ 495,2, resultó 495,2.

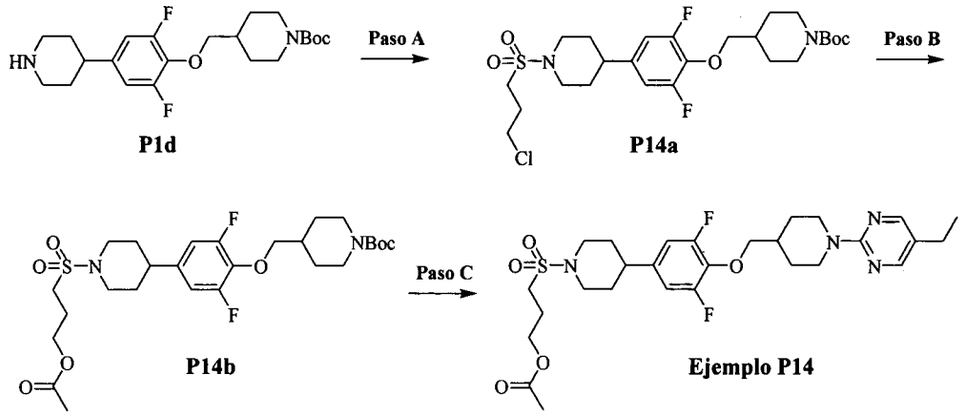
Ejemplo P13: 1–Metilciclopropil 4–((2,6–difluoro–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato.



Siguiendo un procedimiento similar al empleado para la preparación de **E3** a partir de **B4**, excepto que se sustituye **B4** por **P1**, se prepara **P12**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 6,74 (d, *J* = 8,8 Hz, 2H), 4,22 (m, 2H), 3,95 (m, 4H), 2,83 (s, 3H), 2,76 (dt, J = 2,4, 12,0 Hz, 4H), 2,55 (tt, *J* = 3,6, 12,4 Hz, 1H), 1,94 (m, 3H), 1,85 (m, 2H), 1,78 (m, 2H), 1,56 (s, 3H), 1,26 (m, 2H), 0,87 (m, 2H), 0,63 (m, 2H); ESIMS calc, para $C_{23}H_{33}F_2N_2O_5S$ $[M+H]^+$ 487,2, resultó 487,2.

Ejemplo P14: 3–(4–(4–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metoxi)–3,5–difluorofenil)piperidin–1–ilsulfonil)propil acetato.





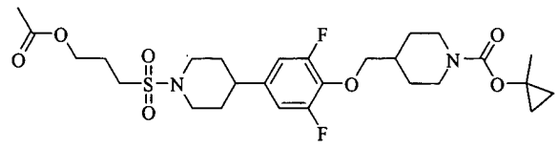
Paso A: Se trata una solución de **P1d** (200 mg, 0,49 mmol) y cloruro de 3–cloropropanesulfonilo (65 µl, 0,54 mmol) en diclorometano (10 ml) con trietilamina (75 µl, 0,54 mmol) y se agita la mezcla a temperatura ambiente por espacio de 1 hora. Se diluye la mezcla con agua (10 ml), se la extrae con diclorometano, se la seca sobre $MgSO_4$, filtra y concentra. Se purifica el residuo en gel de sílice empleando un gradiente lineal de 0 a 100% de acetato de etilo en hexano para producir **P14a**: ^{1}H–NMR (400MHz, $CDCl_3$) δ 6,74 (d, *J* = 9,2 Hz, 2H), 4,06 (m, 2H), 3,87 (m, 4H), 3,64 (t, *J* = 6,0 Hz, 2H), 3,04 (t, *J* = 6,0 Hz, 2H), 2,80 (dt, *J* = 2,4, 12,4 Hz, 2H), 2,65 (m, 2H), 2,49 (tt, *J* = 3,6, 12,4 Hz, 1H), 2,25 (m, 2H), 1,85 (m, 2H), 1,77 (m, 2H), 1,65, m, 2H), 1,39 (s, 9H), 1,18 (m, 2H); ESIMS calc, para $C_{21}H_{30}ClF_2N_2O_5S$ $[M+H - C_4H_8]^+$ 495,2, resultó 495,2.

Paso B: Se calienta una solución de **P14a** (138 mg, 0,25 mmol), NaOAc (62 mg, 0,75 mmol) y NaI (38 mg, 0,25 mmol) en N,N–dimetilformamida (1 ml) a 120 °C por 2 horas. Se enfría la mezcla, se la diluye con agua (10 ml) y se la extrae con acetato de etilo (10 ml). Se lava la capa orgánica con agua (10 ml) y solución salina (10 ml), se la seca ($MgSO_4$), filtra y concentra para producir **P14b** que es utilizado sin más purificación; ESIMS calc. para $C_{23}H_{33}F_2N_2O_7S$ $[M+H - C_4H_8]^+$ 519.2, resultó 519.2.

Paso C: Siguiendo un procedimiento similar al empleado para la preparación de **E1** a partir de **B2**, excepto que se sustituye **B2** por **P14b**, se prepara **P14**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 8,36 (s, 2H), 6,76 (m, 2H), 4,76 (m, 2H), 4,22 (t, *J* = 6,4

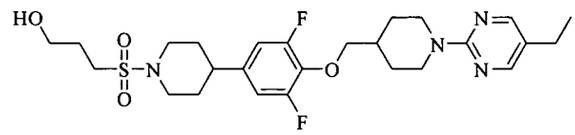
Hz, 2H), 3,96 (m, 4H), 3,06 (m, 4H), 2,88 (dt, *J* = 2,4, 12,0 Hz, 2H), 2,56 (m, 3H), 2,17 (m, 3H), 2,11 (s, 3H), 2,04 (m, 2H), 1,97 (m, 2H), 1,71 (m, 2H), 1,42 (m, 2H), 1,24 (t, *J* = 7,6 Hz, 3H); ESIMS calc, para $C_{28}H_{39}F_2N_4O_5S$ $[M+H]^+$ 581,3, resultó 581,2.

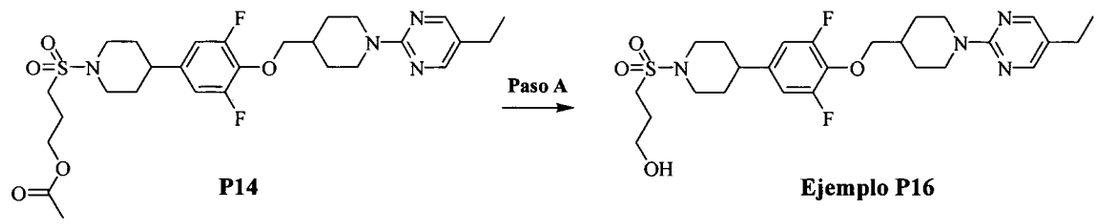
Ejemplo P15: 1–Metilciclopropil 4–((4–(1–(3–acetoxipropilsulfonil)piperidin–4–il)–2,6–difluorofenoxi)metil)piperidin–1–carboxilato.



Siguiendo un procedimiento similar al empleado para la preparación de **P14** a partir de **P1d**, excepto que se sustituye el Paso C por el proceso para la preparación de **P13** a partir de **P1**, se prepara **P15**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 6,75 (m, 2H), 4,22 (t, *J* = 6,0 Hz, 2H), 3,95 (m, 4H), 3,03 (m, 2H), 2,88 (dt, *J* = 2,4, 12,4 Hz, 2H), 2,76 (m, 2H), 2,57 (m, 1H), 2,17 (m, 2H), 2,09 (s, 3H), 1,92 (m, 2H), 1,88 (m, 2H), 1,72 (m, 2H), 1,56 (s, 3H), 1,25 (m, 2H), 0,87 (m, 2H), 0,63 (m, 2H); ESIMS calc, para $C_{27}H_{39}F_2N_2O_7S$ $[M+H]^+$ 573,2, resultó 573,2.

Ejemplo P16: 3–(4–(4–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metoxi)–3,5–difluorofenil)piperidin–1–ilsulfonil)propan–1–ol.

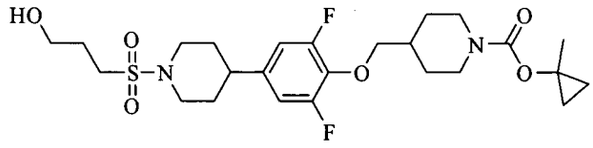




P14 **Ejemplo P16**

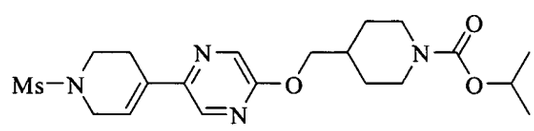
Se trata una solución de **P14** (30 mg, 0,05 mmol) en tetrahidrofurano (3 ml) con LiOH hidrato (50 mg, 1,2 mmol) y se calienta la mezcla a 90 °C por espacio de 12 horas. Se filtra la mezcla, se la concentra y purifica por HPLC de fase inversa iniciada por la masa para producir **P16**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 8,36 (s, 2H), 6,67 (m, 2H), 4,68 (m, 2H), 3,88 (m, 5H), 3,74 (t, *J* = 5,6 Hz, 2H), 3,00 (m, 4H), 2,78 (dt, *J* = 2,4, 12,0 Hz, 2H), 2,45 (m, 3H), 2,17 (m, 3H), 2,11 (s, 3H), 2,04 (m, 4H), 1,97 (m, 2H), 1,84 (m, 2H), 1,65 (m, 2H), 1,31 (m, 2H), 1,47 (t, *J* = 7,6 Hz, 3H); ESIMS calc, para $C_{26}H_{37}F_2N_4O_4S$ $[M+H]^+$ 539,3, resultó 539,2.

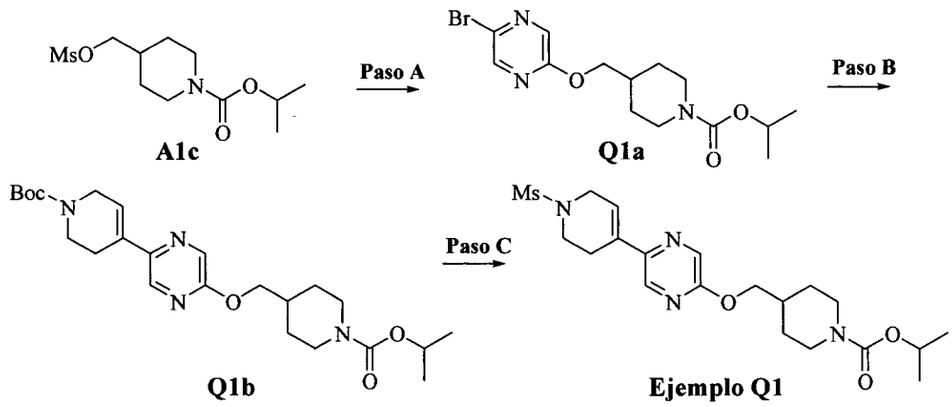
Ejemplo P17: 1–Metilciclopropil 4–((2,6–difluoro–4–(1–(3–hidroxipropilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato.



Siguiendo un procedimiento similar al empleado para la preparación de **P16** a partir de **P14**, excepto que se sustituye **P14** por **P15**, se prepara **P17**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 6,66 (m, 2H), 3,85 (m, 4H), 3,74 (t, *J* = 6,0 Hz, 2H), 3,02 (m, 2H), 2,79 (dt, *J* = 2,4, 12,0 Hz, 2H), 2,71 (m, 2H), 2,48 (m, 2H), 2,03 (m, 2H), 1,80 (m, 5H), 1,69 (m, 2H), 1,48 (s, 3H), 1,19 (m, 2H), 0,87 (m, 2H), 0,63 (m, 2H); ESIMS calc, para $C_{25}H_{37}F_2N_2O_6S$ $[M+H]^+$ 531,2, resultó 531,2.

Ejemplo Q1: Isopropil 4–((5–(1,2,3,6–tetrahidro–1–metansulfonilpiridin–4–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.





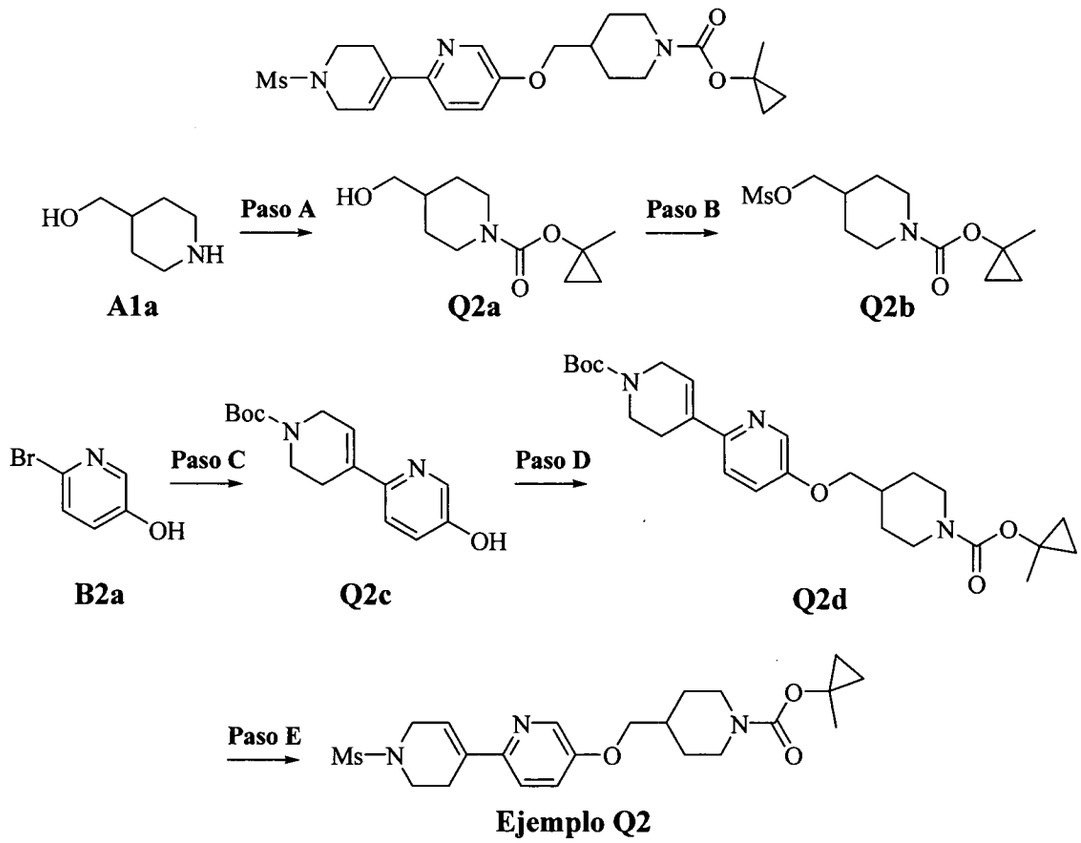
Paso A: Se trata una solución de **A1c** (0,86 g, 3.1 mmol) y 2–bromo–5–hidroxipirazina (0,52 g, 3,0 mmol) en acetonitrilo seco (7 ml) con carbonato de cesio en polvo (1,62 g, 5 mmol) y se agita la mezcla a 60°C por espacio de 24 horas. La filtración, concentración y purificación en gel de sílice empleando un gradiente lineal de 0 a 100% de acetato de etilo en hexano da **Q1a**; ESIMS calc. para $C_{14}H_{21}BrN_3O_3$ ($M+H^+$) 358.1, resultó 358,0.

Paso B: A una solución de **Q1a** (83.5 mg, 0,2 mmol) en 1,2–dimetoxietano (1,5 ml) se agrega *terc*–butil 5,6–dihidro–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)piridin–1(2*H*)–carboxilato (66,7 mg, 0,2 mmol), carbonato de potasio en polvo (0,10 g, 0,7 mmol), y agua (0,5 g). Se desgasifica la mezcla utilizando argón, luego se agrega tetrakis–(trifenilfosfino)paladio(0) (0,08g, 0,07 mmol) y se calienta la mezcla a 180 °C durante 5 min en un reactor de microondas. El enfriamiento, extracción con acetato de etilo, lavado con agua y solución salina, secado sobre Na_2SO_4 y concentración, seguidos por purificación en gel de sílice utilizando un gradiente lineal de 5 a 70% de acetato de etilo en hexano da **Q1b**; ESIMS calc. para $C_{24}H_{37}N_4O_5$ ($M+H^+$) 461.3, resultó 461.1.

Paso C: A una solución de **Q1b** (0,2 mmol) en dioxano (2 ml) se agrega cloruro de hidrógeno en dioxano (4N, 1 ml), lentamente, con agitación. Se agita la solución así obtenida a temperatura ambiente por espacio de 4 horas. Después de eliminar el solvente, se disuelve el residuo en diclorometano (3 ml) y se lo trata con trietilamina (0,2 ml, 1,4 mmol). Luego se agrega gota a gota cloruro de metansulfonilo (0,04 ml, 0,5 mmol), con agitación, en un lapso de 5 minutos. Se agita la solución así obtenida a temperatura ambiente por espacio de 2 horas. Se

separa el solvente y se purifica el residuo utilizando HPLC de fase inversa iniciada por la masa para dar **Q1**; ESIMS calc. para $C_{20}H_{31}N_4O_5S$ ($M+H^+$) 439.2, resultó 439.1.

Ejemplo Q2: 1–Metilciclopropil 4–((6–(1,2,3,6–tetrahidro–1–metansulfonilpiridin–4–il)piridin–3–iloxi)metil)piperidin–1–carboxilato.



Paso A: Se trata una solución de **A1a** (0,51 g, 4,4 mmol) en diclorometano (7 ml) con trietilamina (0,9 ml, 6,4 mmol) en una porción, seguida por **E3b** (0,96 g, 4 mmol). Se agita la suspensión a temperatura ambiente por espacio de 24 horas, se la diluye con más diclorometano (25 ml), se la lava con agua, hidrogenocarbonato de sodio acuoso saturado (3 x 25 ml), y cloruro de amonio acuoso saturado, se lo seca sobre $MgSO_4$ y concentra para dar **Q2a**; ^1H NMR ($CDCl_3$, 400,13 MHz): δ 4,13 (br, s, 1H), 4,03 (br, s, 1H), 3,50 (m, 2H), 2,71

(t, J = 12 Hz, 2H), 1,67 (m, 3H), 1,38 (br, s, 1H), 1,54 (s, 3H), 1,14 (br, s, 2H), 0,86 (m, 2H), 0,62 (m, 2H); ESIMS calc, para $C_{11}H_{20}NO_3$ ($M+H^+$) 214,1, resultó 214,1.

Paso B: A una solución de **Q2a** (0,71 g, 3.4 mmol) en diclorometano (20 ml) se agrega trietilamina (0,9 ml, 6.4 mmol) en una porción. Se enfría la mezcla obtenida en un baño de hielo/agua y se agrega lentamente, con agitación, cloruro de metansulfonilo (0,35 ml, 4.5 mmol). Se retira el baño y se agita la solución así obtenida a temperatura ambiente por espacio de 2 horas. Se diluye la mezcla de reacción con more diclorometano (20 ml), se la lava con agua y cloruro de amonio acuoso saturado, se la seca sobre $MgSO_4$ y se la concentra para dar **Q2b**; ^1H NMR ($CDCl_3$, 400,13 MHz): δ 4,22 (br, s, 2H), 4,07 (s, 2H), 3,23 (m, 1H), 3,17 (s, 3H), 2,72 (m, 2H), 1,92 (m, 1H), 1,74 (m, 2H), 1,54 (s, 3H), 1,22 (br, s, 2H), 0,86 (m, 2H), 0,63 (m, 2H); ESIMS calc, para $C_{12}H_{22}NO_5S$ ($M+H^+$) 292,1, resultó 292,0.

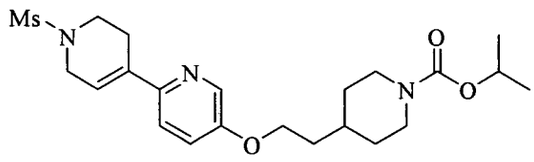
Paso C: A una solución de **B2a** (0,1 g, 0,6 mmol) en 1,2–dimetoxietano (1,5ml) se agrega *terc*–butil 5,6–dihidro–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)piridin–1(2*H*)–carboxilato (0,13 g, 0,4 mmol), carbonato de potasio en polvo (0,15 g, 1,1 mmol), y agua (0,5 g). Se desgasifica la mezcla empleando argón, luego se agrega tetrakis–(trifenilfosfino)paladio(0) (0,08g, 0,07 mmol) y se calienta la mezcla a 180 °C corriente 5 min en un reactor de microondas. El enfriamiento, extracción con acetato de etilo, lavado con agua y solución salina, secado sobre Na_2SO_4 y concentración, seguida por purificación en gel de sílice utilizando un gradiente lineal de 5 a 100% de acetato de etilo en hexano produce **Q2c**. ESIMS calc. para $C_{15}H_{21}N_2O_3$ ($M+H^+$) 277.2, resultó 277,0.

Paso D: Se trata una solución de **Q2b** (0,05 g, 0,17 mmol) y **Q2c** (0,04 g, 0,15 mmol) en acetonitrilo seco (2 ml) carbonato de cesio en polvo (0,1 g, 0,3 mmol) y se agita la mezcla a 60 °C por espacio de 24 horas. La filtración, concentración y purificación en gel de sílice empleando un gradiente lineal de 0 a 100% de acetato de etilo en hexano produce **Q2d**; ESIMS calc. para $C_{26}H_{38}N_3O_5$ ($M+H^+$) 472.3, resultó 472,0.

Paso E: A una solución de **Q2d** (0,15 mmol) en dioxano (2 ml) se agrega cloruro de hidrógeno en dioxano (4N, 0,5 ml), lentamente, con agitación. Se agita la solución así obtenida a temperatura ambiente por espacio de 4 horas. Se

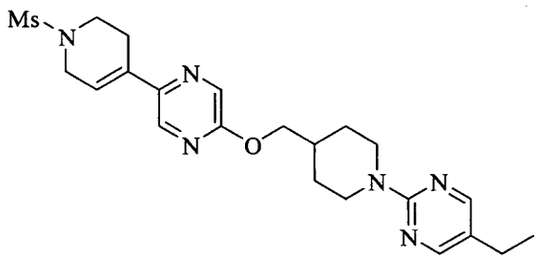
separa el solvente y se disuelve el residuo en diclorometano (3 ml) y se lo trata con trietilamina (0,1 ml, 0,7 mmol) seguido por cloruro de metansulfonilo (0,025 ml, 0,3 mmol) gota a gota, con agitación, en un lapso de 5 minutos. Se agita la solución así obtenida a temperatura ambiente por espacio de 2 horas. Se elimina el solvente y se purifica el residuo obtenido por HPLC iniciada por la masa para producir **Q2**; ESIMS calc. para $C_{22}H_{32}N_3O_5S$ ($M+H^+$) 450,2, resultó 450,1.

Ejemplo Q3: Isopropil 4–(2–(6–(1,2,3,6–tetrahidro–1–metansulfonilpiridin–4–il)piridin–3–iloxi)etil)piperidin–1–carboxilato.



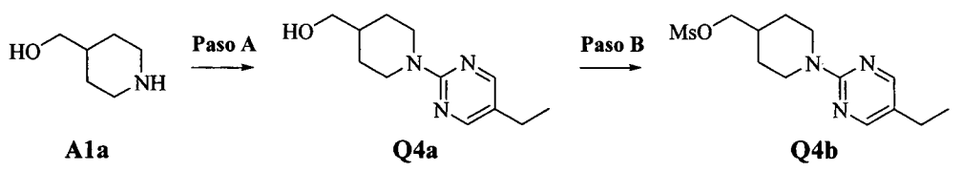
Siguiendo un procedimiento similar al empleado para la preparación de **Q1** a partir de **A1c**, excepto que se sustituye **A1c** por isopropil 4–(2–(metilsulfoniloxi)etil)piperidin–1–carboxilato, se prepara **Q3**; ESIMS calc. para $C_{22}H_{34}N_3O_5S$ ($M+H^+$) 452.2, resultó 452,1.

Ejemplo Q4: 2–(4–((5–(1,2,3,6–Tetrahidro–1–metansulfonilpiridin–4–il)pirazin–2–iloxi)metil)piperidin–1–il)–5–etilpirimidina.



Siguiendo un procedimiento similar al empleado para la preparación de **Q2** a partir de **A1a**, excepto que se sustituye **B2a** por **B4a** en el **Paso A** y **Q2b** por

Q4b (ver el esquema siguiente) en el **Paso D**, se prepara **Q4**; ESIMS calc. para $C_{22}H_{31}N_6O_3S$ ($M+H^+$) 459.2, resultó 459,1.

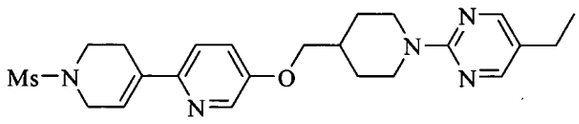


A1a **Q4a** **Q4b**

Paso A: Se trata una solución de **A1a** (1,03 g, 9 mmol) y 2–cloro–5–etilpirimidina (1,1 ml, 9 mmol) en dimetilacetamida (7 ml) con carbonato de cesio en polvo (4 g, 12.3 mmol) y se agita la suspensión a 75 °C por espacio de 48 horas. A continuación se diluye la reacción con agua (150 ml) y se la extrae con acetato de etilo/éter dietílico (1:1) (2 x 100 ml). Se combinan los extractos combinados con agua, cloruro de amonio acuoso saturado y solución salina, se los secó sobre Na_2SO_4 y concentró para dar **Q4a**; ^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 8,16 (s, 2H), 4,74 (m, 2H), 3,53 (t, *J* = 5,9 Hz, 2H), 2,87 (td, *J* = 13,2, 2,4 Hz, 2H), 2,45 (q, *J* =7,6 Hz, 2H), 1,85 (m, 2H), 1,77 (m, 1H), 1,44 (t, *J* = 5,5 Hz, 1H), 1,23 (m, 2H), 1,18 (t, *J* = 7,6 Hz, 3H); ESIMS calc, para $C_{12}H_{20}N_3O$ ($M+H^+$) 222,2, resultó 222,1.

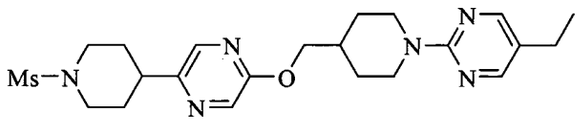
Paso B: A una solución de **Q4a** (0,92 g, 4.2 mmol) en diclorometano (20 ml) se agrega trietilamina (1,0 ml, 7,1 mmol) en una porción. Se enfría la mezcla así obtenida en un baño de hielo/agua y se agrega lentamente, con agitación, cloruro de metansulfonilo (0,45 ml, 5.8 mmol). Se retira el baño y se agita la solución obtenida a temperatura ambiente por espacio de 2 horas. Se diluye la mezcla de reacción con más diclorometano (20 ml), se la lava con agua y cloruro de amonio acuoso saturado, se la seca sobre $MgSO_4$ y concentra para dar **Q4b**; ^{1}H NMR ($CDCl_3$, 400,13 MHz): ^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 8,17 (s, 2H), 4,78 (m, 2H), 4,09 (d, *J* = 6,6 Hz, 2H), 3,02 (s, 3H), 2,88 (td, *J* = 13,2, 2,6 Hz, 2H), 2,46 (q, *J* =7,6 Hz, 2H), 2,05 (m, 2H), 1,84 (m, 1H), 1,29 (ddd, *J* = 4,4, 12,4, 12,7 Hz, 2H), 1,19 (t, *J* = 7,6 Hz, 3H); ESIMS calc. para $C_{13}H_{22}N_3O_3S$ ($M+H^+$) 300,1, resultó 300,0.

Ejemplo Q5: 2–(4–((6–(1,2,3,6–Tetrahidro–1–metansulfonil–piridin–4–il)piridin–3–iloxi)metil)piperidin–1–il)–5–etilpirimidina.

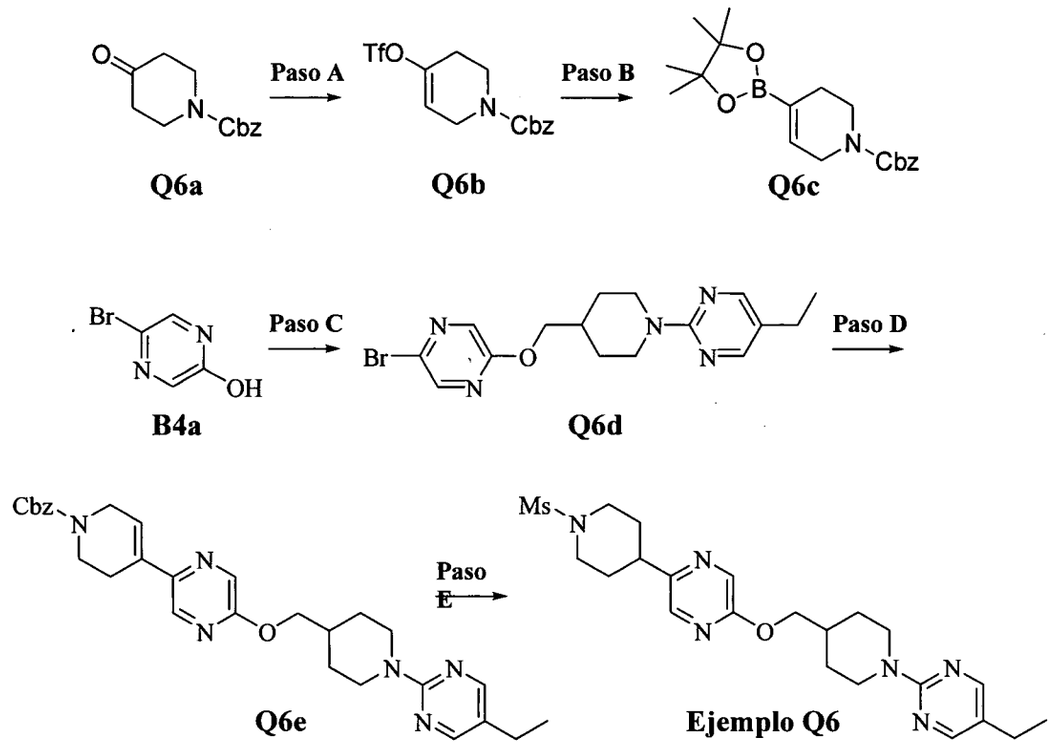


Siguiendo un procedimiento similar al empleado para la preparación de **Q2** a partir de **Q2b**, excepto que se sustituye **Q2b** por **Q4b**, se prepara **Q5**; ESIMS calc. para $C_{23}H_{32}N_5O_3S$ ($M+H^+$) 458,2, resultó 458,1.

Ejemplo Q6: 2–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metoxi)–5–(1–metansulfonilpiperidin–4–il)pirazina.



El Ejemplo **Q6** se puede preparar a partir del **Q5** antes mencionado, por hidrogenación con paladio sobre carbono. Sin embargo, la siguiente es una síntesis alternativa:



Paso A: Se trata una solución de diisopropilamina (2 ml, 14,2 mmol) en tetrahidrofurano seco (10 ml) a –78 °C bajo nitrógeno con *n*–Butil litio (solución 2,46 M en hexanos; 5 ml, 12,25 mmol) y se agita la mezcla por espacio de 15 min a –78 °C. Se agrega lentamente una solución de **Q6a** (2,55 g, 10,9 mmol) en tetrahidrofurano seco (25 ml) y se continúa agitando a –78 °C por espacio de 2 horas. Se agrega por goteo N–feniltriflimida (4,42 g, 12,4 mmol) en tetrahidrofurano seco (25 ml) a –78 °C. Se agita la mezcla a –78 °C por espacio de 2,5 horas y a temperatura ambiente por espacio de 30 minutos. La dilución con acetato de etilo (200 ml) y cloruro de amonio acuoso saturado (50 ml), el lavado con agua y solución salina, secado sobre Na_2SO_4 y concentración, seguidos por purificación en gel de sílice empleando un gradiente lineal de 0 a 40% de acetato de etilo en hexano producen **Q6b**; ^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 7,3 – 7,4 (m, 5H), 5,78 (m, 1H), 5,16 (s, 2H), 4,13 (br, s, 2H), 3,72 (br, s, 2H), 2,47 (br, s, 2H); ^{19}F NMR ($CDCl_3$, 376 MHz): δ –75,32; ESIMS calc, para $C_{14}H_{15}F_3NO_5S$ ($M+H^+$) 366,1, resultó 366,1.

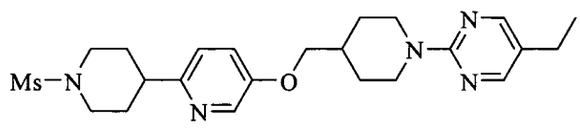
Paso B: A una solución de **Q6a** (1,22 g, 3,3 mmol) en 1,4–dioxano (25 ml) se agrega 4,4,5,5–tetrametil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1,3,2–dioxaborolano (1,02 g, 4 mmol), 1,1'–bis(difenilfosfino)ferroceno (0,08 g, 0,14 mmol), complejo [1,1'–bis(difenilfosfino)ferroceno]dicloropaladio(II) diclorometano (0,11 g, 0,13 mmol) y polvo de acetato de potasio (1,26 g, 12.8 mmol). Se desgasifica la mezcla utilizando argón y se la agita a 80°C por espacio de 18 horas. El enfriamiento, dilución, con agua (50 ml), extracción con acetato de etilo, lavado con agua y solución salina, secado sobre Na_2SO_4 y concentración, seguidos por purificación en gel de sílice empleando un gradiente lineal de 0 a 50% acetato de etilo en hexano produce **Q6b**; ^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 7.3 – 7.4 (m, 5H), 6.5 (m, 1H), 5.16 (s, 2H), 4,05 (m, 2H), 3.54 (m, 2H), 2.27 (br. s, 2H), 1.28 (s, 12H); ESIMS calc. para $C_{19}H_{27}BNO_4$ ($M+H^+$) 344.2, resultó 344.1.

Paso C: Se trata una solución de **B4a** (0,84 g, 4,8 mmol) y el intermediario **Q4b** (1,28 g, 4,3 mmol) en dimetilacetamida seca (25 ml) con carbonato de cesio en polvo (2,31 g, 7,1 mmol) y se agita la mezcla a 65 °C por espacio de 24 horas. La filtración, concentración y purificación en gel de sílice empleando un gradiente lineal de 10 a 50% de acetato de etilo en hexano producen **Q4d**; ^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 8,17 (s, 2H), 8,16 (d, J = 1,4 Hz, 1H), 8,02 (d, J = 1,4 Hz, 1H), 4,77 (m, 2H), 4,17 (d, J = 6,6 Hz, 2H), 2,88 (td, J = 13,1, 2,6 Hz, 2H), 2,46 (q, J =7,6 Hz, 2H), 2,10 (m, 2H), 1,89 (m, 1H), 1,34 (ddd, J = 4,3, 12,4, 12,6 Hz, 2H), 1,19 (t, J = 7,6 Hz, 3H); ESIMS calc, para $C_{16}H_{21}BrN_5O$ ($M+H^+$) 378,1, resultó 378,1.

Paso D: A una solución de **Q6d** (0,8 g, 2,1 mmol) en 1,2–dimetoxietano (5 ml) se le agrega el intermediario **Q6c** (0,91 g, 2.7 mmol), carbonato de potasio en polvo (0,72 g, 5,2 mmol), y agua (0,5 g). Se desgasifica la mezcla empleando argón, luego se agrega tetrakis–(trifenilfosfino)paladio (0) (0,23 g, 0,2 mmol) y se calienta la mezcla a 180 °C por espacio de 20 min en un reactor de microondas. El enfriamiento, dilución con acetato de etilo, secado sobre Na_2SO_4 y concentración, seguidas por purificación en gel de sílice empleando un gradiente lineal de 10 a 50% de acetato de etilo en hexano produce **Q6e**; ESIMS calc. para $C_{29}H_{35}N_6O_3$ ($M+H^+$) 515,3, resultó 515,1.

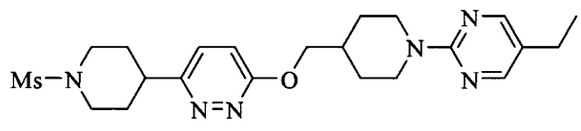
Paso E: Se trata una solución de **Q6e** (0,6 g, 1,2 mmol) en acetato de etilo (100 ml) y etanol (40 ml) con paladio sobre carbón (al 5%; 0,85 g, 0,4 mmol) y se satura la mezcla con gas hidrógeno y luego se la agita a temperatura ambiente bajo 1 atmósfera de hidrógeno por espacio de 3 horas. Después de la filtración de la reacción a través de una plancha de Celite® y la concentración, se disuelve el residuo en diclorometano (10 ml) y trietilamina (0,6 ml, 4,3 mmol). A continuación se agrega lentamente cloruro de metansulfonilo (0,15 ml, 1,9 mmol), con agitación. Al cabo de 2 horas, se concentra la mezcla y se la purifica en gel de sílice utilizando un gradiente lineal de 10 a 65 % de acetato de etilo en hexano para producir **Q6**. ESIMS calc. para $C_{22}H_{33}N_6O_3S$ ($M+H^+$) 461,2, resultó 461,1.

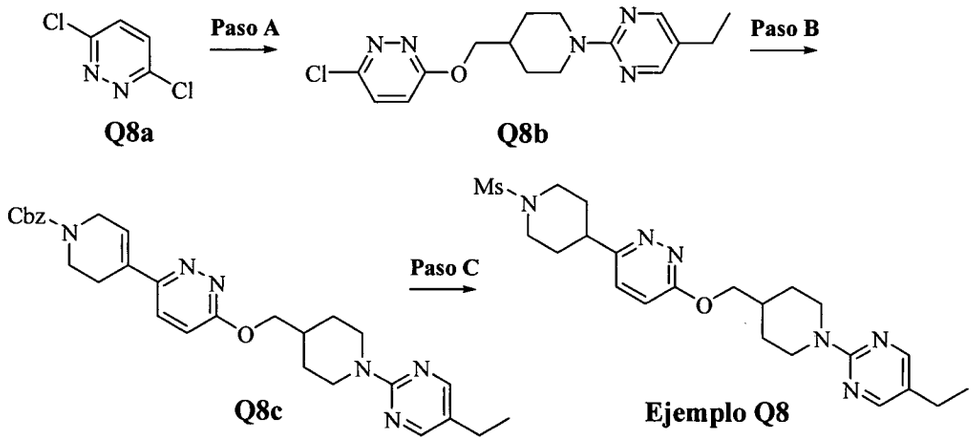
Ejemplo Q7: 2–(4–((6–(1–Metansulfonilpiperidin–4–il)piridin–3–iloxi)metil)piperidin–1–il)–5–etilpirimidina.



Siguiendo un procedimiento similar al empleado para la preparación de **Q6** a partir de **B4a**, excepto que se sustituye **B4a** por **B2a** en el **Paso C**, se prepara **Q7**; ESIMS calc. para $C_{23}H_{34}N_5O_3S$ ($M+H^+$) 460,2, resultó 460,1.

Ejemplo Q8: 3–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metoxi)–6–(1–metansulfonilpiperidin–4–il)piridazina.





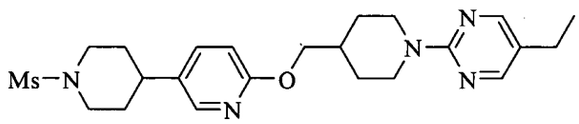
Paso A: Se trata una solución de **Q8a** (0,64 g, 2,9 mmol) y **Q4a** (0,49 g, 3,3 mmol) en dimetilacetamida seca (6 ml) con carbonato de potasio en polvo (0,7 g, 5,0 mmol) y se agita la mezcla a 150 °C por espacio de 2 días. El enfriamiento, dilución con agua (100 ml), extracción con acetato de etilo (2 x 100 ml), secado sobre Na_2SO_4, La filtración, concentración y purificación en gel de sílice utilizando un gradiente lineal de 10 a 100% de acetato de etilo en hexano producen **Q8b**; ^1H NMR ($CDCl_3$, 400,13 MHz): δ 8,17 (s, 2H), 7,67 (d, J = 9,2 Hz, 1H), 6,96 (d, J = 9,2 Hz, 1H), 4,77 (m, 2H), 4,37 (d, J = 6,6 Hz, 2H), 2,90 (td, J = 13,1, 2,6 Hz, 2H), 2,46 (q, J =7,6 Hz, 2H), 2,15 (m, 2H), 1,89 (m, 1H), 1,36 (ddd, J = 4,3, 12,4, 12,6 Hz, 2H), 1,19 (t, J = 7,6 Hz, 3H); ESIMS calc, para $C_{16}H_{21}ClN_5O$ ($M+H^+$) 334,1, resultó 334,1.

Paso B: A una solución de **Q8b** (0,11 g, 0,3 mmol) en 1,2–dimetoxietano (2 ml) se agrega el intermediario **Q6b** (0,15 g, 0,4 mmol), carbonato de potasio en polvo (0,18 g, 1,3 mmol), y agua (0,5 g). Se desgasifica la mezcla empleando argón, luego se agrega tetrakis–(trifenilfosfino)paladio(0) (0,05 g, 0,04 mmol) y se calienta la mezcla a 180 °C por 20 min en un reactor de microondas. El enfriamiento, dilución con acetato de etilo, secado sobre Na_2SO_4 y concentración, seguidos por purificación en gel de sílice utilizando un gradiente lineal de 10 a 75% de acetato de etilo en hexano producen **Q8c**; ESIMS calc. para $C_{29}H_{35}N_6O_3$ ($M+H^+$) 515,3, resultó 515,1.

Paso C: Se trata una solución de **Q8c** (0,15 g, 0,3 mmol) en acetato de etilo (20 ml) y etanol (20 ml) con negro de paladio sobre carbón (5%; 0,4 g, 0,2

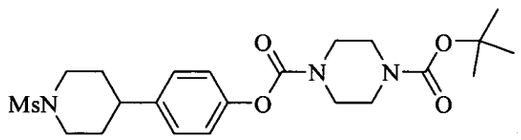
mmol), se la satura con hidrógeno y seguidamente se la agita a temperatura ambiente bajo 1 atmósfera de hidrógeno por espacio de 6 horas. Después de intercambiar la atmósfera por N_2, se filtra la reacción a través de una plancha de Celite® y se la concentra. Se disuelve el aceite obtenido en diclorometano (10 ml) y trietilamina (0,3 ml, 2.1 mmol). A continuación se agrega lentamente cloruro de metansulfonilo (0,05 ml, 0,6 mmol), con agitación. Al cabo de 2 horas, se concentra la mezcla y se la purifica utilizando HPLC de fase inversa iniciada por la masa para producir **Q8**; ESIMS calc. para $C_{22}H_{33}N_6O_3S$ ($M+H^+$) 461,2, resultó 461,1.

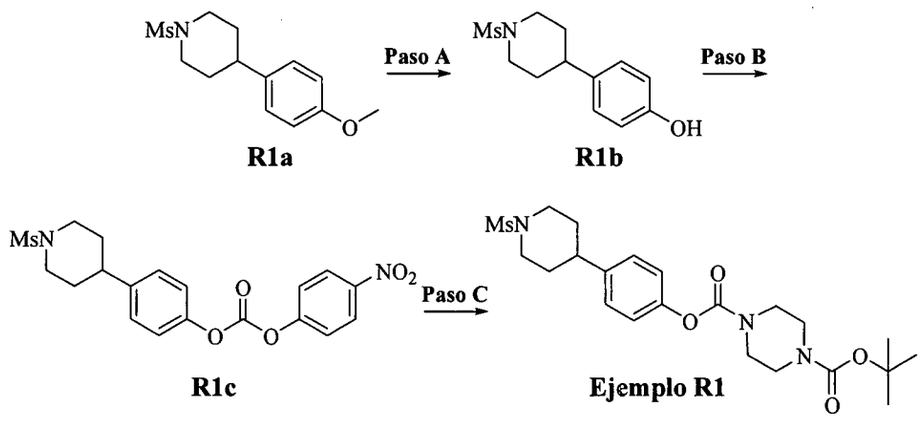
Ejemplo Q9: 2–(4–((5–(1–Metansulfonilpiperidin–4–il)piridin–2–iloxi)metil)piperidin–1–il)–5–etilpirimidina.



Siguiendo un procedimiento similar al empleado para la preparación de **Q8** a partir de **Q8a**, excepto que se sustituye **8a** por **C1a**, se prepara **Q9**; ESIMS calc. para $C_{23}H_{34}N_5O_3S$ ($M+H^+$) 460,2, resultó 460,2.

Ejemplo R1: 1–*terc*–Butil 4–(4–(1–(metilsulfonil)piperidin–4–il)fenil) piperazin–1,4–dicarboxilato.



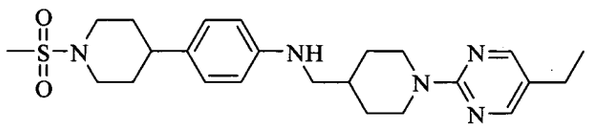


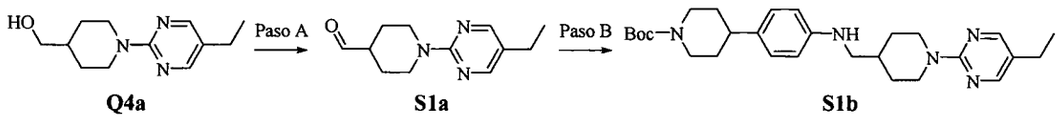
Paso A: Se enfría una solución de **R1a** (2,2 g, 8,2 mmol) en diclorometano (10 ml) en un baño de hielo/agua y se la trata con BBr_3 puro (9,21 g, 37 mmol). Se agita la reacción a la temperatura del baño helado por espacio de 10 minutos y a temperatura ambiente por espacio de 1 hora. A continuación se vierte la reacción sobre hielo triturado y se deja que se inactive. Se recoge el sólido así obtenido y se lo seca para producir **R1b**; ESIMS calc. para $C_{12}H_{17}NO_3S$ ($M+H^+$) 256,1, resultó 256,1.

Paso B: Se trata una solución de **R1b** (100 mg, 0,39 mmol) y nitrofenil cloroformiato (87 mg, 0,43 mmol) en acetonitrilo (5 ml) con K_2CO_3 (108 mg, 0,78 mmol) y se agita la mezcla a temperatura ambiente por espacio de 2 horas, luego se la filtra, concentra y purifica en gel de sílice empleando un gradiente lineal de 0 a 100% de acetato de etilo en hexano para producir **R1c**; ESIMS calc. para $C_{19}H_{21}N_2O_7S$ $[M+H]^+$ 421,1, resultó 421,1.

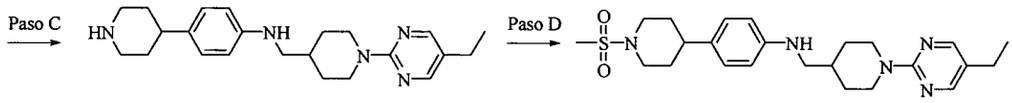
Paso C: Se calienta una solución de **R1c** (41 mg, 0,10 mmol), 1–Boc–piperazina (20 mg, 0,11 mmol) y trietilamina (68 µl, 0,50 mmol) en 1,2–dicloroetano (5 ml) a 50 °C por espacio de 12 horas. Se concentra la mezcla al vacío y se la purifica empleando HPLC de fase inversa iniciada por la masa para producir **R1**; ^1H–NMR (400MHz, $CDCl_3$) δ 7,12 (d, J = 8,4 Hz, 2H), 6,98 (d, J = 8,8 Hz, 2H), 3,87 (m, 3H), 3,56 (m, 2H), 3,45 (m, 6H), 2,75 (s, 3H), 2,70 (m, 3H), 2,55 (m, 2H), 1,90 (m, 3H), 1,77 (m, 3H), 1,42 (s, 9H); ESIMS calc, para $C_{22}H_{33}N_3NaO_6S$ $[M+Na]^+$ 490,2, resultó 490,1.

Ejemplo S1: *N*–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metil)–4–(1–(metilsulfonil)piperidin–4–il)anilina.





Q4a S1a S1b



S1c Ejemplo S1

Paso A: Se agrega una solución de **Q4a** (444 mg, 2mmol) en diclorometano anhidro (5 ml) a una solución de peryodinano de Dess–Martin (1,018 g, 2,4 mmol) en diclorometano anhidro (10 ml) y se la agita de un día para otro a temperatura ambiente. Se agrega más diclorometano (30 ml) y se filtra la reacción a través de Celite® y se la concentra. La purificación en gel de sílice empleando un gradiente lineal de 0 a 50% de acetato de etilo en hexano produce **S1a**; ESIMS calc. para $C_{12}H_{18}N_3O$ ($M+H^+$) 220,1, resultó 220,1.

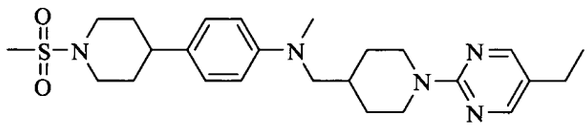
Paso B: Se agita a temperatura ambiente una mezcla de **S1a** (318 mg, 1,5 mmol), *terc*–butil 4–(4–aminofenil)piperidin–1–carboxilato (482 mg, 1,74 mmol), y $NaBH(OAc)_3$ (636 mg, 3 mmol) en diclorometano (7 ml) por espacio de 5 horas. Se inactiva la reacción con agua (20 ml) y se la extrae con diclorometano (3 x 20 ml), se la lava con agua (20 ml), seca (Na_2SO_4), y concentra. La purificación en gel de sílice empleando un gradiente lineal de 0 a 50% de acetato de etilo en hexano producen **S1b**; ESIMS calc. para $C_{28}H_{42}N_5O_2$ ($M+H^+$) 480,3, resultó 480,4.

Paso C: Se trata una solución de **S1b** (600 mg, 1,25 mmol) en MeOH (10 ml) con una solución 4 M de HCl en dioxano (25 ml, 100 mmol) y se la agita a temperatura ambiente de un día para otro. Se concentra la mezcla de reacción, se le agrega

dioxano (20 ml) y se la vuelve a concentrar para formar la sal de clorhidrato de **S1c**; ESIMS calc. para $C_{23}H_{34}N_5$ ($M+H^+$) 380,3, resultó 380,3.

Paso D: Se trata por goteo ml, 6,4 mmol) en diclorometano (30 ml) con cloruro de metansulfonilo (0,152 ml, 1.96 mmol) y se la agita a temperatura ambiente por espacio de 3 horas. Se agrega más trietilamina (0,5 ml, 3,6 mmol) y cloruro de metansulfonilo (0,076 ml, 0,98 mmol) y se agita la reacción a temperatura ambiente por espacio de 30 minutos más. Se inactiva la reacción con agua (20 ml), se la extrae con diclorometano (3 x 20 ml), se la lava con agua (20 ml), seca sobre Na_2SO_4, y concentra. La purificación utilizando HPLC de fase inversa iniciada por la masa produce **S1**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8,24 (s, 2H), 7,05 (m, 2H), 6,70 (m, 2H), 4,61 (m, 2H), 3,64 (m, 2H), 2,96 (m, 2H), 2,88 (s, 3H), 2,80 (m, 4H), 2,42 (q, J = 7,6 Hz, 2H), 1,84 (m, 5H), 1,60 (m, 2H), 1,12 (m, 5H); ESIMS calc, para $C_{24}H_{36}N_5O_2S$ ($M+H^+$) 458,3, resultó 458,3.

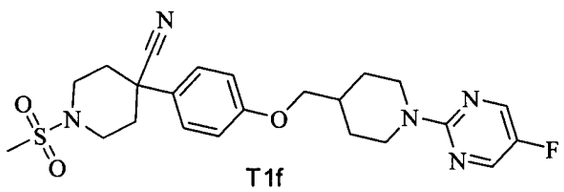
Ejemplo S2: *N*–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metil)–*N*–metil–4–(1–(metilsulfonil)piperidin–4–il)anilina.



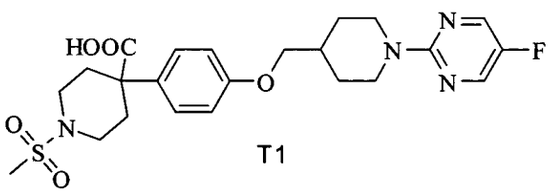
Se agrega una solución de **S1** (46 mg, 0,1 mmol) en tetrahidrofurano (1 ml) gota a gota a una solución helada de H_2SO_4 acuoso al 10 % (0,2 ml) y formaldehído acuoso al 37 % (0,1 ml, 1,2 mmol) en tetrahidrofurano (0,5 ml). Se agrega $NaBH_4$ (30 mg, 0,79 mmol) y se calienta la mezcla de reacción a temperatura ambiente. Después de agitar durante 30 minutos, se inactiva la reacción con NaOH 0,2 M (10 ml) y se la extrae con acetato de etilo (3 x 15 ml), se la lava con solución salina (10 ml), se la seca sobre Na_2SO_4 y concentra. Se purifica el compuesto utilizando HPLC de fase inversa iniciada por la masa para producir **S2**; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8,23 (s, 2H), 7,08 (m, 2H), 6,68 (m, 2H), 4,60 (m, 2H), 3,64 (m, 2H), 3,19 (m, 2H), 2,92 (bs, 3H), 2,88 (s, 3H), 2,78 (m, 4H), 2,42 (q, J = 7,6

Hz, 2H), 1,93 (m, 1H), 1,81 (m, 2H), 1,62 (m, 4H), 1,12 (m, 5H); ESIMS calc, para $C_{25}H_{38}N_5O_2S$ ($M+H^+$) 472,3, resultó 472,3.

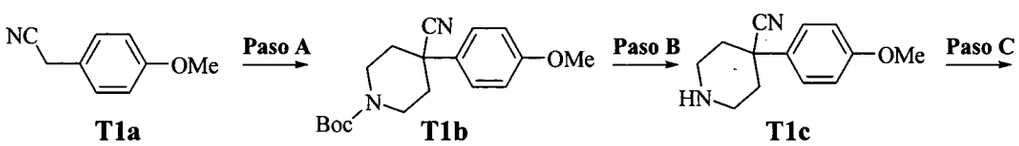
Ejemplos T1f y T1: 4–(4–((1–(5–fluoropirimidin–2–il)piperidin–4–il)metoxi)fenil)–1–(metilsulfonil)piperidin–4–carbonitrilo y ácido 4–(4–((1–(5–fluoropirimidin–2–il)piperidin–4–il)metoxi)fenil)–1–(metilsulfonil)piperidin–4–carboxílico

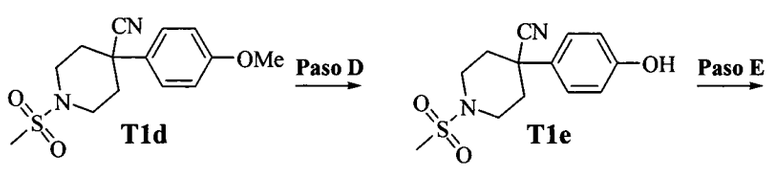


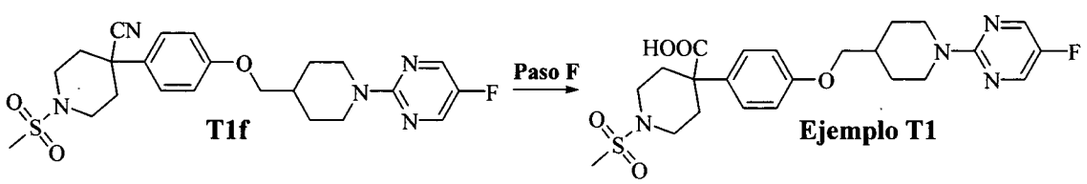
T1f



T1







Paso A: A una suspensión helada de NaH (60% en aceite, 120 mg, 3 mmol) en N, N–dimetilformamida anhidra (2 ml) se agrega **T1a** (142 µl, 1,05 mmol) y se la agita por espacio de 30 minutos bajo atmósfera de nitrógeno. A la solución marrón así obtenida se agrega *terc*–butil bis(2–cloroetil)carbamato (242 mg, 1 mmol) en N,N–dimetilformamida (0,2 ml) y se retira el baño refrigerante al cabo de 15 min. Se calienta la mezcla de reacción de un día para otro a 75 °C, se la enfría a temperatura ambiente y se la inactiva con agua (1 ml). Se agrega más agua (50 ml) y se extrae la reacción con diclorometano (3 x 30 ml), se la seca sobre Na_2SO_4 y concentra. La purificación en gel de sílice empleando un gradiente lineal de 0 a 50% acetato de etilo en hexano producen **T1b;** ^{1}H–NMR (400MHz, $CDCl_3$) δ 7,38 (m, 2H), 6,93 (m, 2H), 4,26 (m, 2H), 3,82 (s, 3H), 3,19 (m, 2H), 2,08 (d, J = 12,9 Hz, 2H), 1,90 (td, J = 13,0, 4,0 Hz, 2H), 1,48 (s, 9H); ESIMS calc, para $C_{18}H_{24}N_2NaO_3$ ($M+Na^+$) 339,2, resultó 388,8.

Paso B: A una solución de **T1b** (218 mg, 0,69 mmol) en dioxano (1 ml) se agrega una solución 4 M de HCl en dioxano (2 ml, 8 mmol) y se agita la reacción por espacio de 2 horas a temperatura ambiente. Se separa el solvente y se coevapora el residuo con dioxano (10 ml) para producir **T1c**; ESIMS calc. para $C_{13}H_{17}N_2O$ ($M+H^+$) 217,1, resultó 216,9.

Paso C: Se trata gota a gota una solución fría (baño de hielo/agua) de **T1c** (0,69 mmol) y trietilamina (385 µl, 2,76 mmol) en diclorometano seco (10 ml) con cloruro de metansulfonilo (64 µl, 0,83 mmol). Se agita la solución obtenida a temperatura ambiente de un día para otro. Se agrega la mezcla de reacción al agua (40 ml) y se la extrae con diclorometano (3 x 40 ml). Se secan las capas orgánicas combinadas sobre Na_2SO_4 y se las concentra para dar **T1d**; ESIMS calc. para $C_{14}H_{19}N_2O_3S$ ($M+H^+$) 295,1, resultó 295,0.

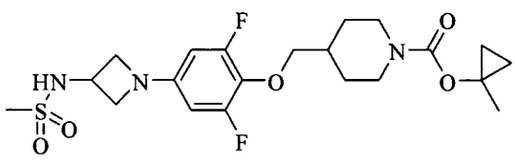
Paso D: Se enfría una solución de **T1d** (208 mg, 0,7 mmol) en diclorometano anhidro (3,5 ml) a –78 °C bajo atmósfera de nitrógeno y se le agrega gota a gota una solución 1 M de BBr_3 (3,5 ml, 3,5 mmol) en diclorometano. Se agita la reacción a temperatura ambiente de un día para otro, luego se la enfría a 0 °C y se la inactiva con MeOH (2 ml). Se concentra repetidamente la mezcla de

reacción con MeOH (3 x 20 ml) para producir **T1e**; ESIMS calc. para $C_{13}H_{17}N_2O_3S$ ($M+H^+$) 281,1, resultó 281,0.

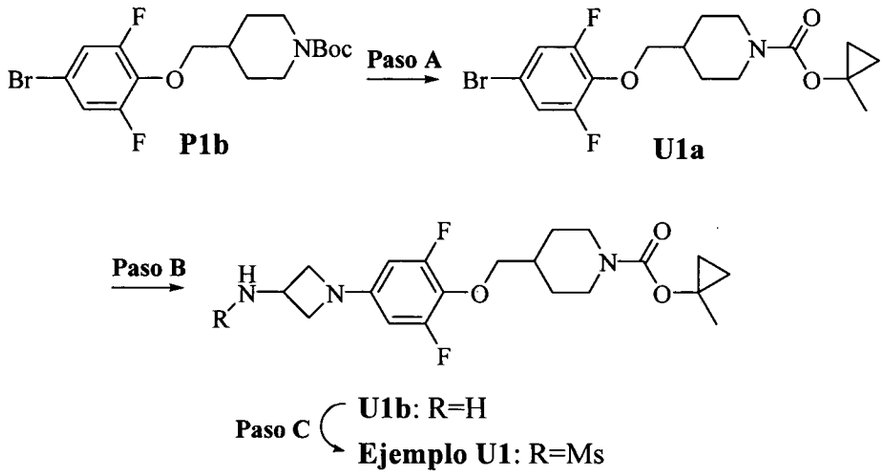
Paso E: Se calienta una mezcla de **T1e** (196 mg, 0,7 mmol), (1–(5–fluoropirimidin–2–il)piperidin–4–il)metil metansulfonato (202 mg, 0,7 mmol; preparada siguiendo el procedimiento utilizado para **Q4a** excepto que se usa 2–cloro–5–fluoropirimidina como electrófilo), y Cs_2CO_3 (456 mg, 1,4 mmol) en acetonitrilo (10 ml) a 70 °C por espacio de 48 horas. Se concentra la mezcla de reacción y se la reparte entre agua (20 ml) y acetato de etilo, se extrae la fase acuosa con acetato de etilo (2 x 20 ml). Se lavan los extractos orgánicos combinados con agua (2 x 10), se los seca sobre Na_2SO_4 y concentra. La purificación en gel de sílice empleando un gradiente lineal de 0 a 60% de acetato de etilo en hexano produce **T1f**; ^{1}H–NMR (400MHz, DMSO) δ 8,43 (d, J = 0,8 Hz, 2H), 7,46 (m, 2H), 7,00 (m, 2H), 4,61 (m, 2H), 3,87 (d, J = 6,4 Hz, 2H), 3,74 (m, 2H), 3,00 (m, 5H), 2,92 (m, 2H), 2,24 (m, 2H), 2,05 (m, 3H), 1,83 (m, 2H), 1,23 (m, 2H); ESIMS calc, para $C_{23}H_{29}FN_5O_3S$ ($M+H^+$) 474,2, resultó 474,2,

Paso F: Se calienta una solución de **T1f** (30 mg, 0,063 mmol) y KOH (105 mg, 2.6 mmol) en 2–metoxietanol (1 ml) y agua (0,5 ml) a 110 °C por 72 horas. Se acidifica la mezcla de reacción con HCl 1 N a pH 2–3 y se la extrae con acetato de etilo (3 x 20 ml). Se secan los extractos orgánicos combinados sobre Na_2SO_4, y se los concentra. Se purifica el residuo empleando HPLC de fase inversa iniciada por la masa para producir **T1**; ^{1}H–NMR (400MHz, DMSO–d6) δ 8,42 (d, J = 0,8 Hz, 2H), 7,30 (m, 2H), 6,92 (m, 2H), 4,60 (m, 2H), 3,83 (d, J = 6,4 Hz, 2H), 2,88 (m, 7H), 2,48 (m, 2H), 2,04 (m, 1H), 1,83 (m, 4H), 1,22 (m, 2H), ESIMS calc, para $C_{23}H_{30}FN_4O_5S$ ($M+H^+$) 493,2, resultó 493,1

Ejemplo U1: 1–metilciclopropil 4–((2,6–difluoro–4–(3–(metilsulfonamido)azetidin–1–il)fenoxi)metil)piperidin–1–carboxilato.



458

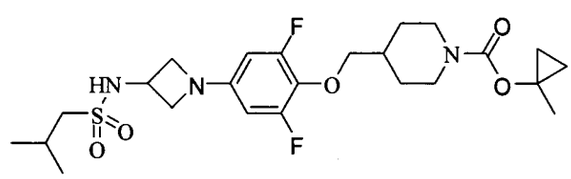


Paso A: Siguiendo un procedimiento similar al utilizado para la preparación de **E3** a partir de **E3a**, excepto que se sustituye **E3a** por **P1b**, se prepara **U1a**; ESIMS calc. para $C_{17}H_{21}BrF_2NO_3$ $[M+H]^+$: 404,1, resultó: 404,0.

Paso B: Siguiendo un procedimiento similar al utilizado para la preparación de **B2** a partir de **B2b**, excepto que se sustituye bencil piperazin–1–carboxilato por bencil azetidin–3–ilcarbamato, se prepara **U1b**; Se observa que el grupo Cbz se elimina en las condiciones de reacción; ESIMS calc. para $C_{20}H_{28}F_2N_3O_3$ $[M+H^+]$ 396,2, resultó 369,3.

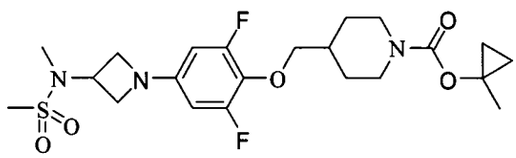
Paso C: Siguiendo un procedimiento similar al utilizado para la preparación de **G1** a partir de **G1a**, excepto que se sustituye **G1a** por **U1b**, se prepara **U1**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 5,95 (d, *J* = 9,7 Hz, 2H), 4,85 (d, *J* = 9,4 Hz, 1H), 4,40 (m, 1H), 4,20 (t, *J* = 7,5 Hz, 2H), 4,29–3,94 (m, 2H), 3,80 (d, *J* = 6,0 Hz, 2H), 3,65 (dd, *J* = 5,3, 8,0 Hz, 2H), 3,00 (s, 3H), 2,74 (t, *J* = 12,4 Hz, 2H), 1,9 (m, 1H), 1,82 (d, *J* = 13,1 Hz, 2H), 1,54 (s, 3H), 1,22 (m, 2H), 0,86 (t, *J* = 6,4 Hz, 2H), 0,62 (t, *J* = 6,4 Hz, 2H), ESIMS calc, para $C_{21}H_{30}F_2N_3O_5S$ $[M+H^+]$ 474,2, resultó 474,1,

Ejemplo U2: 1–metilciclopropil 4–((2,6–difluoro–4–(3–(2–metilpropilsulfonamido)azetidin–1–il)fenoxi)metil)piperidin–1–carboxilato.



Siguiendo un procedimiento similar al utilizado para la preparación de **U1** a partir de **U1c**, excepto que se sustituye el cloruro de metansulfonilo por cloruro de isobutansulfonilo, se prepara **U2**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 5,96 (d, *J* = 9,6 Hz, 2H), 4,87 (d, *J* = 9,5 Hz, 1H), 4,40 (m, 1H), 4,20 (t, *J* = 7,5 Hz, 2H), 4,29–3,94 (m, 2H), 3,82 (d, *J* = 4,8 Hz, 2H), 3,65 (dd, *J* = 7,9, 5,4 Hz, 2H), 2,93 (d, *J* = 6,4 Hz, 2H), 2,75 (m, 2H), 2,28 (septete, *J* = 6,7 Hz, 1H), 1,92 (m, 1H), 1,83 (d, *J* = 12,6 Hz, 2H), 1,56 (s, 3H), 1,24 (m, 2H), 1,13 (d, *J* = 6,7 Hz, 6H), 0,87 (t, *J* = 6,3 Hz, 2H), 0,63 (t, *J* = 6,3 Hz, 2H). ESIMS calc. para $C_{24}H_{36}F_2N_3O_5S$ [M+H$^+$] 516,2, resultó 516,2.

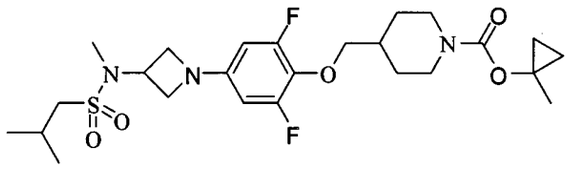
Ejemplo U3: 1–metilciclopropil 4–((2,6–difluoro–4–(3–(N–metilmetilsulfonamido)azetidin–1–il)fenoxi)metil)piperidin–1–carboxilato.



A una solución de **U1** (25 mg, 0,05 mmol) y yodometano (4 ul, 0,06 mmol) en N,N–dimetilformamida seca (1 ml) a 0 °C se agrega hidruro de sodio (5 mg, 0,2 mmol) en una porción. Se deja entibiar lentamente la mezcla a temperatura ambiente y se la agita durante 1 hora más. Se reparte la mezcla entre agua y diclorometano y se lava la capa orgánica con solución salina, se la seca sobre $MgSO_4$, filtra, evapora y purifica en gel de sílice. Se deja entibiar la mezcla lentamente a temperatura ambiente y se la agita durante 1 hora más. Se reparte la mezcla entre agua y diclorometano y se lavan los extractos orgánicos con solución salina, se los seca sobre $MgSO_4$, filtra, evapora y purifica en gel de sílice empleando acetato de etilo al 0–50 % en diclorometano para producir **U3**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 5,97 (d, *J* = 9,6 Hz, 2H), 4,71 (m, 1H), 4,06 (t, *J* = 7,8 Hz, 2H), 4,29–3,95 (m, 2H), 3,88 (dd, *J* = 8,0, 5,6 Hz, 2H), 3,81 (d, *J* = 5,8 Hz, 2H),

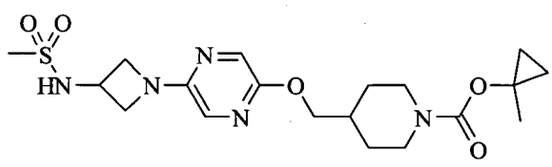
2,97 (s, 3H), 2,83 (s, 3H), 2,74 (m, 2H), 1,91 (m, 1H), 1,83 (d, *J* = 13,4 Hz, 2H), 1,54 (s, 3H), 1,24 (m, 2H), 0,86 (t, *J* = 6,3 Hz, 2H), 0,62 (t, *J* = 6,3 Hz, 2H), ESIMS calc, para $C_{22}H_{32}F_2N_3O_5S$ [M+H$^+$] 488,2, resultó 488,2.

Ejemplo U4: 1–metilciclopropil 4–((4–(3–(N,2–dimetilpropilsulfonamido)azetidin–1–il)–2,6–difluorofenoxi)metil)piperidin–1–carboxilato.



Siguiendo un procedimiento similar al utilizado para la preparación de **U3** a partir de **U1**, excepto que se sustituye **U1** por **U2**, se prepara **U2**; ^{1}H–NMR (400MHz, $CDCl_3$) δ 5,96 (d, *J* = 9,7 Hz, 2H), 4,77 (m, 1H), 4,04 (t, *J* = 7,9 Hz, 2H), 4,25–3,96 (m, 2H), 3,87 (dd, *J* = 5,6, 7,8 Hz, 2H), 3,81 (d, *J* = 6,3 Hz, 2H), 2,97 (s, 3H), 2,77 (d, *J* = 6,7 Hz, 2H), 2,74 (m, 2H), 2,24 (septete, *J* = 6,6 Hz, 1H), 1,91 (m, 1H), 1,83 (d, *J* = 13,3 Hz, 2H), 1,54 (s, 3H), 1,24 (m, 2H), 1,11 (d, *J* = 6,5 Hz, 6H), 0,86 (t, *J* = 6,3 Hz, 2H), 0,61 (t, *J* = 6,3 Hz, 2H), ESIMS calc, para $C_{25}H_{38}F_2N_3O_5S$ [M+H$^+$] 530,3, resultó 530,2.

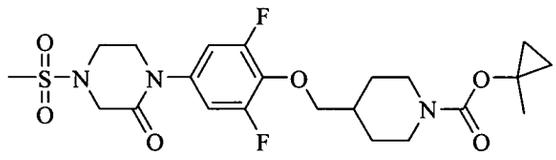
Ejemplo U5: 1–Metilciclopropil 4–((5–(3–(metilsulfonamido)azetidin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato.



Siguiendo un procedimiento similar al utilizado para la preparación de **M1** a partir de **M1a**, excepto que se sustituye el bencil piperazin–1–carboxilato por

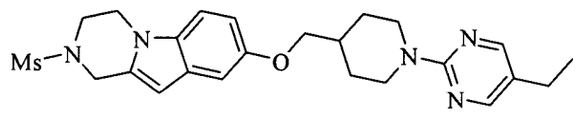
bencil azetidin–3–ilcarbamato en el **Paso A** y metil 3–(clorosulfonil)propanoato por cloruro de metansulfonilo en el **Paso d**, se prepara **U5**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7,72 (d, J = 1,4 Hz, 1H), 7,24 (d, J = 1,4 Hz, 1H), 4,73 (d, J = 9,2 Hz, 1H), 4,37 (m, 1H), 4,28 (m, 2H), 3,97 (d, J = 6,4 Hz, 2H), 3,75 (m, 2H), 3,27 (s, 3H), 2,65 (m, 2H), 1,85 (m, 1H), 1,70 (m, 2H), 1,46 (s, 3H), 1,17 (m, 3H), 0,77 (m, 2H), 0,53 (m, 2H); ESIMS *m/z* por $(M+H)^+$ $C_{19}H_{30}N_5O_5S$ calc.: 440,2, resultó: 440,2.

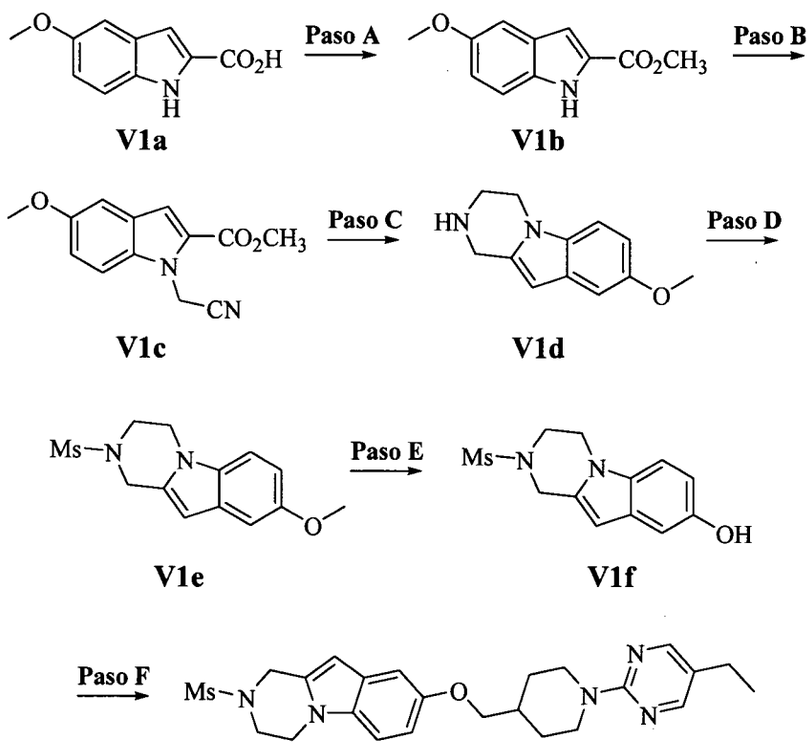
Ejemplo U6: 1–Metilciclopropil 4–((2,6–difluoro–4–(4–(metilsulfonil)–2–oxopiperazin–1–il)fenoxi)metil)piperidin–1–carboxilato.



Siguiendo un procedimiento similar al utilizado para la preparación de **O2** a partir de **B4b**, excepto que se sustituye **B4b** por **P1b**, se prepara **U6**; ^{1}H–NMR (400MHz, DMSO–d6) δ 7,28 (m, 2H), 3,94 (m, 6H), 3,77 (m, 2H), 3,53 (m, 2H), 3,05 (s, 3H), 2,75 (m, 2H), 1,88 (m, 2H), 1,74 (m, 2H), 1,46 (s, 3H), 1,14 (m, 2H), 0,76 (m, 2H), 0,59 (m, 2H); ESIMS calc, para $C_{22}H_{30}F_2N_3O_6S$ $[M+H]^+$ 502,2, resultó 502,2.

Ejemplo V1: 8–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metoxi)–2–(metilsulfonil)–1,2,3,4–tetrahidropirazino[1,2–*a*]indol.





Ejemplo V1

Paso A: Se trata gota a gota una suspensión de **V1a** (2,26 g, 11.8 mmol) en metanol (20 ml) con cloruro de tionilo (1,0 ml, 13.8 mmol), con agitación. Se agita la mezcla obtenida a temperatura ambiente por espacio de 18h, y luego se la concentra a sequedad. Se tritura el sólido obtenido con agua/ hidrogenocarbonato de sodio acuoso saturado 1:1, se lo filtra, se lo lava con agua y seca para producir **V1b**; ^{1}H NMR (DMSO–d_6, 400,13 MHz): δ 11,80 (s, 1H), 7,37 (d, *J* = 8,9 Hz, 1H), 7,11 (d, *J* = 2,2 Hz, 1H), 7,06 (d, *J* = 2,2 Hz, 1H), 6,92 (dd, *J* = 2,4, 8,9 Hz, 1H), 3,86 (s, 3H), 3,76 (s, 3H); ESIMS calc, para $C_{11}H_{12}NO_3$ ($M+H^+$) 206,1, resultó 206,1.

Paso B: Se trata una solución de **V1b** (1,86 g, 9.1 mmol) en *N,N*–dimetilacetamida (25 ml) con carbonato de cesio en polvo (5,31 g, 16,3 mmol) y cloroacetonitrilo (0,90 ml, 14,3 mmol) y se agita la mezcla a 65 °C por espacio de 18 horas. El enfriamiento a temperatura ambiente, la dilución con acetato de etilo, el lavado con agua (2x) cloruro de amonio acuoso saturado y solución salina, el secado sobre Na_2SO_4, la filtración y concentración rinde un sólido. Se purifica el

residuo en gel de sílice empleando acetato de etilo al 5–30% en hexanos para producir **V1c**; ^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 7,33 (d, *J* = 8,9 Hz, 1H), 7,30 (d, *J* = 1,0 Hz, 1H), 7,12 (m, 2H), 5,59 (s, 2H), 3,95 (s, 3H), 3,87 (s, 3H); ESIMS calc, para $C_{13}H_{13}N_2O_3$ ($M+H^+$) 245,1, resultó 245,0.

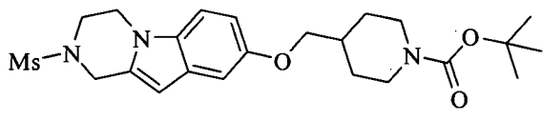
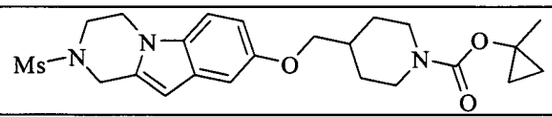
Paso C: **V1d** se prepara a partir de **V1c** de acuerdo con el procedimiento dado a conocer en la literatura en *Bioorg. Med. Chem. Lett.* **2002**, *12*, 155–158; ESIMS calc. para $C_{12}H_{15}N_2O$ ($M+H^+$) 203,1, resultó 203,1.

Paso D: A una solución de **V1d** (0,58 g, 2,5 mmol) en diclorometano (15 ml) se agrega trietilamina (0,7 ml, 5 mmol) en una porción. Se enfría la mezcla así obtenida en un baño de hielo/agua y se agrega gota a gota cloruro de metansulfonilo (0,25 ml, 3,2 mmol), con agitación, en un lapso de 5 minutos. Se retira el baño y se agita la solución así obtenida a temperatura ambiente por espacio de 30 minutos. Se agrega la mezcla de reacción a agua (40 ml) y se la extrae con diclorometano (2 x 40 ml). Se lavan los extractos orgánicos combinados con una solución acuosa saturada de cloruro de amonio, se los seca sobre $MgSO_4$, y se la concentra para dar **V1e**; ESIMS calc. para $C_{13}H_{17}N_2O_3S$ ($M+H^+$) 281,1, resultó 281,2.

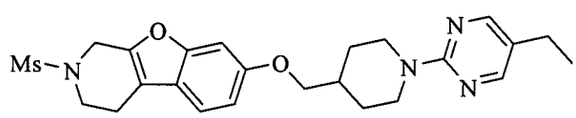
Paso E: Se trata una solución de **V1e** (0,60 g, 2.1 mmol) en diclorometano (15 ml) con tribromuro de boro puro (0,8 ml, 8,3 mmol) a temperatura ambiente. Se agita la solución así obtenida a temperatura ambiente por espacio de 30 minutos. Se agrega cuidadosamente la mezcla de reacción a metanol (50 ml), se la trata con Na_2CO_3 sólido (0,4 g), se la filtra y concentra a sequedad. Se utiliza el **V1f** crudo tal como está en el siguiente Paso; ESIMS calc. para $C_{12}H_{15}N_2O_3S$ ($M+H^+$) 267,1, resultó 267,1.

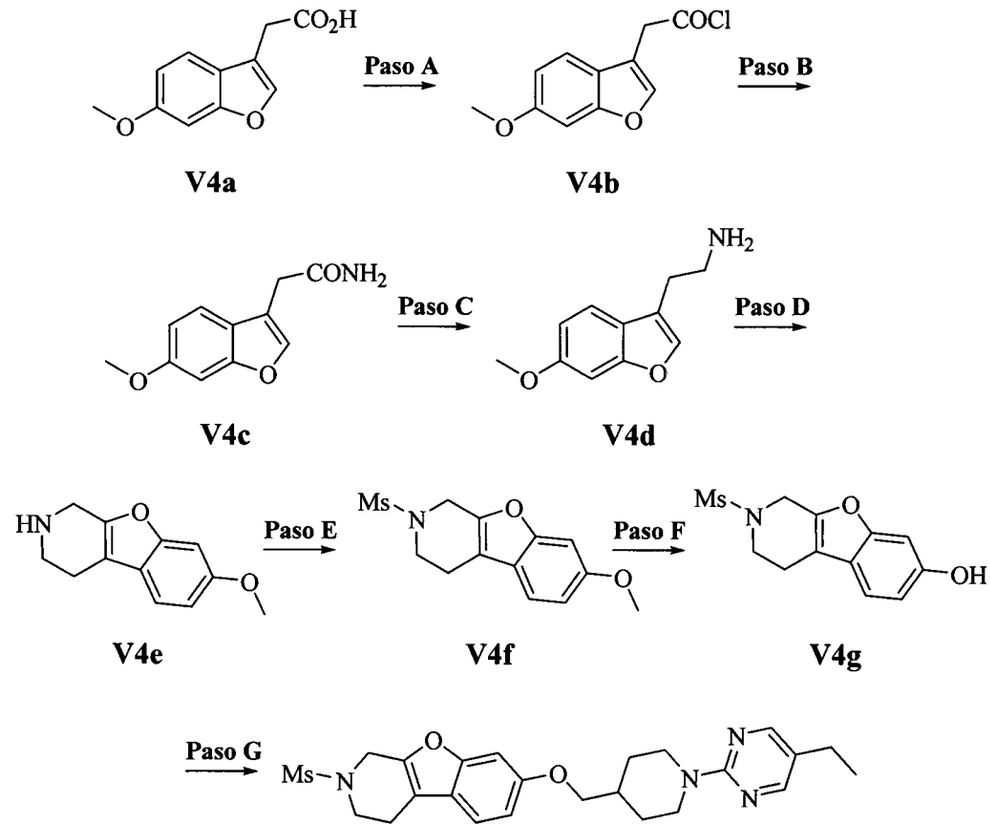
Paso F: Se trata una solución de **V1f** y **Q4b** (0,03 g, 0,1 mmol) en acetonitrilo seco (2 ml) con carbonato de cesio en polvo (0,1 g, 0,3 mmol) y se agita la mezcla a 75 °C por espacio de 24 horas. La filtración y HPLC de fase inversa dirigida a la masa da **V1**; ESIMS calc. para $C_{24}H_{32}N_5O_3S$ ($M+H^+$) 470,2, resultó 470,1.

Siguiendo un procedimiento similar al utilizado para la preparación de **V1** a partir de **V1f** excepto que se sustituye **Q4b** por el mesilato apropiado, se preparan los siguientes compuestos;

Ejemplo	Estructura	Datos analíticos
V2		^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 7,17 (d, *J* = 8,8 Hz, 1H), 7,03 (d, *J* = 2,3 Hz, 1H), 6,85 (dd, *J* = 2,3, 8,8 Hz, 1H), 6,24 (d, *J* = 0,7 Hz, 1H), 4,67 (s, 2H), 4,16 (br, 2H), 4,15 (t, *J* = 5,4 Hz, 2H), 3,84 (m, 4H), 2,87 (s, 3H), 2,76 (t, *J* = 12,2 Hz, 2H), 1,98 (m, 1H), 1,85 (t, *J* = 12,6 Hz, 2H), 1,47 (s, 9H), 1,28 (ddd, *J* = 4,7, 12,4, 12,4 Hz, 2H); ESIMS calc, para $C_{23}H_{34}N_3O_5S$ ($M+H^+$) 464,2, resultó 464,1.
V3		ESIMS calc, para $C_{23}H_{32}N_3O_5S$ ($M+H^+$) 462,2, resultó 462,2,

Ejemplo V4: 7–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metoxi)–2–(metilsulfonil)–1,2,3,4–tetrahidrobenzofuro[2,3–*c*]piridina.





Ejemplo V4

Paso A: Se trata una suspensión de **V4a** (3,99 g, 19,4 mmol) en diclorometano (50 ml) con cloruro de oxalilo (1,8 ml, 21,3 mmol) lentamente, con agitación, y luego se agrega dimetilformamida (0,01 ml). Se agita la mezcla así obtenida a temperatura ambiente por espacio de 1 hora, y luego se la concentra a sequedad para dar **V4b**; ^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 7,58 (t, *J* = 1,0 Hz, 1H), 7,37 (d, *J* = 8,6 Hz, 1H), 7,03 (d, *J* = 2,2 Hz, 1H), 6,92 (dd, *J* = 2,2, 8,6 Hz, 1H), 4,21 (d, *J* = 1,0 Hz, 2H), 3,84 (s, 3H).

Paso B: Se trata una solución de **V4b** (19,4 mmol) en diclorometano (100 ml) con amoniaco gaseoso mediante burbujeo lento a través de la solución en agitación, por espacio de 5 minutos. Se agita la suspensión así obtenida en un matraz cerrado durante 2 horas. Se filtra la suspensión obtenida, se lavan los sólidos colectados con más diclorometano y se los seca en aire para dar **V4c**; ^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 7,52 (t, *J* = 0,7 Hz, 1H), 7,43 (d, *J* = 8,6 Hz, 1H), 7,03 (d, *J* = 2,2 Hz, 1H), 6,92 (dd, *J* = 2,2, 8,6 Hz, 1H), 5,61 (s, 1H), 5,45 (s, 1H), 3,86 (s,

3H), 3,63 (d, J = 0,7 Hz, 2H); ESIMS calc, para $C_{11}H_{12}NO_3$ ($M+H^+$) 206,1, resultó 206,1,

Paso C: Se trata una solución de **V4c** (2,79 g, 13,6 mmol) en tetrahidrofurano seco (100 ml) con una solución de borano en tetrahidrofurano (1,0 N; 50 ml, 50 mmol) y se agita la solución así obtenida en un matraz cerrado de un día para otro. Se trata cuidadosamente la mezcla de reacción con metanol (50 ml) y se la concentra a sequedad. Se purifica el residuo por cromatografía en gel de sílice utilizando un gradiente lineal de acetato de etilo al 20 a 100% en hexanos para producir **V4d**; ^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 7,46 (s, 1H), 7,38 (d, J = 8,6 Hz, 1H), 7,02 (d, J = 2,2 Hz, 1H), 6,90 (dd, J = 2,2, 8,6 Hz, 1H), 3,85 (s, 3H), 3,63 (br, s, 2H), 3,14 (tt, J = 6,4, 6,8 Hz, 2H), 3,02 (t, J = 6,4 Hz, 2H); ESIMS calc, para $C_{11}H_{14}NO_2$ ($M+H^+$) 192,1, resultó 192,1.

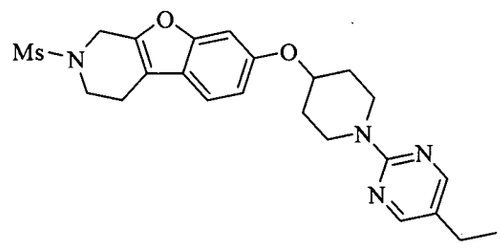
Paso D: **V4e** Se prepara la sal de ácido acético a partir de **V4d** de acuerdo con el procedimiento descripto en WO2000/020421, p. 15; ^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 7,30 (d, J = 8,5 Hz, 1H), 6,99 (d, J = 2,2 Hz, 1H), 6,86 (dd, J = 2,2, 8,5 Hz, 1H), 3,88 (br, s, 2H), 3,85 (s, 3H), 3,06 (t, J = 5,8 Hz, 2H), 2,85 (m, 2H), 2,72 (m, 1H); ESIMS calc, para $C_{12}H_{14}NO_2$ ($M+H^+$) 204,1, resultó 204,1.

Paso E: Se trata una solución de la sal de ácido acético de **V4e** (0,18 g, 0,7 mmol) en diclorometano (5 ml) con trietilamina (0,2 ml, 1,4 mmol) y anhídrido metansulfónico (0,15 g, 0,86 mmol) y se agita la mezcla a temperatura ambiente por espacio de 1 hora. El lavado con agua, secado sobre $MgSO_4$ y concentración **V4f**; ^{1}H NMR ($CDCl_3$, 400,13 MHz): δ 7,29 (d, J = 8,5 Hz, 1H), 6,98 (d, J = 2,2 Hz, 1H), 6,84 (dd, J = 2,2, 8,5 Hz, 1H), 3,84 (s, 3H), 2,77 (m, 2H), 2,73 (m, 2H), 2,54 (s, 3H); ESIMS calc, para $C_{13}H_{16}NO_4S$ ($M+H^+$) 282,1, resultó 282,0.

Paso F: Se trata una solución de **V4f** (0,15 g, 0,5 mmol) en diclorometano (5 ml) con tribromuro de boro puro (0,2 ml, 2,1 mmol) a temperatura ambiente. Se agita la solución así obtenida a temperatura ambiente por espacio de 30 minutos. –Se agrega la mezcla de reacción, con cuidado, a metanol (50 ml) se la trata con Na_2CO_3 sólido (0,4 g), se la filtra y concentra a sequedad para producir **V4g**; ESIMS calc. para $C_{12}H_{14}NO_4S$ ($M+H^+$) 268,1, resultó 268,1.

Paso G: Se trata una solución de **V4g** y **Q4b** (0,03 g, 0,1 mmol) en acetonitrilo seco (2 ml) con carbonato de cesio en polvo (0,08 g, 0,2 mmol) y se agita la mezcla a 75 °C por espacio de 24 horas. La filtración y purificación por HPLC dirigida a la masa da origen a **V4**; ESIMS calc. para $C_{24}H_{31}N_4O_4S$ ($M+H^+$) 471,2, resultó 471,2.

Ejemplo V5: 7–(1–(5–Etilpirimidin–2–il)piperidin–4–iloxi)–2–(metilsulfonil)–1,2,3,4–tetrahidrobenzofuro[2,3–c]piridina.



Siguiendo un procedimiento similar al utilizado para la preparación de **V4** a partir de **V4g** excepto que se sustituye **Q4b** por 1–(5–etilpirimidin–2–il)piperidin–4–il metansulfonato se prepara el **V5**; ESIMS calc. para $C_{23}H_{29}N_4O_4S$ ($M+H^+$) 457,2, resultó 457,1.

Ensayos Biológicos

Generación de una Línea Celular Estable

Se mantienen célula Flp–In–CHO (Invitrogen, Cat.# R758–07) en medio F12 de Ham sumplementado con suero fetal bovino al 10 %, mezcla de antibióticos al 1 % y L–glutamina 2 mM. Se transfectan las células con una mezcla de ADN que contiene GPR119 humano (hGPR119) o GPR119 de ratón in (mGPR119) en el vector pcDNA5/FRT (Invitrogen) y el vector pOG44 (Invitrogen) en una proporción de 1:9 utilizando Fugene6 (Roche), de acuerdo con las instrucciones del fabricante. Al cabo de 48 horas, se cambia el medio por un medio suplementado con 400 µg/ml de higromicina B para iniciar la selección de las células transfectadas de manera estable. Las líneas celulares así obtenidas son designadas CHO–hGPR119 y CHO–mGPR119 respectivamente.

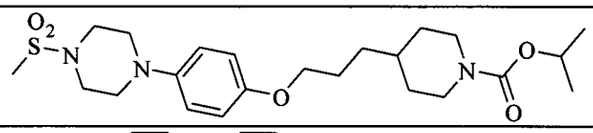
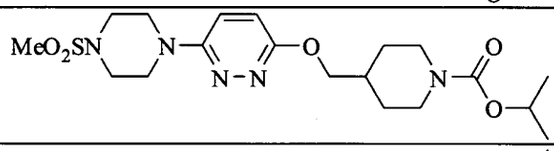
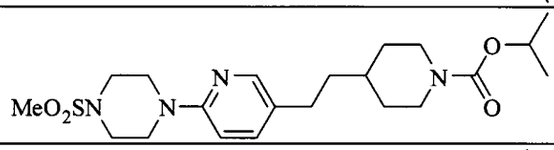
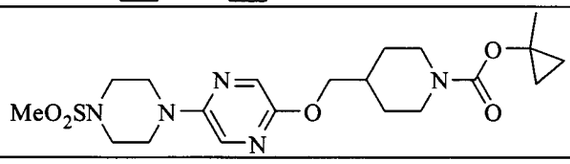
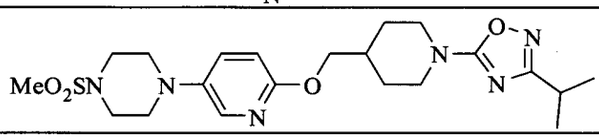
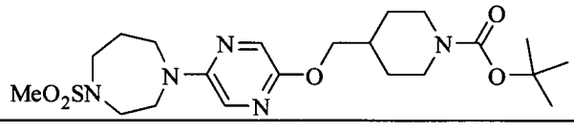
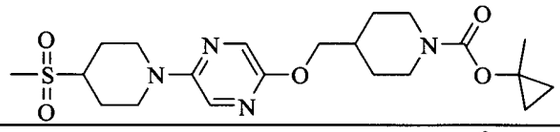
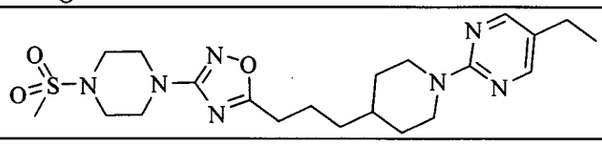
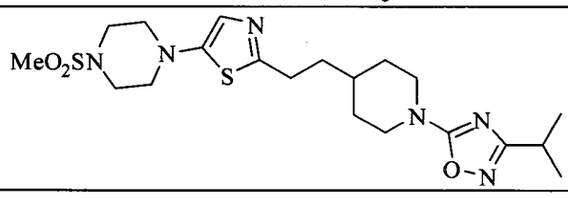
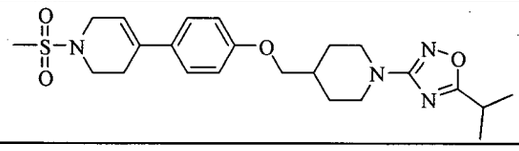
Ensayos de AMP Cíclico

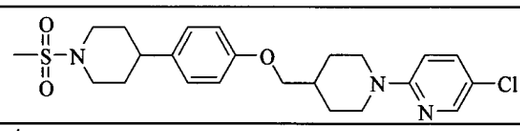
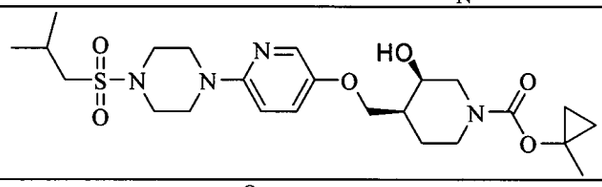
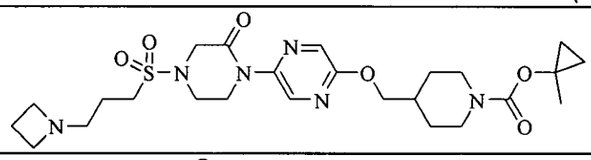
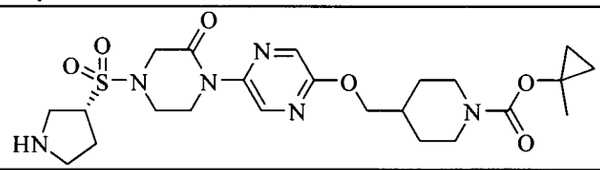
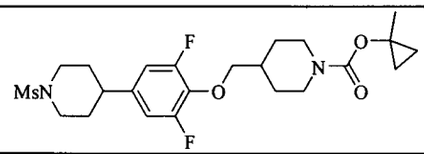
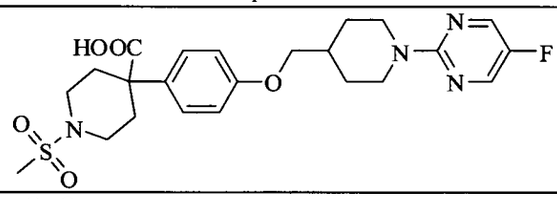
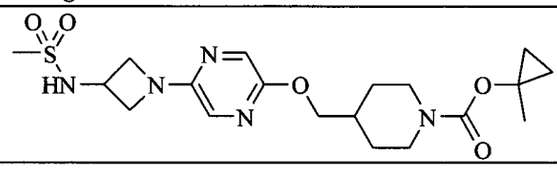
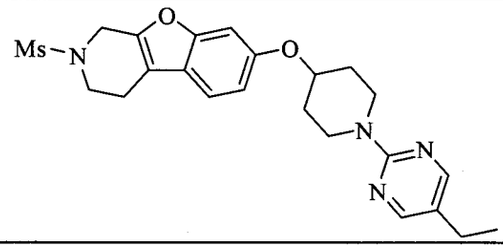
Con el propósito de evaluar la actividad de los compuestos de la presente invención sobre el GPR119 humano, se cosechas células CHO–hGPR119 y se las resuspende a razón de 300.000 células/ml en medio de ensayo (medio F12 de Ham más 3 % de suero fetal bovino privado de lípidos, 3–isobutil–1–metil–xanthine 1 mM (IBMX)). Se colocan las células (5 µl) en cada pocillo de una placa blanca de 1536 pocillos. Se introduce en cada pocillo un compuesto de la presente invención (50 nl) diluido en dimetilsulfóxido al 100 % (DMSO) y se incuban las placas a 37°C durante 30 minutos. A continuación se miden las concentraciones de cAMP utilizando el kit dinámico 2 de cAMP (Cisbio Bioassays) de acuerdo con las instrucciones del fabricante. Se agregan 2,5 µl de cAMP–XL665 diluido a cada pocillo, seguidos por 2,5 µl de anti–cAMP–Criptato diluido. Se tapa la placa y se la incuba por espacio de una hora a temperatura ambiente, luego se la lee en un lector de placas Envision (Perkin Elmer) empleando el método HTRF con excitación a 337 nm, y emisiones medidas a 620 nm y 655 nm.

Se mide la actividad de los compuestos de la presente invención sobre el GPR119 de ratón mediante un método similar en placas de 384 pocillos. Se cosechan las células CHO–mGPR119 y se las resuspende en medios de ensayo a razón de 500.000 células/ml. Se colocan 50 µl de células en cada pocillo de una placa blanca de 384 pocillos. Se introduce en cada pocillo un compuesto de la presente invención (500 nl) diluido en DMSO al 100 % y se incuban las placas a 37°C por espacio de 30 minutos. Se miden las concentraciones de cAMP de la manera antes expuesta, excepto que se agregan a cada pocillo 20 µl de cAMP–XL665 diluido seguido por 20 µl de anti–cAMP–Criptato diluido.

Los compuestos de la presente invención, en forma libre o en forma de sal aceptable para uso farmacéutico, produjeron un aumento dependiente de la concentración en el nivel de cAMP intracelular. Los compuestos de la presente invención exhiben una CE_{50} de entre $1x10^{-5}$ y $1x\ 10^{-10}$M, preferentemente menos de 500 mM, más preferentemente menos de 100 nM. La siguiente tabla enumera

una muestra no limitante de mediciones de CE_{50} correspondientes a los compuestos de la presente invención, donde +, ++ y +++ representan rangos de CE_{50} de >800nM, 200–800nM y <200nM, respectivamente:

Compuesto	Estructura	CE_{50}
A3		Actividad +
C2		+
D2		++
E3		+++
E9		++
G1		+
G4		+++
H3		+++
I1		+++
J7		+++

J22		+++
K3		+++
O9		+++
O41		+++
P13		+++
T1		++
U5		+++
V5		+++

Ensayo de GLUTag GLP–1

Se puede estudiar el efecto de los compuestos de la presente invención sobre la secreción de GLP–1 en células GLUTag (una línea celular enteroendocrina de ratón que secreta GLP–1). Se preparan células GLUTag en placas de 96 pocillos revestidos con poly–D–lysina el día uno en medio completo

(DMEM/ FBS al 10%). El día dos, se reemplaza el medio de cultivo con un medio con bajo contenido de glucosa (DMEM/ glucosa 5,5 mM /FBS al 10 %). El día tres, se lavan las células dos veces y se las preincuba en buffer de EBSS libre de glucosa (NaCl 100 mM, KCl 5 mM $MgSO_4 \cdot 7H_2O$, 0,8 mM, $NaH_2PO_4 \cdot 2H_2O$1,65 mM, $NaHCO_3$ 26 mM, $CaCl_2$ 1,6 mM, albúmina sérica bovina sin ácidos grasos al 0,1% f, pH 7,35) por espacio de dos horas a 37 °C con 5% de CO_2. Después de este período de pre–incubación, se lavan las células una vez más con buffer EBSS sin glucosa y luego se las estimula con un compuesto de la presente invención en diversas concentraciones en Buffer EBSS más glucosa 10 mM y un inhibidor de DPP–4 a 37 °C en presencia de CO_2 al 5%. Al final de la incubación, se recogen los sobrenadantes y se los transfiere a una línea celular HEK293 que sobreexpresa el receptor GLP–1 humano y una construcción reportera de CRE–luciferasa. La construcción CRE–luciferasa expresa el gen de luciferasa bajo el control de un elemento de respuesta a cAMP (CRE). El receptor GLP–1 estimulado por GLP–1 da lugar a la producción de cAMP, lo que a su vez regula en ascenso la expresión de luciferasa. Las células reporteras HEK293–GLP–1R son aplicadas la noche anterior en placas blancas de 384 pocillos. Después de la incubación con los sobrenadantes obtenidos de las células GLUTag tratadas con un compuesto de la presente invención, se incuban las células reporteras HEK293–GLP–1R a 37°C en presencia de CO_2 al 5 % por espacio de 18 horas. Se mide la luciferasa producida como resultado del tratamiento mediante la adición de reactivo Steady–Glo (Promega, Cat. # E2550). Se calculan los valores de CE_{50} por regresión no lineal utilizando Graphpad Prism.

Ensayo con insulina en HIT–T15

Se estudia el efecto del agonista de GPR119 sobre la secreción de insulina en células HIT–T15 (una células de células beta de hámster que secreta insulina). Se obtienen células HIT–T15 de la ATCC y se las cultiva en medio F2 de Hams de Kaighn más suero equino al 10 % y suero fetal bovino al 2,5 %. El día uno, se aplican las células HIT–T15 en placas de 96 pocillos por espacio de 24 horas y luego se reemplaza el medio con un medio con bajo contenido de glucosa (medio RPMI 1640 suplementado con suero equino al 10%, suero fetal bovino al 2,5 % y

D–(+)–glucosa) 3,0 mM . El día tres se lavaron las células dos veces y luego se las preincubó con buffer de bicarbonato de Krebs–Ringer libre de glucosa (KRBB) que contiene NaCl 119 mM, KCl 4,74 mM, $CaCl_2$ 2,54 mM, KH_2PO_4 1,19 mM, $MgCl_2$ 1,19 mM, $NaHCO_3$ 25 mM, HEPES 10 mM y seroalbúmina bovina libre de ácidos grasos al 0,1% a pH 7,4. Una hora más tarde se lavaron las células una vez más tres veces y se las incubó con un compuesto de la presente invención en KRBB más glucosa 16,5 mM por espacio de 3 horas a 37 °C. Al cabo de 5 minutos de centrifugación a 1.000 rpm, se retira el sobrenadante de cada pocillo y se lo transfiere a una placa separada para la medición de la insulina siguiendo las instrucciones del kit de ensayo de HTRF de Cisbio (Cisbio, Cat. # 62INSPEC). Se calculan los valores de CE_{50} con regresión no lineal empleando Graphpad Prism.

Análisis de GLP–1

Se utilizan ratones macho C57BL/6J de tipo salvaje (9 semanas de edad, JAX) como animales experimentales. En todos los experimentos, se alberga a los ratones en un recinto con ciclos de luz/oscuridad de 12 horas (luz a partir de las 5:00 de la mañana hasta las 17:00 hs) y se les da acceso a alimento (Purina 5001) y agua a voluntad. Se divide a los ratones, en forma aleatoria (8 por grupo) en grupos de tratamiento basándose en su peso corporal inicial. Se les administra, por vía oral, vehículo, inhibidor de DPP4 solo o inhibidor de DPP4 y un compuesto de la presente invención, en una sola dosis. Se administra un bolo de glucosa (2 g/kg) sesenta minutos después de la dosificación. Se extrae una muestra 2 minutos después del bolo de glucosa.

Se mide la GLP–1 plasmática activa en los ratones C57BL/6 después de una administración oral única de cantidades en aumento de un compuesto de la presente invención (3, 10 y 30 mg/kg). Se mantiene en ayuno a los animales por espacio de 16 horas antes de la administración del compuesto. Se administran dosis orales aproximadamente a las 10:00 horas en una suspensión de 75% de PEG300:25% de D5W. Se extrae sangre (por sangrado retroorbital) para medir los niveles plasmáticos de GLP–1 activa. Se extraen muestras de aproximadamente 200 µl de sangre para el análisis a los 62 minutos de la

dosificación (2 minutos después del bolo de glucosa). Todos los datos se expresan en términos de media ± SEM por cada grupo de ratones del experimento. Se realiza el análisis estadístico de los datos empleando un ANOVA de un solo factor con una Prueba de Comparación Múltiple Post de Bonferroni (GraphPad Prism 4,02).

El tratamiento de los ratones con dosis crecientes de un compuesto de la presente invención (en combinación con un inhibidor de la DPP4) da lugar a niveles crecientes de GLP–1 activa en plasma. La magnitud del aumento de GLP–1 observado en el grupo de 10 mg/kg demuestra que algunos compuestos de la presente invención puede aumentar los niveles circulantes de GLP–1 activa aproximadamente 2,2 veces con respecto al efecto sobre un inhibidor de la DPP4 solo.

Ensayo con OGTT

Se utilizan ratas macho Zucker fa/fa (11 semanas de edad, Charles River Labs) como animales experimentales. En todos los experimentos, se alberga a las ratas en un recinto con ciclos de luz/oscuridad de 12 horas (luz a partir de las 5:00 de la mañana hasta las 17:00 hs) y se les da acceso a alimento (Purina 5001) y agua a voluntad. Se divide a las ratas, en forma aleatoria (6 por grupo) en grupos de tratamiento basándose en su peso corporal inicial. Se les administra, por vía oral, vehículo (vía oral), inhibidor de DPP4 solo o un compuesto de la presente invención. Sesenta minutos después de la administración, se administra un bolo de glucosa de 3 g/kg.

Se disuelve un compuesto de la presente invención en vehículo para la dosificación (por vía oral utilizando una aguja de alimentación forzada) en una concentración final de 0,2, 2 o 6 mg/ml. Se administran dosis orales aproximadamente a las 7:30 horas en 75% de PEG300:25% de D5W.

Se llevan a cabo las evaluaciones en las ratas concientes de 11 semanas de edad. Se mantiene a las ratas en ayunas, retirándoles el alimento a las 18:00

hs del día anterior. Se extrae una muestra de sangre basal a t = cero minuto y a continuación se les administra a los animales un bolo de glucosa oral (3 g/kg) de inmediato. Se obtiene sangre (mediante sangrado del rabo) para medir la glucosa sanguínea (utilizando un glucómetro). Se mide una sola gota de sangre del rabo para determinar la glucosa utilizando un glucómetro a t = –60, 0, 10, 30, 60, 90, 120 y 180 minutos.

Se calcula el área bajo la curva (AUC) empleando una regla trapezoidal. Todos los datos se expresan en términos de media ± SEM por cada grupo de ratas del experimento. Se realiza el análisis estadístico de los datos empleando un ANOVA de un solo factor con una Prueba de Comparación Múltiple Post de Bonferroni (GraphPad Prism 4,02).

Algunos compuestos de la presente invención exhiben un claro efecto dependiente de la dosis sobre el clearance de glucosa mejorado a razón de 3, 10, y 30 mg/kg (una reducción de aproximadamente 31%, aproximadamente 48%, y aproximadamente 56% del ABC de glucosa, respectivamente), cuando se los administra en una formulación de 75% de PEG300 / 25% de D5W. Los resultados demuestran que algunos compuestos de la presente invención pueden reducir la glucosa sanguínea en respuesta al desafío con glucosa.

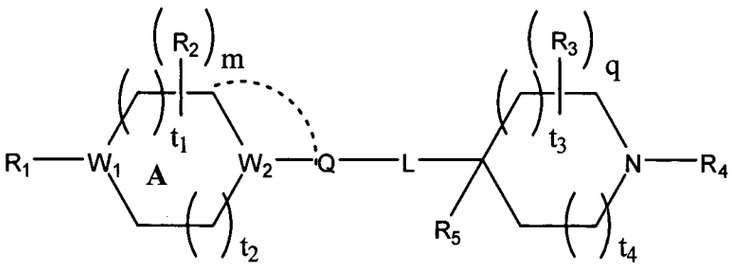
Se entiende que los ejemplos y realizaciones aquí descriptos tienen sólo fines ilustrativos y que las personas con capacitación normal en la técnica podrán idear diversas modificaciones o cambios a la luz de los mismos y que han de considerarse incluidos en el espíritu y alcance de la presente solicitud y el alcance de las reivindicaciones adjuntas. Todas las publicaciones, patentes y solicitudes de patente citadas en este documento se incorporan a la presente como referencia para todo fin.

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REIVINDICACIONES

Habiendo así especialmente descripto y determinado la naturaleza de la presente invención y la forma en que la misma ha de ser llevada a la práctica, se declara reivindicar como de propiedad y derecho exclusivo.

1. Un compuesto de la Fórmula I:



en la cual:

Q es un radical bivalente o trivalente seleccionado entre arilo C_{6-10}, heteroarilo C_{1-10}, cicloalquilo C_{3-8} y heterocicloalquilo C_{3-8}; donde dicho arilo, heteroarilo, cicloalquilo o heterocicloalquilo de Q está optativamente sustituido con hasta 3 radicales independientemente seleccionados entre halo, alquilo C_{1-6}, alquilo C_{1-6} sustituido con halo, alcoxi C_{1-6}, alcoxi C_{1-6} sustituido con halo, $-C(O)R_{20}$ y $-C(O)OR_{20}$; donde R_{20} es seleccionado entre hidrógeno y alquilo C_{1-6}; y que optativamente conecta a un carbono adyacente a W_2 a través de una CR_{31}, O, S o NR_{31} con un carbono de Q (indicado por la línea de puntos) para formar un anillo de 5 miembros fusionado a los anillos A y Q; donde R_{31} es seleccionado entre hidrógeno y alquilo C_{1-6};

W_1 y W_2 son independientemente seleccionados entre CR_{21} y N; donde R_{21} es seleccionado entre hidrógeno, ciano, alquilo C_{1-6} y $-C(O)OR_{25}$; donde R_{25} es seleccionado entre hidrógeno y alquilo C_{1-6}; el anillo A puede tener hasta 2 carbonos del anillo sustituidos con un grupo seleccionado entre $-C(O)-$, $-C(S)-$ y $-C(=NOR_{30})-$ y puede estar parcialmente insaturado con hasta 2 enlaces dobles, donde R_{30} es seleccionado entre hidrógeno y alquilo C_{1-6};

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L es seleccionado entre alquileno C_{1-6}, alquenileno C_{2-6}, $-(CH_2)_nO-$, $-OC(O)(CH_2)_n-$, $-C(O)O(CH_2)_n-$, $-NR_{26}(CH_2)_n-$ y $-O(CH_2)_n-$; donde R_{26} es seleccionado entre hidrógeno y alquilo C_{1-6} y n es seleccionado entre 0, 1, 2, 3, 4 y 5; donde cualquier alquilo de L puede estar optativamente sustituido con 1 a 3 radicales independientemente seleccionados entre halo, alquilo C_{1-6}, alquilo C_{1-6} sustituido con halo, alcoxi C_{1-6}, alcoxi C_{1-6} sustituido con halo, $-C(O)R_{22}$ y $-C(O)OR_{22}$; donde R_{22} es seleccionado entre hidrógeno y alquilo C_{1-6};

m es seleccionado entre 0, 1, 2, 3 y 4;

q es seleccionado entre 0, 1, 2, 3 y 4;

cada uno de t_1, t_2, t_3 y t_4 es independientemente seleccionado entre 0, 1 y 2;

R_1 es seleccionado entre $-X_1S(O)_{0-2}X_2R_{6a}$, $-X_1S(O)_{0-2}X_2OR_{6a}$, $-X_1S(O)_{0-2}X_2C(O)R_{6a}$, $-X_1S(O)_{0-2}X_2C(O)OR_{6a}$, $-X_1S(O)_{0-2}X_2OC(O)R_{6a}$ y $-X_1S(O)_{0-2}NR_{6a}R_{6b}$; donde X_1 es seleccionado entre un enlace, O, $NR_{7a}R_{7b}$ y alquileno C_{1-4}; X_2 es seleccionado entre un enlace y alquileno C_{1-4}; R_{6a} es seleccionado entre hidrógeno, halo, alquilo C_{1-6}, alquenilo C_{2-6}, arilo C_{6-10}, heteroarilo C_{1-10}, heterocicloalquilo C_{3-8} y cicloalquilo C_{3-8}; donde dichos arilo, heteroarilo, cicloalquilo y heterocicloalquilo de R_{6a} está optativamente sustituido con 1 a 3 radicales independientemente seleccionados entre hidroxi, halo, alquilo C_{1-6}, alquilo C_{1-6} sustituido con halo, alquilo C_{1-6} sustituido con hidroxi, alquilo C_{1-6} sustituido con ciano, alcoxi C_{1-6}, alcoxi C_{1-6} sustituido con halo y aril C_{6-10}–alcoxi C_{1-4}; R_{6b} es seleccionado entre hidrógeno y alquilo C_{1-6}; y R_{7a} y R_{7b} son independientemente seleccionados entre hidrógeno y alquilo C_{1-6};

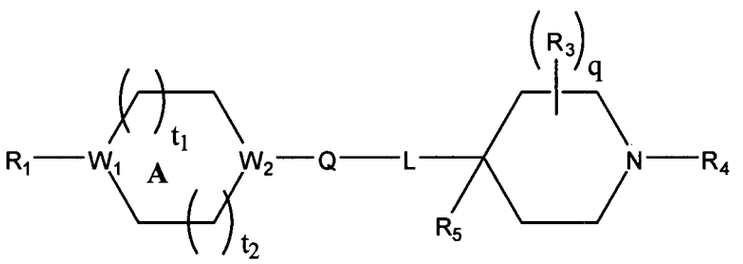
R_2 y R_3 son independientemente seleccionados entre hidrógeno, halo, hidroxi, alquilo C_{1-6}, alquilo C_{1-6} sustituido con halo, alquilo C_{1-6} sustituido con hidroxi, alcoxi C_{1-6}, alcoxi C_{1-6} sustituido con halo, $-C(O)R_{23}$, y $-C(O)OR_{23}$; donde R_{23} es seleccionado entre hidrógeno y alquilo C_{1-6};

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R_4 es seleccionado entre R_8 y $-C(O)OR_8$; donde R_8 es seleccionado entre alquilo C_{1-6}, arilo C_{6-10}, heteroarilo C_{1-10}, cicloalquilo C_{3-8} y heterocicloalquilo C_{3-8}; donde dicho arilo, heteroarilo, cicloalquilo o heterocicloalquilo de R_8 está optativamente sustituido con 1 a 3 radicales independientemente seleccionados entre halo, alquilo C_{1-6}, cicloalquilo C_{3-12}, heterocicloalquilo C_{3-8}, alquilo C_{1-6} sustituido con halo, alquilo C_{1-6} sustituido con hidroxi, alcoxi C_{1-6} y alcoxi C_{1-6} sustituido con halo;

R_5 es seleccionado entre hidrógeno, alquilo C_{1-6}, alquilo C_{1-6} sustituido con halo, alquilo C_{1-6} sustituido con hidroxi, alcoxi C_{1-6} y alcoxi C_{1-6} sustituido con halo, o las sales aceptables para uso farmacéutico del mismo.

2. El compuesto de acuerdo con la reivindicación 1 de la Formula Ia:



en la cual

Q es un radical bivalente o trivalente seleccionado entre arilo C_{6-10}, heteroarilo C_{1-10}, cicloalquilo C_{3-8} y heterocicloalquilo C_{3-8}; donde dicho arilo, heteroarilo, cicloalquilo o heterocicloalquilo de Q está optativamente sustituido con hasta 3 radicales independientemente seleccionados entre halo, alquilo C_{1-6}, alquilo C_{1-6} sustituido con halo, alcoxi C_{1-6}, alcoxi C_{1-6} sustituido con halo, $-C(O)R_{20}$ y $-C(O)OR_{20}$; donde R_{20} es seleccionado entre hidrógeno y alquilo C_{1-6}; y que optativamente conecta un carbono adyacente a W_2 a través de un CR_{31} u O con un carbono de Q para formar un anillo de 5 miembros fusionado a los anillos A y Q (tal como los anillos fusionados de los ejemplos V1–V5, expuestos más adelante); donde R_{31} es seleccionado entre hidrógeno y alquilo C_{1-6};

W_1 y W_2 son independientemente seleccionados entre CR_{21} y N, donde R_{21} es seleccionado entre hidrógeno, ciano, alquilo C_{1-6} y $-C(O)OR_{25}$; donde R_{25} es seleccionado entre hidrógeno y alquilo C_{1-6}; el anillo A puede tener hasta 2 carbonos del anillo sustituidos con un grupo seleccionado entre –C(O)–, –C(S)– y $-C(=NOR_{30})-$ y puede estar parcialmente insaturado con hasta 2 enlaces dobles, donde R_{30} es seleccionado entre hidrógeno y alquilo C_{1-6};

L es seleccionado entre alquileno C_{1-6}, alquenileno C_{2-6}, $-(CH_2)_nO-$, $-NR_{26}CH_2)_n-$, $-OC(O)(CH_2)_n-$, $-C(O)O(CH_2)_n-$ y $-O(CH_2)_n-$; donde R_{26} es seleccionado entre hidrógeno y alquilo C_{1-6}; donde n es seleccionado entre 0, 1, 2, 3, 4 y 5; donde cualquier alquilo de L puede estar optativamente sustituido con 1 a 3 radicales independientemente seleccionados entre halo, alquilo C_{1-6}, alquilo C_{1-6} sustituido con halo, alcoxi C_{1-6}, alcoxi C_{1-6} sustituido con halo, $-C(O)R_{22}$ y $-C(O)OR_{22}$; donde R_{22} es seleccionado entre hidrógeno y alquilo C_{1-6}; cada uno de t_1 y t_2 es independientemente seleccionado entre 0, 1 y 2;

q es seleccionado entre 0, 1, 2, 3 y 4;

R_1 es seleccionado entre $-X_1S(O)_{0-2}X_2R_{6a}$, $-X_1S(O)_{0-2}X_2OR_{6a}$, $-X_1S(O)_{0-2}X_2C(O)R_{6a}$, $-X_1S(O)_{0-2}X_2C(O)OR_{6a}$, $-X_1S(O)_{0-2}X_2OC(O)R_{6a}$ y $-X_1S(O)_{0-2}NR_{6a}R_{6b}$; donde X_1 es seleccionado entre un enlace, O, $NR_{7a}R_{7b}$ y alquileno C_{1-4}; X_2 es seleccionado entre un enlace y alquileno C_{1-4}; R_{6a} es seleccionado entre hidrógeno, halo, alquilo C_{1-6}, alquenilo C_{2-6}, arilo C_{6-10}, heteroarilo C_{1-10}, heterocicloalquilo C_{3-8} y cicloalquilo C_{3-8}; donde dichos arilo, heteroarilo, cicloalquilo y heterocicloalquilo de R_{6a} están optativamente sustituidos con 1 a 3 radicales independientemente seleccionados entre hidroxi, halo, alquilo C_{1-6}, alquilo C_{1-6} sustituido con halo, alquilo C_{1-6} sustituido con hidroxi, alquilo C_{1-6} sustituido con ciano, alcoxi C_{1-6}, alcoxi C_{1-6} sustituido con halo y aril–C_{6-10}alcoxi C_{1-4}; R_{6b} es seleccionado entre hidrógeno y alquilo C_{1-6}; y R_{7a} y R_{7b} son independientemente seleccionados entre hidrógeno y alquilo C_{1-6};

R_3 es seleccionado entre hidrógeno, halo, hidroxi, alquilo C_{1-6}, alquilo C_{1-6} sustituido con halo, alquilo C_{1-6} sustituido con hidroxi, alcoxi C_{1-6}, alcoxi C_{1-6} sustituido con halo, $-C(O)R_{23}$, y $-C(O)OR_{23}$; donde R_{23} es seleccionado entre hidrógeno y alquilo C_{1-6};

R_4 es seleccionado entre R_8 y $-C(O)OR_8$; donde R_8 es seleccionado entre alquilo C_{1-6}, arilo C_{6-10}, heteroarilo C_{1-10}, cicloalquilo C_{3-8} y heterocicloalquilo C_{3-8}; donde dichos arilo, heteroarilo, cicloalquilo o heterocicloalquilo de R_8 están optativamente sustituidos con 1 a 3 radicales independientemente seleccionados entre halo, alquilo C_{1-6}, cicloalquilo C_{3-12}, heterocicloalquilo C_{3-8}, alquilo C_{1-6} sustituido con halo, alquilo C_{1-6} sustituido con hidroxi, alcoxi C_{1-6}, y alcoxi C_{1-6} sustituido con halo;

R_5 es seleccionado entre hidrógeno, alquilo C_{1-6}, alquilo C_{1-6} sustituido con halo, alquilo C_{1-6} sustituido con hidroxi, alcoxi C_{1-6} y alcoxi C_{1-6} sustituido con halo.

3. El compuesto de acuerdo con la reivindicación 2 en el cual Q es un radical bivalente o trivalente seleccionado entre fenilo, piridinilo, pirazinilo, piridazinilo, pirimidinilo, 1,2,4–oxadiazolilo, y tiazolilo; donde dichos fenilo, piridinilo, pirazinilo, piridazinilo, pirimidinilo y tiazolilo de Q están optativamente sustituidos con hasta 3 radicales independientemente seleccionados entre halo, alquilo C_{1-6}, alcoxi C_{1-6}, alquilo C_{1-6} sustituido con halo, $-C(O)OR_{20}$ y $-C(O)R_{20}$; donde R_{20} es seleccionado entre hidrógeno y alquilo C_{1-6}; y que optativamente conectan un átomo de carbono adyacente a W_2 a través de un CR_{31} u O con un carbono de Q para formar un anillo de 5 miembros fusionado a los anillos A y Q; donde R_{31} es seleccionado entre hidrógeno y alquilo C_{1-6}.

4. El compuesto de acuerdo con la reivindicación 3 en el cual: W_1 y W_2 son independientemente seleccionados entre CR_{21} y N; donde R_{21} es

seleccionado entre hidrógeno, ciano, , alquilo C_{1-6} y $-C(O)OR_{25}$; donde R_{25} es seleccionado entre hidrógeno y alquilo C_{1-6}; el anillo A puede contener una sustitución de un carbono del anillo con un grupo seleccionado entre $-C(O)-$, $-C(S)-$ y $-C(=NOR_{30})-$ y puede estar parcialmente insaturado con un doble enlace; donde R_{30} es seleccionado entre hidrógeno y alquilo C_{1-6}; y L es seleccionado entre $-O(CH_2)_{0-4}-$, $-(CH=CH)-$, $-OC(O)-$, $-NH(CH_2)_{0-4}-$, $-NCH_3(CH_2)_{0-4}-$ y $-(CH_2)_{1-4}-$.

5. El compuesto de acuerdo con la reivindicación 4 en el cual: R_1 es seleccionado entre $-X_1S(O)_{0-2}X_2R_{6a}$, $-X_1S(O)_{0-2}X_2OR_{6a}$, $-X_1S(O)_{0-2}X_2C(O)OR_{6a}$, $-X_1S(O)_{0-2}X_2OC(O)R_{6a}$ y $-X_1S(O)_{0-2}NR_{6a}R_{6b}$; donde X_1 es seleccionado entre un enlace y O; X_2 es seleccionado entre un enlace y alquileno C_{1-4}; R_{6a} es seleccionado entre hidrógeno, halo, ciano, metilo, etilo, propilo, isopropilo, etenilo, piridinilo, pirrolidinilo, piperidinilo, morfolino, isoxazolilo, tetrazolilo, fenilo y imidazolilo; donde dichos piperidinilo, piridinilo, pirrolidinilo, morfolino, isoxazolilo, tetrazolilo, fenilo o imidazolilo de R_{6a} están optativamente sustituidos con 1 a 3 radicales independientemente seleccionados entre hidroxi, halo, alquilo C_{1-6} y benzoxi; y R_{6b} es seleccionado entre hidrógeno, metilo y etilo

6. El compuesto de acuerdo con la reivindicación 5 en el cual: R_4 es seleccionado entre R_8 y $-C(O)OR_8$; donde R_8 es seleccionado entre isopropilo, ciclopropilo, t–butilo, 1,2,4–oxadiazolilo, pirimidinilo, piridinilo, piridazinilo, tetrahidro–2H–piranilo, tetrahidrofuranilo, oxetanilo, 2H–tetrazolilo y tiazolilo; donde dicho ciclopropilo, 1,2,4–oxadiazolilo, pirimidinilo, piridinilo, piridazinilo, tetrahidro–2H–piranilo, tetrahidrofuranilo, oxetanilo, 2H–tetrazolilo o tiazolilo de R_8 está optativamente sustituido con 1 a 3 radicales

independientemente seleccionados entre halo, trifluorometilo, isopropilo, t–butilo, metilo, etilo y ciclopropilo optativamente sustituido con metilo; y R_5 es seleccionado entre hidrógeno y metoxi.

7. El compuesto de acuerdo con la reivindicación 1 seleccionado entre los siguientes: 1–Metilciclopropil 4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, isopropil 4–((4–((4–metansulfonilpiperazin)–1–il)fenoxi)metil)piperidin–1–carboxilato, isopropil 4–(2–(4–(4–(metilsulfonil)piperazin–1–il)fenoxi)etil)piperidin–1–carboxilato, isopropil 4–(3–(4–(4–(metilsulfonil)piperazin–1–il)fenoxi)propil)piperidin–1–carboxilato, isopropil 4–(4–(4–(4–(metilsulfonil)piperazin–1–il)fenoxi)butil)piperidin–1–carboxilato, Isopropil 4–((6–(4–(metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato, terc–Butil 4–((6–(4–(metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato, Isopropil 4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, terc–Butil 4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, 3–Ciclopropil–5–(4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–il)–1,2,4–oxadiazol, 5–Ciclopropil–3–(4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–il)–1,2,4–oxadiazol, 2–(4–(Metilsulfonil)piperazin–1–il)–5–((1–(5–(trifluorometil)piridin–2–il)piperidin–4–il)metoxi)pirazina, 5–Isopropil–3–(4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–il)–1,2,4–oxadiazol, Tetrahidro–2H–piran–4–il 4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, (S)–Tetrahidrofuran–3–il 4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, (R)–Tetrahidrofuran–3–il 4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, 2–Isopropil–5–(4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–

iloxi)metil)piperidin–1–il)tiazol, 2–((1–(2–metil–2H–tetrazol–5–il)piperidin–4–il)metoxi)–5–(4–(metilsulfonil)piperazin–1–il)pirazina, Oxetan–3–il 4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, Isopropil 4–((5–(4–(metilsulfonil)piperazin–1–il)piridin–2–iloxi)metil)piperidin–1–carboxilato, Isopropil 4–((6–(4–(metilsulfonil)piperazin–1–il)piridazin–3–iloxi)metil)piperidin–1–carboxilato, Isopropil 4–((5–(4–(metilsulfonil)piperazin–1–il)pirimidin–2–iloxi)metil)piperidin–1–carboxilato, (E)–isopropil 4–(2–(6–(4–(metilsulfonil)piperazin–1–il)piridin–3–il)vinil)piperidin–1–carboxilato, Isopropil 4–(2–(6–(4–(metilsulfonil)piperazin–1–il)piridin–3–il)etil)piperidin–1–carboxilato, (E)–Isopropil 4–(2–(2–(4–(metilsulfonil)piperazin–1–il)pirimidin–5–il)vinil)piperidin–1–carboxilato, 5–Etil–2–(4–((6–(4–(metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–il)pirimidina, 1–(Metilsulfonil)–4–(5–((1–(5–(trifluorometil)piridin–2–il)piperidin–4–il)metoxi)piridin–2–il)piperazina, 5–Etil–2–(4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–il)pirimidina, 2–((1–(5–Metilpiridin–2–il)piperidin–4–il)metoxi)–5–(4–(metilsulfonil)piperazin–1–il)pirazina, 1–Metilciclopropil 4–((5–(4–(metilsulfonil)piperazin–1–il)piridin–2–iloxi)metil)piperidin–1–carboxilato, 5–Etil–2–(4–((5–(4–(metilsulfonil)piperazin–1–il)piridin–2–iloxi)metil)piperidin–1–il)pirimidina, 3–Isopropil–5–(4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–il)–1,2,4–oxadiazol, 3–Isopropil–5–(4–((5–(4–(metilsulfonil)piperazin–1–il)piridin–2–iloxi)metil)piperidin–1–il)–1,2,4–oxadiazol, 1–Metilciclopropil 4–((6–(4–(metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato, 5–Isopropil–3–(4–((6–(4–(metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–il)–1,2,4–oxadiazol, 2–((1–(5–Fluoropiridin–2–il)piperidin–4–il)metoxi)–5–(4–(metilsulfonil)piperazin–1–il)pirazina, 3–Isopropil–5–(4–((6–(4–(metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–il)–1,2,4–oxadiazol, terc–Butil 4–((5–(4–(metilsulfonil)–

1,4–diazepan–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, terc–Butil 4–((5–(4–(metilsulfonil)–1,4–diazepan–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, terc–butil 4–((5–(4–(metilsulfonil)piperidin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, 1–Metilciclopropil 4–((5–(4–(metilsulfonil)piperidin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, terc–Butil 4–(2–(3–(4–(metilsulfonil)piperazin–1–il)–1,2,4–oxadiazol–5–il)etil)piperidin–1–carboxilato, terc–Butil 4–(3–(3–(4–(metilsulfonil)piperazin–1–il)–1,2,4–oxadiazol–5–il)propil)piperidin–1–carboxilato, 5–(3–(1–(5–etilpirimidin–2–il)piperidin–4–il)propil)–3–(4–(metilsulfonil)piperazin–1–il)–1,2,4–oxadiazol, Isopropil 4–(3–(3–(4–(metilsulfonil)piperazin–1–il)–1,2,4–oxadiazol–5–il)propil)piperidin–1–carboxilato, 3–Isopropil–5–(4–(2–(5–(4–(metilsulfonil)piperazin–1–il)tiazol–2–il)etil)piperidin–1–il)–1,2,4–oxadiazol, Isopropil 4–((4–(1–metansulfonil–1,2,3,6–tetrahidropiridin–4–il)fenoxi)metil)piperidin–1–carboxilato, isopropil 4–(4–(1–(metilsulfonil)–1,2,3,6–tetrahidropiridin–4–il)fenoxi)piperidin–1–carboxilato, isopropil 4–(2–(4–(1–(metilsulfonil)–1,2,3,6–tetrahidropiridin–4–il)fenoxi)etil)piperidin–1–carboxilato, isopropil 4–(3–(4–(1–(metilsulfonil)–1,2,3,6–tetrahidropiridin–4–il)fenoxi)propil)piperidin–1–carboxilato, isopropil 4–(4–(4–(1–(metilsulfonil)–1,2,3,6–tetrahidropiridin–4–il)fenoxi)butil)piperidin–1–carboxilato, 1–metilciclopropil 4–((4–(1–(metilsulfonil)–1,2,3,6–tetrahidropiridin–4–il)fenoxi)metil)piperidin–1–carboxilato, 5–isopropil–3–(4–((4–(1–(metilsulfonil)–1,2,3,6–tetrahidropiridin–4–il)fenoxi)metil)piperidin–1–il)–1,2,4–oxadiazol, Isopropil 4–((4–(1–metansulfonilpiperidin–4–il)fenoxi)metil)piperidin–1–carboxilato, isopropil 4–(4–(1–(metilsulfonil)piperidin–4–il)fenoxi)piperidin–1–carboxilato, isopropil 4–(2–(4–(1–(metilsulfonil)piperidin–4–il)fenoxi)etil)piperidin–1–carboxilato, isopropil 4–(3–(4–(1–(metilsulfonil)piperidin–4–il)fenoxi)propil)piperidin–1–carboxilato, isopropil 4–(4–(4–(1–

(metilsulfonil)piperidin–4–il)fenoxi)butil)piperidin–1–carboxilato, 1–Metilciclopropil 4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato, 2–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)–5–(trifluorometil)piridina, 5–isopropil–3–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)–1,2,4–oxadiazol, 3–cloro–2–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)–5–(trifluorometil)piridina, 5–cloro–2–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)piridina, 3–cloro–6–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)piridazina, 5–bromo–2–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)pirimidina, 5–etil–2–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)pirimidina, 5–fluoro–2–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)piridina, 3–isopropil–5–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)–1,2,4–oxadiazol, 3–terc–butil–6–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)piridazina, 5–fluoro–2–(4–((4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)pirimidina, Isopropil 4–(2–(3–(1–metansulfonil–1,2,3,6–tetrahidropiridin–4–il)fenoxi)etil)piperidin–1–carboxilato, 1–Metilciclopropil 4–metoxi–4–((5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, 1–metilciclopropil 4–((6–formil–5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, 1–Metilciclopropil 4–((6–cloro–5–(4–(metilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, 1–Metilciclopropil 4–((5–(4–(3–metoxi–3–oxopropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato, ácido 3–(4–(5–((1–((1–metilciclopropoxi)carbonil)–piperidin–4–il)metoxi)pirazin–2–il)piperazin–1–ilsulfonil)propanoico, ácido 3–(4–(5–((1–((1–metilciclopropoxi)carbonil)piperidin–4–il)metoxi)pirazin–2–il)piperazin–1–ilsulfonil)propanoico, ácido 3–(4–(5–((1–((1–metilciclopropoxi)carbonil)piperidin–

4–il)metoxi)pirazin–2–il)piperazin–1–ilsulfonil)propanoico, ácido 3–(4–(5–((1–((1–metilciclopropoxi)carbonil)piperidin–4–il)metoxi)pirazin–2–il)piperazin–1–ilsulfonil)propanoico, ácido 3–(4–(5–((1–((1–metilciclopropoxi)carbonil)piperidin–4–il)metoxi)pirazin–2–il)piperazin–1–ilsulfonil)propanoico, ácido 3–(4–(5–((1–((1–metilciclopropoxi)carbonil)piperidin–4–il)metoxi)pirazin–2–il)piperazin–1–ilsulfonil)propanoico; 1–metilciclopropil 4–((5–(4–(3–cianopropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(3–(1H–tetrazol–5–il)propilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(vinilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(2–(piperidin–1–il)etilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(2–morfolinoetilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(2–(dimetilamino)etilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; terc–butil 4–((5–(4–(3–cloropropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; terc–butil 4–((5–(4–(3–acetoxipropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(3–aminopropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(2–etoxietilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(3–(pirrolidin–1–il)propilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(3–(2–metil–1H–imidazol–1–il)propilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(3–(dimetilamino)propilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(propilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–

(etilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(isopropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(isobutilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(sec–butilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(3–acetoxi–2,2–dimetilpropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((5–(4–(3–hidroxi–2,2–dimetilpropilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–Metilciclopropil 4–((5–(4–(2–(piridin–3–il)etilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–Metilciclopropil 4–((5–(4–(2–(piridin–4–il)etilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–Metilciclopropil 4–((5–(4–sulfamoilpiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; terc–Butil 4–((5–(4–(morfolinosulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((6–(4–(etilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((6–(4–(etilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((6–(4–(etilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((6–(4–(etilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((6–(4–(etilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato; 1–Metilciclopropil 4–((5–fluoro–6–(4–(metilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato; terc–Butil 4–((5–(4–(metilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–Metilciclopropil 4–((5–(4–(metilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–Metilciclopropil 4–((5–(2–oxo–4–

(propilsulfonil)piperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–Metilciclopropil 4–((5–(4–(isopropilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–Metilciclopropil 4–((5–(4–(isopropilsulfonil)–2–oxopiperazin–1–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((6–(2–oxo–4–(propilsulfonil)piperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato; 1–metilciclopropil 4–((6–(4–(isopropilsulfonil)–2–oxopiperazin–1–il)piridin–3–iloxi)metil)piperidin–1–carboxilato; 1–(5–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metoxi)pirazin–2–il)–4–(metilsulfonil)piperazin–2–ona; 1–(5–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metoxi)piridin–2–il)–4–(metilsulfonil)piperazin–2–ona; terc–Butil 4–((2,6–difluoro–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; terc–butil 4–((2–metil–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; terc–butil 4–((3–metoxi–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; terc–butil 4–((2,6–dimetil–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; terc–butil 4–((2,5–dimetil–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; terc–butil 4–((2–(metoxicarbonil)–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; terc–butil 4–((2–cloro–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; terc–butil 4–((3–metil–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; terc–butil 4–((2,3–dimetil–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; terc–butil 4–((2–fluoro–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; terc–butil 4–((4–(1–(metilsulfonil)piperidin–4–il)–2–(trifluorometil)fenoxi)metil)piperidin–1–carboxilato; 2–(4–((2,6–Difluoro–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–il)–5–etilpirimidina; 1–Metilciclopropil 4–((2,6–difluoro–4–(1–(metilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; 3–(4–(4–((1–(5–

Etilpirimidin–2–il)piperidin–4–il)metoxi)–3,5–difluorofenil)piperidin–1–ilsulfonil)propil acetato; 1–Metilciclopropil 4–((4–(1–(3–acetoxipropilsulfonil)piperidin–4–il)–2,6–difluorofenoxi)metil)piperidin–1–carboxilato; 3–(4–(4–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metoxi)–3,5–difluorofenil)piperidin–1–ilsulfonil)propan–1–ol; 1–Metilciclopropil 4–((2,6–difluoro–4–(1–(3–hidroxipropilsulfonil)piperidin–4–il)fenoxi)metil)piperidin–1–carboxilato; Isopropil 4–((5–(1,2,3,6–tetrahidro–1–metansulfonilpiridin–4–il)pirazin–2–iloxi)metil)piperidin–1–carboxilato; 1–Metilciclopropil 4–((6–(1,2,3,6–tetrahidro–1–metansulfonilpiridin–4–il)piridin–3–iloxi)metil)piperidin–1–carboxilato; Isopropil 4–(2–(6–(1,2,3,6–tetrahidro–1–metansulfonilpiridin–4–il)piridin–3–iloxi)etil)piperidin–1–carboxilato; 2–(4–((5–(1,2,3,6–Tetrahidro–1–metansulfonilpiridin–4–il)pirazin–2–iloxi)metil)piperidin–1–il)–5–etilpirimidina; 2–(4–((6–(1,2,3,6–Tetrahidro–1–metansulfonil–piridin–4–il)piridin–3–iloxi)metil)piperidin–1–il)–5–etilpirimidina; 2–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metoxi)–5–(1–metansulfonilpiperidin–4–il)pirazina; 2–(4–((6–(1–Metansulfonilpiperidin–4–il)piridin–3–iloxi)metil)piperidin–1–il)–5–etilpirimidina; 3–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metoxi)–6–(1–metansulfonilpiperidin–4–il)piridazina, 2–(4–((5–(1–Metansulfonilpiperidin–4–il)piridin–2–iloxi)metil)piperidin–1–il)–5–etilpirimidina; 1–terc–Butil 4–(4–(1–(metilsulfonil)piperidin–4–il)fenil) piperazin–1,4–dicarboxilato; N–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metil)–4–(1–(metilsulfonil)piperidin–4–il)anilina; N–((1–(5–Etilpirimidin–2–il)piperidin–4–il)metil)–N–metil–4–(1–(metilsulfonil)piperidin–4–il)anilina; ácido 4–(4–((1–(5–fluoropirimidin–2–il)piperidin–4–il)metoxi)fenil)–1–(metilsulfonil)piperidin–4–carboxílico; ácido 2–[(2–{4–[5–({1–[(1–metilciclopropoxi)carbonil]piperidin–4–il}metoxi)pirazin–2–il]–3–oxopiperazin–1–sulfonil}etil)amino]acético; 1–metilciclopropil 4–{[(5–{4–[(2–carbamimidamidoetan)sulfonil]–2–oxopiperazin–1–il}pirazin–2–

il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(3–metil–3–nitrobutane)sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–(1–bencilpirrolidin–3–sulfonil)–2–oxopiperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(carbamoilmetan)sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(1–carbamoil–1–metiletan)sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(2–oxo–4–{[2–(pirrolidin–1–il)etan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[2–(morfolin–4–il)etan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[3–(dimetilamino)propan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[2–(1,3–dioxo–2,3–dihidro–1H–isoindol–2–il)etan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[(dimetilcarbamoil)metan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[1–(2–metilpropil)pirrolidin–3–sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(2–oxo–4–{[3–(1H–pirazol–1–il)propan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[2–oxo–4–(pirrolidin–3–sulfonil)piperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(2–amino–2–metilpropan)sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[(1–metilpirrolidin–3–il)metan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[2–(azetidin–1–il)etan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–

carboxilato; 1–metilciclopropil 4–({[5–(2–oxo–4–{[2–(1H–pirazol–1–il)etan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–(1–metilpirrolidin–3–sulfonil)–2–oxopiperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[1–(dimetilcarbamoil)–1–metiletan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[2–(3,3–difluoroazetidin–1–il)etan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[3–(dimetilamino)–3–metilbutan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(2–{[2–(terc–butoxi)–2–oxoetil]amino}etan)sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–(azetidin–3–sulfonil)–2–oxopiperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[3–(3,3–difluoroazetidin–1–il)propan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[3–(azetidin–1–il)propan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{2–oxo–4–[(3S)–pirrolidin–3–sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(3S)–1–metilpirrolidin–3–sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(3R)–1–metilpirrolidin–3–sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(3S)–pirrolidin–3–sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(3R)–pirrolidin–3–sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–(azetidin–3–sulfonil)piperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{2–oxo–4–[(pirrolidin–3–ilmetan)sulfonil]piperazin–1–

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il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–(1–hidroxi–2–metilpropan–2–sulfonil)piperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(2–hidroxietan)sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(azetidin–3–ilmetan)sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[(1–metilpirrolidin–2–il)metan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{2–oxo–4–[(3R)–pirrolidin–3–sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–(1–metilazetidin–3–sulfonil)piperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–(1–metilazetidin–3–sulfonil)–2–oxopiperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[(1–metilazetidin–3–il)metan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[(1–metilazetidin–3–il)metan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–({3–[(3S,4S)–3,4–dihidroxipirrolidin–1–il]propan}sulfonil)–2–oxopiperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–({2–[(3S,4S)–3,4–dihidroxipirrolidin–1–il]etan}sulfonil)–2–oxopiperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(azetidin–3–ilmetan)sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{2–oxo–4–[(pirrolidin–2–ilmetan)sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(3–aminopropan)sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(2–aminoetan)sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(3–metansulfonamidoazetidin–1–il)pirazin–

2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[2–(dimetilamino)etan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(2–oxo–4–{[3–(pirrolidin–1–il)propan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[3–(morfolin–4–il)propan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[(3–metiloxetan–3–il)metan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[3–(acetiloxi)propan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(3,3,3–trifluoropropan)sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[(2E)–2–(hidroxiimino)–4–metansulfonilpiperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(3–cloropropan)sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(3–hidroxipropan)sulfonil]–2–oxopiperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–({[1–(dimetilamino)ciclopropil]metan}sulfonil)–2–oxopiperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–({[1–(dimetilamino)ciclopropil]metan}sulfonil)piperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(3–hidroxi–3–metilbutane)sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{2–oxo–4–[(3R)–oxolan–3–sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{2–oxo–4–[(3S)–oxolan–3–sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[3–(acetiloxi)–3–metilbutan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–[({6–[4–({[1–(azetidin–1–

il)ciclopropil]metan}sulfonil)piperazin–1–il]piridin–3–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–({[1–(bencilamino)ciclopropil]metan}sulfonil)piperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–({[1–(azetidin–1–il)ciclopropil]metan}sulfonil)piperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[(1–hidroxiciclopropil)metan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[2–(1–hidroxiciclopropil)etan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–({2–[1–(acetiloxi)ciclopropil]etan}sulfonil)piperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–({[1–(benciloxi)ciclopropil]metan}sulfonil)piperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[(1–aminociclopropil)metan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[2–(1–hidroxiciclopropil)etan]sulfonil}–2–oxopiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–{2,6–difluoro–4–[3–(N–metilmetansulfonamido)azetidin–1–il]fenoximetil}piperidin–1–carboxilato; 1–metilciclopropil 4–[2,6–difluoro–4–(3–metansulfonamidoazetidin–1–il)fenoximetil]piperidin–1–carboxilato; 1–metilciclopropil 4–{2,6–difluoro–4–[3–(2–metilpropan–1–sulfonamido)azetidin–1–il]fenoximetil}piperidin–1–carboxilato; 1–metilciclopropil 4–{4–[3–(N,2–dimetilpropan–1–sulfonamido)azetidin–1–il]–2,6–difluorofenoximetil}piperidin–1–carboxilato; 5–etil–2–{4–[({2–metansulfonil–1H,2H,3H,4H–pirazino[1,2–a]indol–8–il}oxi)metil]piperidin–1–il}pirimidina; 11–{[1–(5–etilpirimidin–2–il)piperidin–4–il]oxi}–5–metansulfonil–8–oxa–5–azatriciclo[7.4,0,0{2,7}]trideca–1(13),2(7),9,11–tetraeno; 11–{[1–(5–etilpirimidin–2–il)piperidin–4–il]metoxi}–5–metansulfonil–8–

oxa–5–azatriciclo[7.4,0,0{2,7}]trideca–1(13),2(7),9,11–tetraeno; terc–butil 4–[({2–metansulfonil–1H,2H,3H,4H–pirazino[1,2–a]indol–8–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–[({2–metansulfonil–1H,2H,3H,4H–pirazino[1,2–a]indol–8–il}oxi)metil]piperidin–1–carboxilato; propan–2–il 4–{3–[3–(1–metansulfonilpiperidin–4–il)fenoxi]propil}piperidin–1–carboxilato; propan–2–il 4–{2–[3–(1–metansulfonilpiperidin–4–il)fenoxi]etil}piperidin–1–carboxilato; propan–2–il 4–[3–(1–metansulfonilpiperidin–4–il)fenoximetil]piperidin–1–carboxilato; propan–2–il 4–{3–[3–(1–metansulfonil–1,2,3,6–tetrahidropiridin–4–il)fenoxi]propil}piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–metansulfonil–2–sulfanilidenepiperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil (3S,4S)–3–hidroxi–4–{[(6–{4–[(2–metilpropan)sulfonil]piperazin–1–il}piridin–3–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil (3R,4S)–3–hidroxi–4–{[(6–{4–[(2–metilpropan)sulfonil]piperazin–1–il}piridin–3–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–hidroxi–4–{[(6–{4–[(2–metilpropan)sulfonil]piperazin–1–il}piridin–3–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(6–{4–[(2–hidroxi–2–metilpropan)sulfonil]piperazin–1–il}piridin–3–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil (3S,4R)–3–metoxi–4–{[(6–{4–[(2–metilpropan)sulfonil]piperazin–1–il}piridin–3–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[3–(3,3–difluoroazetidin–1–il)propan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[3–(azetidin–1–il)propan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–{[(5–{4–[(3–metoxipropan)sulfonil]piperazin–1–il}pirazin–2–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–{[(6–{4–[(3–cloropropan)sulfonil]–2–oxopiperazin–1–il}piridin–3–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[2–(azetidin–1–il)etan]sulfonil}piperazin–1–il)pirazin–2–

il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–({[6–(4–{[3–(azetidin–1–il)propan]sulfonil}piperazin–1–il)piridin–3–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–[({5–[4–(pirrolidin–3–sulfonil)piperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato; 1–metilciclopropil 4–({[5–(4–{[2–(3,3–difluoroazetidin–1–il)etan]sulfonil}piperazin–1–il)pirazin–2–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–{[(6–{4–[(3–hidroxipropan)sulfonil]–2–oxopiperazin–1–il}piridin–3–il)oxi]metil}piperidin–1–carboxilato; 1–metilciclopropil 4–({[6–(4–{[3–(azetidin–1–il)propan]sulfonil}–2–oxopiperazin–1–il)piridin–3–il]oxi}metil)piperidin–1–carboxilato; 1–metilciclopropil 4–[2,6–difluoro–4–(4–metansulfonil–2–oxopiperazin–1–il)fenoximetil]piperidin–1–carboxilato y 1–metilciclopropil 4–[({5–[4–(oxetan–3–sulfonil)–2–oxopiperazin–1–il]pirazin–2–il}oxi)metil]piperidin–1–carboxilato.

8. Una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de un compuesto de acuerdo con la reivindicación 1 en combinación con un excipiente aceptable para uso farmacéutico.

9. Un método para modular la actividad de GPR119, que comprende administrar a un sistema o un sujeto que lo necesita una cantidad terapéuticamente efectiva del compuesto de acuerdo con la reivindicación 1 o sales aceptables para uso farmacéutico o composiciones farmacéuticas del mismo, para modular así dicha actividad de GPR119.

10. El método de acuerdo con la reivindicación 9, en el cual el compuesto de acuerdo con la reivindicación 1 tiene contacto directo con GPR119.

11. El método de acuerdo con la reivindicación 10, en el cual el contacto se produce in vitro o in vivo.

12. Un método para el tratamiento de una enfermedad o trastorno en el cual la modulación de la actividad de GPR119 puede prevenir, inhibir o mejorar la patología y/o sintomatología de la enfermedad o trastorno, que comprende administrar a un sistema o un sujeto que lo necesita una cantidad terapéuticamente efectiva del compuesto de acuerdo con la reivindicación 1 o sales aceptables para uso farmacéutico o composiciones farmacéuticas del mismo.

13. El método de acuerdo con la reivindicación 12, en el cual dicha enfermedad o trastorno es seleccionado entre obesidad, diabetes tipo 1, diabetes mellitus tipo 2, hiperlipidemia, diabetes idiopática tipo 1, diabetes autoinmune latente en adultos, diabetes tipo 2 de inicio temprano, diabetes atípica de inicio en la juventud, diabetes del joven de inicio en la madurez, diabetes relacionada con la desnutrición y diabetes gestacional.

14. El método de acuerdo con la reivindicación 12, dicha enfermedad o trastorno es seleccionado entre enfermedad cardiaca coronaria, accidente cerebrovascular isquémico, restenosis posterior a la angioplastia, enfermedad vascular periférica, claudicación intermitente, infarto de miocardio, dislipidemia, lipemia postprandial trastornos de tolerancia a la glucosa alterada, trastornos de glucosa plasmática en ayunas alterada, acidosis metabólica, cetosis, artritis, osteoporosis, hipertensión, insuficiencia cardiaca congestiva, hipertrofia del ventrículo izquierdo, enfermedad arterial periférica, retinopatía diabética, degeneración macular, cataratas, nefropatía diabética,

glomerulosclerosis, insuficiencia renal crónica, neuropatía diabética, síndrome metabólico, síndrome X, síndrome premenstrual, enfermedad cardiaca coronaria, angina pectoris, trombosis, aterosclerosis, infarto de miocardio, ataques isquémicos transitorios, accidente cerebrovascular, restenosis vascular, hiperglucemia, hiperinsulinemia, hiperlipidemia, hipertrigliceridemia, resistencia a la insulina, metabolismo de la glucosa alterado, trastornos de tolerancia a la glucosa alterada, trastornos de glucosa plasmática alterada, obesidad, disfunción eréctil, trastornos de la piel y los tejidos conectivos, ulceraciones del pie y colitis ulcerativa, disfunción endotelial y flexibilidad vascular deteriorada.

p. de: IRM LLC.

RESUMEN DE LA DESCRIPCIÓN

La invención da a conocer compuestos, composiciones farmacéuticas que comprenden dichos compuestos y métodos para usar dichos compuestos para el tratamiento o prevención de enfermedades o trastornos asociados con la actividad de GPR119.

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PATENT COOPERATION TREATY

GNF Legal Department
RECEIVED
DEC 15 2008
BY:

From the INTERNATIONAL SEARCHING AUTHORITY

To:

GENOMICS INSTITUTE OF THE NOVARTIS RESEARCH FOUNDATION
Attn. Reid, Scott
10675 John Jay Hopkins Drive
San Diego, CA 92121
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 15/12/2008
Applicant's or agent's file reference P1299PC20	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US2008/075145	International filing date *(day/month/year)* 03/09/2008
Applicant IRM LLC	

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority	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	Chantal Gottar

Form PCT/ISA/220 (October 2005) *(See notes on accompanying sheet)*

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

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NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1–10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1*bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43*bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

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PATENT COOPERATION TREATY

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GNF Legal Department
RECEIVED
DEC 15 2008
BY: _____

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
P1299PC20		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2008/075145	03/09/2008	20/09/2007
Applicant		
IRM LLC		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/075145

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/10 C07D401/14 C07D413/06 C07D413/14 C07D417/14
C07D487/04 C07D491/048 A61K31/44 A61K31/496 A61K31/4965
A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/003964 A (PROSIDION LTD [GB]; BARBA OSCAR [GB]; BRADLEY STUART EDWARD [GB]; FYFE) 11 January 2007 (2007-01-11) page 1, line 1 - page 2, line 2 page 21 - page 55; examples 1-4,11,42-89 claim 1	1-14
A	WO 2007/003960 A (PROSIDION LTD [GB]; BRADLEY STUART EDWARD [GB]; DAWSON GRAHAM JOHN [GB) 11 January 2007 (2007-01-11) page 1, line 1 - page 2, line 4 page 34 - page 66; examples 1-238 claim 1	1-14

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 December 2008	15/12/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bissmire, Stewart

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/075145

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/061489 A (PROSIDION LTD [GB]; FYFE MATTHEW [GB]; GARDNER LISA [GB]; KING-UNDERWO) 7 July 2005 (2005-07-07) page 1, line 1 - page 2, line 10 page 31 - page 149; examples 1-149 claim 1	1-14
A	WO 2007/003962 A (PROSIDION LTD [GB]; BRADLEY STUART EDWARD [GB]; FYFE MATTHEW COLIN THO) 11 January 2007 (2007-01-11) page 1, line 1 - page 2, line 4 page 18 - page 76; examples 1-265 claim 1	1-14

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/075145

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007003964 A	11-01-2007	AU 2006264651 A1	11-01-2007
		CA 2613236 A1	11-01-2007
		EP 1909791 A1	16-04-2008
		KR 20080025190 A	19-03-2008
		NO 20080052 B	23-01-2008
WO 2007003960 A	11-01-2007	EP 1907383 A1	09-04-2008
WO 2005061489 A	07-07-2005	AU 2004303604 A1	07-07-2005
		BR PI0418149 A	17-04-2007
		CA 2549955 A1	07-07-2005
		CN 1898235 A	17-01-2007
		EP 1711491 A1	18-10-2006
		JP 2007517010 T	28-06-2007
		KR 20060127011 A	11-12-2006
WO 2007003962 A	11-01-2007	AU 2006264649 A1	11-01-2007
		CA 2613235 A1	11-01-2007
		EP 1910290 A2	16-04-2008
		KR 20080027908 A	28-03-2008
		NO 20080010 B	30-01-2008

505

PATENT COOPERATION TREATY

GNF Legal Department
RECEIVED

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT DEC 15 2008
BY: _____

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2008/075145	03.09.2008	20.09.2007

International Patent Classification (IPC) or both national classification and IPC
INV. C07D401/10 C07D401/14 C07D413/06 C07D413/14 C07D417/14 C07D487/04 C07D491/048 A61K31/44 A61K31/496 A61K31/4965 A61P3/10

Applicant
IRM LLC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ 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 Rule 43*bis*.1(a)(i) 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

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Bissmire, Stewart Telephone No. +49 89 2399-2830

Form PCT/ISA/237 (Cover Sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2008/075145

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2008/075145

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

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. 1-2

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 1-2

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2008/075145

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	3-14
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations

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

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/US2008/075145

Re Item III.

The present claim 1-2 relates to an extremely large number of possible compounds. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the compounds claimed, see pages 46-206 examples A1-V5. The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of claim 1-2 (PCT Guidelines 9.19 and 9.23).

The search of claim 1-2 was restricted to those claimed compounds which appear to be supported and a generalisation of their structural formulae i.e the subject-matter of claim 3.

Re Item V.

1. Claims 9-14 relate to subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv)/67.1(iv) PCT. Patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for in a first or further medical treatment.

2. Reference is made to the following documents:

   D1: WO 2007/003964 A (PROSIDION LTD [GB]; BARBA OSCAR [GB]; BRADLEY STUART EDWARD [GB]; FYFE) 11 January 2007 (2007-01-11)
   D2: WO 2007/003960 A (PROSIDION LTD [GB]; BRADLEY STUART EDWARD [GB]; DAWSON GRAHAM JOHN [GB) 11 January 2007 (2007-01-11)
   D3: WO 2005/061489 A (PROSIDION LTD [GB]; FYFE MATTHEW [GB]; GARDNER LISA [GB]; KING-UNDERWO) 7 July 2005 (2005-07-07)
   D4: WO 2007/003962 A (PROSIDION LTD [GB]; BRADLEY STUART EDWARD [GB]; FYFE MATTHEW COLIN THO) 11 January 2007 (2007-01-11)

3. The current application discloses piperidine derivatives and their use as modulators

of GPR119 modulators for the treatment of diabetes and obesity. The compounds of the current application differ from those of D1 (claim 1 and examples 1-4, 11 and 42-89) as the position of ring Z and the saturated ring system have been reversed (Z in claim 1 of D1 is equivalent to Q in the current application). They differ from those of D2 and D3 (claims and examples) both these rings are aromatic. The compounds of D4 only contain 1 further ring system linked to the piperidine moiety. The subject-matter of claims 3-14 is therefore novel over D1-D4 in the sense of Art. 33(2) PCT.

4. The current application discloses piperidine derivatives and their use as modulators of GPR119 modulators for the treatment of diabetes and obesity. Document D1 is considered the most relevant state of the art and discloses piperidine derivatives with the same activity. The problem to be solved by the current application is therefore considered to be the provision of further piperidine derivatives with the same activity. the compounds of the current application differ from those of D1 (claim 1 and examples 1-4, 11 and 42-89) as the position of ring Z and the saturated ring system have been reversed (Z in claim 1 of D1 is equivalent to Q in the current application). Neither D1 nor any of the other documents cited suggest that such an alteration is possible starting from D1. D2-D4 all teach that the terminal cyclic system must be aromatic. The results of biological test provided (table, pages 207-209) demonstrates that the compounds of the current application provide a solution to the above mentioned technical problem. It is therefor possible to acknowledge an inventive step in the sense of Art. 33(3) PCT.

Re Item VIII.

1. Claims 9-12 are defined in functional terms that are not considered to be clear in the sense of Art. 6 PCT. The therapeutic application is defined by means of a mechanism of action which does not allow for a practical application in the treatment of a specific pathological condition (disease).

2. Many embodiments of the invention (pages 84-88, examples J1-J9; pages 142-173, examples O1-O63) do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT. As these specific embodiments are also claimed individually in claim 7 (dependent on

claim 1), an inconsistency between claims 1 and 7 also arises.

3. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D4 is not mentioned in the description, nor are these documents identified therein.

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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-035482- -00000-0000
Fecha: 2010-03-25 17:18:39 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 511

PATENTE DE INVENCIÓN ☐ **MODELO DE UTILIDAD** ☐ **Art 33 Decisión 486/00**

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☑ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

- ☑ Indicación que se solicita una PCT
- ☑ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☑ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

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Industria y Comercio
SUPERINTENDENCIA

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
IRM LLC

REFERENCIA	Radicación No.	10 35482
	Solicitud internacional	PCT/US2008/075145
	Fecha inicio fase nacional	20/04/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	10 05272

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, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

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
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 23 ABR. 2010
adpa11

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Industria y Comercio
SUPERINTENDENCIA

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
IRM LLC

REFERENCIA	Radicación No.	10 35482
	Solicitud internacional	PCT/US2008/075145
	Fecha inicio fase nacional	20/04/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	15 U 5213

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de diez reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del titulo primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 23 ABR. 2010
adpa11