SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 14-133538- -00000-0000

Fecha: 2014-06-19 15:56:30 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 10

Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD
PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** _____

54. **TÍTULO** ARIL DIHIDROPIRIDINONA Y PIPERIDINONA COMO INHIBIDORES DE MONOACILGLICEROL ACILTRANSFERASA (MGAT2)

51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** BRISTOL MYERS SQUIBB

DOMICILIO PRINCENTON, ESTADOS UNIDOS.

74. **APODERADO** ALVARO CORREA.

22. **BOGOTÁ, D.C.,** 19 JUNIO DE 2014.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

adicación

No. 14-133538- -00000-0000

Fecha: 2014-06-19 15:56:30 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 10

DIRECCIÓN DE NUEVAS CREACIONES
SOLICITUD FASE NACIONAL -PCT

1	TIPO DE SOLICITUD	☒ Patente de invención ☒ Capítulo I	☐ Patente de Modelo de Utilidad ☐ Capitulo II

2 DATOS SOLICITUD INTERNACIONAL PCT (86)

Solicitud Internacional No.	PCT/US2012/067173	Fecha	30/11/2012
Publicación Internacional No.	WO/2013/082345	Fecha	06/06/2013

3 TÍTULO DE LA INVENCIÓN (200 caracteres o espacios máximos)

ARIL DIHIDROPIRIDINONA Y PIPERIDINONA COMO INHIBIDORES DE MONOACILGLICEROL ACILTRANSFERASA (MGAT2)

4 CLASIFICACIÓN INTERNACIONAL (CIP)

C07D 211/86 (2006.01), A61K 31/4418 (2006.01), A61K 31/4427 (2006.01), A61P 3/00 (2006.01), C07D 211/90 (2006.01), C07D 401/04 (2006.01), C07D 401/10 (2006.01), C07D 401/12 (2006.01), C07D 401/14 (2006.01), C07D 407/14 (2006.01), C07D 413/04 (2006.01), C07D 413/12 (2006.01), C07D 417/04 (2006.01), C07D 417/14 (2006.01), C07F 9/40 (2006.01)

5 SOLICITANTE (S) ☐ Esta persona también es inventor. Para datos adicionales utilizar hoja de información complementaria

	APELLIDOS O RAZÓN SOCIAL	NOMBRE	IDENTIFICACIÓN	TIPO
1.	BRISTOL-MYERS SQUIBB COMPANY			

6 DATOS DEL SOLICITANTE

DIRECCIÓN	P.O. Box 4000 Route 206 and ProvinceLine Road Princeton, New Jersey 08543-4000	No. TELÉFONO	6341500
CIUDAD	Princeton	CORREO ELECTRÓNICO	Alvaro.correa@bakermckenzie.com
DEPARTAMENTO/ESTADO	New Jersey	NACIONALIDAD O LUGAR DE CONSTITUCIÓN	Estados Unidos de América
PAÍS DE RESIDENCIA	Estados Unidos de América		

7 INVENTOR (ES) Para datos adicionales utilizar hoja de información complementaria

APELLIDOS	NOMBRES	NACIONALIDAD
1. TURDI	Huji	Estados Unidos de América
2. HANGELAND	Jon J.	Estados Unidos de América
3. LAWRENCE R.	Michael	Estados Unidos de América
4. CHENG	Dong	Estados Unidos de América
5. AHMAD	Saleem	Estados Unidos de América

DIRECCIÓN DE CORREO ELECTRÓNICO:

8 DATOS INVENTOR (ES)

PAÍS RESIDENCIA	DEPARTAMENTO/ESTADO	CIUDAD	DIRECCIÓN
1. Estados Unidos de América	New Jersey	Pennington	Bristol-Myers Squibb Company 311 Pennington-Rocky Hill Road Pennington, New Jersey 08534
2. Estados Unidos de América	New Jersey	Pennington	Bristol-Myers Squibb Company 311 Pennington-Rocky Hill Road Pennington, New Jersey 08534
3. Estados Unidos de América	New Jersey	Pennington	Bristol-Myers Squibb Company 311 Pennington-Rocky Hill Road Pennington, New Jersey 08534
4. Estados Unidos de América	New Jersey	Pennington	Bristol-Myers Squibb Company 311 Pennington-Rocky Hill Road Pennington, New Jersey 08534

5. Estados Unidos de América	New Jersey	Pennington	Bristol-Myers Squibb Company Route 206 & Province Line Road Princeton, New Jersey 08543

OTRO(S) SOLICITANTE(S) Y/O (OTRO(S)) INVENTOR(ES)

☒ Los demás solicitantes y/o (demás) inventores se indican en una hoja a continuación.

9 ☐ **REPRESENTANTE LEGAL** ☒ **APODERADO**

APELLIDOS	NOMBRES	IDENTIFICACIÓN
Correa	Alvaro	C.C . 79.143.366 T.P . 20.281

DIRECCIÓN	Av. 82 No. 10-62 Piso 5	No. TELÉFONO	6341500
CIUDAD	Bogotá	CORREO ELECTRÓNICO	Alvaro.correa@bakermckenzie.com
PAÍS	Colombia	No. RADICACIÓN DE PROTOCOLO DE PODER GENERAL	

10 DECLARACIONES DE PRIORIDAD ☒ SI ☐ NO

(33) PAÍS DE ORIGEN	CÓDIGO PAÍS	(31) NÚMERO	(32) FECHA (AAAA/MM/DD)
1. Estados Unidos de América	US	61/566,039	02/12/2011
2. Estados Unidos de América	US	13/688,584	29/11/2012

11 DECLARACIÓN SOBRE USO DE RECURSOS GENÉTICOS O BIOLÓGICOS

Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de recursos genéticos o biológicos de los que cualquiera de los países miembros de la Comunidad Andina es país de origen.

☐ SI ☒ NO

Nota: En caso afirmativo deberá anexar copia del contrato de acceso de recursos genéticos o productos derivados, o certificado o número de registro, expedido por la Autoridad competente.

12 DECLARACIÓN SOBRE USO DE CONOCIMIENTOS TRADICIONALES

Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de conocimientos tradicionales de comunidades indígenas, afroamericanas o locales de países miembros de la Comunidad Andina.

☐ SI ☒ NO

Nota: En caso afirmativo deberá anexar la licencia o autorización de uso de conocimiento tradicional, o certificado, o número de registro expedido por la Autoridad competente.

13 REDUCCIÓN DE TASAS

Declaro que carezco de medios económicos para presentar la solicitud de patente.

☐ SI ☒ NO

Nota: En caso de ser persona natural y carecer de medios económicos, y por lo tanto, aplique la reducción de tasas a que se refiere la resolución vigente en tarifas, debe firmar la presente solicitud bajo la gravedad de juramento.

Micro, pequeñas y medianas empresas ☐

Universidades públicas o privadas ☐

Entidades sin ánimo de lucro ☐

Debe aportar los documentos que se indican en el numeral 17 de anexos

14 AUTORIZACIÓN DE NOTIFICACIÓN EN LÍNEA ☒ SI ☐ NO

Manifiesto que he leído y entendido perfectamente los términos y condiciones de uso de medios electrónicos para las notificaciones en línea a través de Internet de los actos administrativos proferidos por la Superintendencia de Industria y Comercio que deben ser notificados personalmente y, en consecuencia, autorizo el servicio de notificación a través de internet.

15	**COMPROBANTE DE PAGO O PAGO ELECTRÓNICO**	**N°** 14-0059264	**Fecha** 04/06/2014

16 FIRMA DEL SOLICITANTE, DEL APODERADO O DEL REPRESENTANTE LEGAL

Junto a cada firma, indicar el nombre del firmante y su calidad (si tal calidad no es obvia al leer el petitorio)

17 ANEXOS

Documentación Técnica
Solicitud Internacional en castellano

1. ☒ Descripción N° de folios:
2. ☒ Reivindicaciones N° Reivindicaciones: 15
3. ☐ Dibujos y/o figuras N° folios:

Documentación Jurídica

9. ☒ Poderes, si fuera el caso.
10. ☒ Documento que legalmente pruebe la cesión del inventor al solicitante o a su causante.
11. ☐ Copia del contrato de acceso de recursos genéticos o productos derivados, certificado o número de registro, si fuera el caso.

4. ☒ Resumen.
5. ☐ Certificado de depósito de material biológico si fuera el caso.
6. ☐ Listado de secuencias de nucleótidos y/o aminoácidos en forma digital si fuera el caso.
7. ☐ Arte final 12 x 12.
8. ☒ Anexo formato digital.

12. ☐ Copia de la licencia o autorización de Conocimientos Tradicionales, certificado o número de registro, si fuera el caso.
13. **Reducción de tasas**

Micro, pequeñas o medinas empresas

☐ Copia simple de la declaración de renta del año inmediatamente anterior, o en su defecto prueba documental idónea.

☐ Documento de constancia de cumplimiento con lo establecido en la ley 905 de 2004.

Universidades públicas o privadas

☐ Copia acto de reconocimiento institucional emitido por el Ministerio de Educación

Entidades sin ánimo de lucro

☐ Copia de registro vigente en Cámara de comercio.
☐ Hoja de información complementaria.
☐ Otros, especificar

14. ☒ Comprobante de pago de la tasa de presentación de la solicitud.
15. ☐ Comprobante de pago por reivindicación de prioridad.
16. ☐ Comprobante de pago de la tasa por concepto de excedente de palabras en la publicación.
17. ☐ Comprobante de pago por reivindicación adicional a 10.

Industria y Comercio
SUPERINTENDENCIA

HOJA DE INFORMACIÓN COMPLEMENTARIA PCT

1	(12) TIPO DE SOLICITUD	NUMERO DE RADICACIÓN
☐ Patente de invención ☐ Patente de Modelo de Utilidad		FECHA DE PRESENTACIÓN

4	(71) SOLICITANTE (S)			
	APELLIDOS O RAZÓN SOCIAL	NOMBRE	IDENTIFICACIÓN	TIPO
	2. 3. 4.			

5	DATOS DEL SOLICITANTE			
	PAÍS DE RESIDENCIA	DEPARTAMENTO/ESTADO	CIUDAD	DIRECCIÓN
	2. 3. 4.			
	TELÉFONO	FAX	E-MAIL	NACIONALIDAD
	2. 3. 4.			

6	(72) INVENTOR (ES)		
	APELLIDOS	NOMBRE	NACIONALIDAD
	6. MENG	Wei	Estados Unidos de América
	7. BRIGANCE	Robert Paul	Estados Unidos de América
	8. DEVASTHALE	Pratik	Estados Unidos de América
	9. ZHAO	Guohua	Estados Unidos de América

7	DATOS INVENTOR (ES)			
	DIRECCIÓN	CIUDAD	DEPARTAMENTO/ESTADO	PAÍS RESIDENCIA
	6. Bristol-Myers Squibb Company` 311 Pennington-Rocky Hill Road Pennington, New Jersey 08534	Pennington	New Jersey	Estados Unidos de América
	7. Bristol-Myers Squibb Company 311 Pennington-Rocky Hill Road Pennington, New Jersey 08534	Pennington	New Jersey	Estados Unidos de América
	8. Bristol-Myers Squibb Company 311 Pennington-Rocky Hill Road Pennington, New Jersey 08534	Pennington	New Jersey	Estados Unidos de América
	9. Bristol-Myers Squibb Company 311 Pennington-Rocky Hill Road Pennington, New Jersey 08534	Pennington	New Jersey	Estados Unidos de América

9	(30) DECLARACIONES DE PRIORIDAD

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 14 - 0059264

Bogotá D.C., Junio 04 de 2014 - 12:56:08

RECIBIDO DE : BAKER NI 900.532.339

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	596597481	04/06/2014	105.078.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	515.000.00	515.000.00
				$515.000.00

SON: **QUINIENTOSQUINCE MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-******-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 14-133538- -00000-0000

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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 10

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad

(31) *No.*	32) *Fecha*	(33) *País*
61/566,039	02/12/2011	US
13/688,584	29/11/2012	US

(51) Int Cl:

(71)Solicitante(s) **BRISTOL-MYERS SQUIBB COMPANY**

(72) Inventor(es) **TURDI, Huji;**
HANGELAND, Jon J.;
LAWRENCE, R. Michael;
CHENG, Dong;
AHMAD, Saleem;
MENG, Wei;
BRIGANCE, Robert Paul;
DEVASTHALE, Pratik;
ZHAO, Guohua

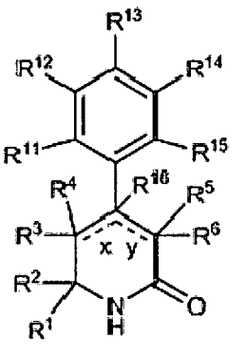
(74) Apoderado: **ALVARO CORREA ORDOÑEZ**

(85) Fecha limite inicio fase nacional: ***02/07/2014***
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: ***30/11/2012***
No. de solicitud **PCT/US2012/067173**

(87) Publicación internacional
Fecha: **06/06/2013**
N° publicación: ***WO/2013/082345***

(54) Titulo: **ARIL DIHIDROPIRIDINONA Y PIPERIDINONA COMO INHIBIDORES DE MONOACILGLICEROL ACILTRANSFERASA (MGAT2)**

Resumen:
La presente invención provee compuestos de la Fórmula (I):



(I)

o un estereoisómero o una sal de aquel aceptable desde el punto de vista farmacéutico, en donde todas las variables son como se definen en la presente. Estos compuestos son inhibidores de monoacilglicerol aciltransferasa tipo 2 (MGAT2) que se pueden usar como medicamentos.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION ___ PCT X MODELO DE UTILIDAD ___ DISEÑO INDUSTRIAL ___

(21) N° de solicitud: (22) Fecha de solicitud:
(51) Clasificación Internacional :

(71)Solicitante(s)
BRISTOL-MYERS SQUIBB COMPANY

(72) Inventor(es)
TURDI, Huji; HANGELAND, Jon J.; LAWRENCE, R. Michael; CHENG, Dong; AHMAD, Saleem; MENG, Wei; BRIGANCE, Robert Paul; DEVASTHALE, Pratik; ZHAO, Guohua

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad	(31) *No. Prioridad*	32) *Fecha*	(33) *País*
	61/566,039	**02/12/2011**	**US**
	13/688,584	**29/11/2012**	**US**

(85) Fecha inicio fase nacional: ***02/07/2014***
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: ***30/11/2012***
No. de solicitud **PCT/US2012/067173**

(87) Publicación internacional
Fecha: **06/06/2013**
N° publicación: ***WO/2013/082345***

(54) Titulo:
ARIL DIHIDROPIRIDINONA Y PIPERIDINONA COMO INHIBIDORES DE MONOACILGLICEROL ACILTRANSFERASA (MGAT2)

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO TEMATICO

PATENTE DE INVENCION ____ PCT X MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ___

(21) N° de solicitud: (22) Fecha de solicitud:
(51) Clasificación Internacional :

(71)Solicitante(s)
BRISTOL-MYERS SQUIBB COMPANY

(72) Inventor(es)
TURDI, Huji; HANGELAND, Jon J.; LAWRENCE, R. Michael; CHENG, Dong; AHMAD, Saleem; MENG, Wei; BRIGANCE, Robert Paul; DEVASTHALE, Pratik; ZHAO, Guohua

(74) Apoderado: ALVARO CORREA ORDOÑEZ

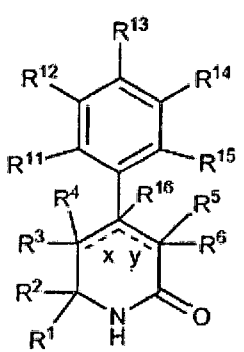
(30) Prioridad	(31) *No. Prioridad*	32) *Fecha*	(33) *País*
	61/566,039	**02/12/2011**	**US**
	13/688,584	**29/11/2012**	**US**

(85) Fecha límite inicio fase nacional: ***02/07/2014***
) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud: ***30/11/2012***
No. de solicitud **PCT/US2012/067173**

(87) Publicación internacional:
Fecha: **06/06/2013**
No. Publicación : ***WO/2013/082345***

(54) Titulo:
ARIL DIHIDROPIRIDINONA Y PIPERIDINONA COMO INHIBIDORES DE MONOACILGLICEROL ACILTRANSFERASA (MGAT2)

(57) Resumen:
La presente invención provee compuestos de la Fórmula (I):



(I)

o un estereoisómero o una sal de aquel aceptable desde el punto de vista farmacéutico, en donde todas las variables son como se definen en la presente. Estos compuestos son inhibidores de monoacilglicerol aciltransferasa tipo 2 (MGAT2) que se pueden usar como medicamentos.

9

Industria y Comercio
SUPERINTENDENCIA

PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

Dependencia: 2020	Fecha: ____/____/____ AAAA MM DD	Recorrido:
Tipo de Radicación: Entrada: ☐ Salida: ☐ Traslado: ☐ Convenio: ☐		
Radicador:		Planilla:

ID	No. Radicación	Consecutivo	Item
1	14-133538	0	7
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			

Item	Unidad de Conservación
1	Bolsa
2	Caja
3	Libro
4	Sobre
5	Tomo
6	Otro
Item	*Soporte Documental*
7	CD
8	Disquete
9	DVD
10	Folleto
11	Foto
12	Periódico
13	Plano
14	Publicación Periódica
15	USB
16	Otro

Observaciones:
El CD Anexo contiene un total de 7 Archivos 7 en formato pdf, los cuales fueron procesados. Folio 9

Graciela

10

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 14-133538- -00000-0000

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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 10

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 ☐

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 June 2013 (06.06.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/082345 A1

(51) International Patent Classification:
C07D 211/86 (2006.01) *C07D 413/12* (2006.01)
C07D 211/90 (2006.01) *C07D 417/04* (2006.01)
C07D 401/04 (2006.01) *C07D 417/14* (2006.01)
C07D 401/10 (2006.01) *C07F 9/40* (2006.01)
C07D 401/12 (2006.01) *A61K 31/4418* (2006.01)
C07D 401/14 (2006.01) *A61K 31/4427* (2006.01)
C07D 407/14 (2006.01) *A61P 3/00* (2006.01)
C07D 413/04 (2006.01)

(21) International Application Number:
PCT/US2012/067173

(22) International Filing Date:
30 November 2012 (30.11.2012)

(25) Filing Language: English

(26) Publication Language: English

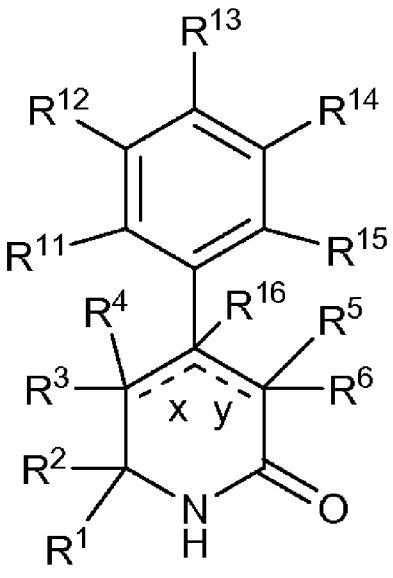
(30) Priority Data:
61/566,039 2 December 2011 (02.12.2011) US
13/688,584 29 November 2012 (29.11.2012) US

(71) Applicant: **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; P.O. Box 4000, Route 206 and ProvinceLine Road, Princeton, New Jersey 08543-4000 (US).

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(54) Title: ARYL DIHYDROPYRIDINONE AND PIPERIDINONE AS MGAT2 INHIBITORS



(I)

(57) Abstract: The present invention provides compounds of Formula (I), or a stereoisomer, or a pharmaceutically acceptable salt thereof, wherein all of the variables are as defined herein. These compounds are monoacylglycerol acyltransferase type 2 (MGAT2) inhibitors which may be used as medicaments.

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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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ARYL DIHYDROPYRIDINONES AND PIPERIDINONES AS MGAT2 INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the priority benefit of U.S. Provisional Application No. 61/566,039 filed December 2, 2011 and the priority benefit of U.S. Non-Provisional Application No. 13/688,584 filed November 29, 2012, both of which are incorporated fully herein by reference.

FIELD OF THE INVENTION

[0002] The present invention provides novel aryl dihydropyridinone and piperidinone compounds, and their analogues thereof, which are MGAT2 inhibitors, compositions containing them, and methods of using them, for example, for the treatment or prophylaxis of diabetes, obesity, dyslipidemia and related conditions.

BACKGROUND OF THE INVENTION

[0003] The prevalence of obesity and diabetes is increasing at an alarming rate. According to WHO, in 2008, 70% of the U.S. adult population was overweight, and among them 33% were obese. Parallel to the explosive number of people becoming overweight and obese, in 2008, it was estimated that 12.3% of the U.S. population had elevated blood glucose [http://www.who.int/diabetes/facts/en/]. The obesity/diabetes epidemic is not unique to the U.S. According to WHO (Fact Sheet No. 312, September 2012), 347 million people worldwide have diabetes. Treating obesity and improving glycemic control effectively and safely remain major challenges for modern medicine.

[0004] Monoacylglycerol acyltransferase 2 (MGAT2) has emerged as an attractive target for the treatment of obesity and type II diabetes [Yen, C.L. et al., *Nat. Med.*, 15(4):442-446 (2009)]. MGAT2 is highly and selectively expressed in the small intestine where it exerts a pivotal role in the monoacylglycerol-pathway for the absorption of dietary fat. When dietary fat is ingested, pancreatic lipase digests triglycerides into free fatty acids and 2-monoacylglycerol, which are absorbed by intestinal epithelial enterocytes. Once inside enterocytes, free fatty acids and 2-monoacylglycerol are used as building blocks to resynthesize triglycerides by two sequential acylation steps; first by MGAT and then by DGAT enzyme reactions. Triglycerides are then incorporated into

chylomicrons and secreted into lymph to be utilized as an energy supply for the body. MGAT2 knockout mice exhibit a healthy metabolic phenotype and show resistance to high-fat diet induced obesity, improvement in insulin sensitivity and decreased fat accumulation in liver and adipose tissue. In addition, genetic deletion of MGAT2 produces mice with increased levels of GLP1 [Yen, C.L. et al., *Nat. Med.*, 15(4):442-446 (2009)]. Taken together, these data show that MGAT2 inhibitors hold promise to treat metabolic disorders such as obesity, type II diabetes and dyslipidemia.

SUMMARY OF THE INVENTION

[0005] The present invention provides aryl dihydropyridinone and piperidinone compounds, and their analogues thereof, which are useful as MGAT2 inhibitors, including stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof.

[0006] The present invention also provides processes and intermediates for making the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof.

[0007] The present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof.

[0008] The compounds of the invention may be used in the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2, such as diabetes, obesity, dyslipidemia and related conditions, such as microvascular and macrovascular complications associated with diabetes, cardiovascular diseases, Metabolic Syndrome and its component conditions, disorders of glucose and lipid metabolism and other maladies.

[0009] The compounds of the invention may be used in therapy.

[0010] The compounds of the invention may be used for the manufacture of a medicament for the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2.

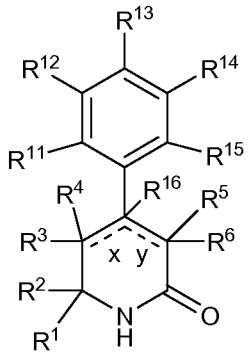
[0011] The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more other agent(s).

[0012] Other features and advantages of the invention will be apparent from the following detailed description and claims.

DETAILED DESCRIPTION OF THE INVENTION

I. COMPOUNDS OF THE INVENTION

[0013] In a first aspect, the present invention provides, *inter alia*, a compound of Formula (I):



(I)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, wherein:

$\overline{---}$ designates a single or double bond;

x and y can be both a single bond; when x is a double bond, then y is a single bond and R^4 and R^{16} are absent; when y is a double bond, then x is a single bond and R^5 and R^{16} are absent;

R^1 is independently selected from the group consisting of: -CONH(C_{4-18} alkyl), -CONHC_{2-8} haloalkyl, -CONH$(CH_2)_{1-8}$Ph, -CONHCH_2COC_{2-8} alkyl, -$(CH_2)_m$-(C_{3-10} carbocycle substituted with 0-2 R^b and 0-2 R^g), -$(CH_2)_m$-(5- to 6-membered heteroaryl comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O and S; wherein said heteroaryl is substituted with 0-1 R^b and 0-2 R^g), and a C_{1-12} hydrocarbon chain substituted with 0-3 R^a; wherein said hydrocarbon chain may be straight or branched, saturated or unsaturated;

R^2 is independently selected from the group consisting of: C_{1-4} alkyl, C_{3-4} cycloalkyl, and C_{1-4} haloalkyl;

R^3 is independently selected from the group consisting of: H, F, Cl, C_{1-4} alkyl and CN;

R^4 and R^5 are independently selected from the group consisting of: H, F, Cl, and C_{1-4} alkyl;

when x is a single bond, R^3 and R^4 may be combined with the carbon atom to which they are attached to form a 3- to 6-membered carbocycle;

R^6 is independently selected from the group consisting of: H, halo, C_{1-4} alkyl, CN, NO_2, R^c, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$, NH_2, $-CONH(C_{1-6}$ alkyl), $-NHCOX_1SO_2R^j$, $-NHCOCH_2PO(OEt)_2$, $-NHCOCOR^j$, $-NHCOCH(OH)R^j$, $-NHCOCH_2COR^j$, $-NHCONHR^j$, and $-OCONR^fR^j$;

X is independently selected from the group consisting of: O, S, NH, CONH, and NHCO;

X_1 is independently C_{1-4} hydrocarbon chain optionally substituted with C_{1-4} alkyl or C_{3-4} cycloalkyl;

when y is a single bond, R^5 and R^6 may be combined with the carbon atom to which they are attached to form a 3- to 6-membered carbocycle;

R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are independently selected from the group consisting of: H, halo, C_{1-4} alkyl substituted with 0-2 R^i, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, $-(CH_2)_m-C_{3-6}$ cycloalkyl, CN, NR^fR^j, OR^j, SR^j, $NHCO_2(C_{1-4}$ alkyl), $NHSO_2(C_{1-4}$ alkyl), and a 4- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S;

alternatively, R^{11} and R^{12}, together with the carbon atoms to which they are attached, combine to form a 5 to 6-membered carbocyclic ring or a 5 to 6-membered heterocyclic ring comprising: carbon atoms and 1-3 heteroatoms selected from N, NR^e, O, and S;

alternatively, R^{12} and R^{13}, together with the carbon atoms to which they are attached, combine to form a 5 to 6-membered carbocyclic ring or a 5 to 6-membered heterocyclic ring comprising: carbon atoms and 1-3 heteroatoms selected from N, NR^e, O, and S;

R^{16} is independently selected from the group consisting of: H and C_{1-4} alkyl;

R^a is, at each occurrence, independently selected from the group consisting of: halo, OH, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $N(C_{1-4}$ alkyl$)_2$, $-(CH_2)_n-(X)_t-(CH_2)_m R^c$, and $-(CH_2)_n-(CH_2O)_m-(CH_2)_n R^f$;

R^b is, at each occurrence, independently selected from the group consisting of: halo, OH, C_{1-10} alkyl, C_{1-10} alkoxy, C_{1-10} haloalkyl, C_{1-10} haloalkoxy, C_{1-10} alkylthio, C_{1-10} haloalkyltho, $N(C_{1-4}$ alkyl$)_2$, $-CONH(CH_2)_{4-20}H$, $-O(CH_2)_sO(C_{1-6}$ alkyl), R^c, $-(CH_2)_n-(X)_t-(CH_2)_m R^c$, and $-(CH_2)_n-(CH_2O)_m-(CH_2)_n R^f$;

R^c is, at each occurrence, independently selected from the group consisting of: C_{3-6} cycloalkyl substituted with 0-2 R^d, C_{3-6} cycloalkenyl substituted with 0-2 R^d, $-(CH_2)_m$-(phenyl substituted with 0-3 R^d), and a 5- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S; wherein said heterocycle is substituted with 0-2 R^d;

R^d is, at each occurrence, independently selected from the group consisting of: halo, OH, CN, NO_2, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, tetrazolyl, OBn and phenyl substituted with 0-2 R^h;

R^e is, at each occurrence, independently selected from the group consisting of: H, C_{1-8} alkyl, C_{1-8} haloalkyl, benzyl optionally substituted with C_{1-4} alkoxy, $CO(C_{1-4}$ alkyl) and COBn;

R^f is, at each occurrence, independently selected from the group consisting of: H and C_{1-4} alkyl;

R^g, R^h and R^i are, at each occurrence, independently selected from the group consisting of: halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

R^j is, at each occurrence, independently selected from the group consisting of: C_{1-4} alkyl, C_{3-4} cycloalkyl and phenyl;

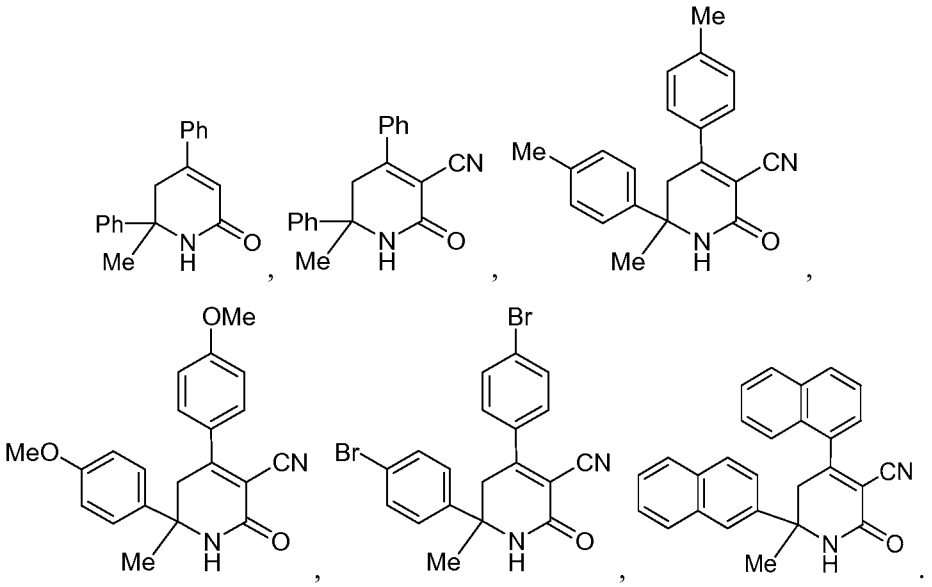
n, at each occurrence, is independently 0 or 1;

m, at each occurrence, is independently 0, 1, 2, 3, or 4;

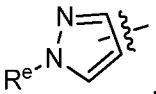
s, at each occurrence, is independently 1, 2, or 3; and

t, at each occurrence, is independently 0 or 1;

provided that the following compounds are excluded:



[0014] In a second aspect, the present invention includes a compound of Formula (I), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of the first aspect, wherein:

R^1 is independently selected from the group consisting of: $-CONHC_{4-18}$ alkyl, $-CONH(CH_2)_{1-8}$ Ph, C_{1-12} alkyl substituted with 0-2 R^a, C_{1-12} alkenyl substituted with 0-2 R^a, C_{1-12} alkynyl substituted with 0-2 R^a, $-(CH_2)_m$-(phenyl substituted with 0-1 R^b and 0-2 R^g), $-(CH_2)_m$-(C_{3-6} cycloalkyl substituted with 0-1 R^b), and $-(CH_2)_m$-(5- to 6-membered heteroaryl substituted with 0-1 R^b and 0-2 R^g), wherein said heteroaryl is selected from: pyridyl, oxazolyl, thiazolyl and  .

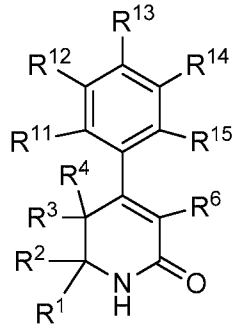
[0015] In a third aspect, the present invention includes a compound of Formula (I), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of the first or second aspect, wherein:

R^{11} and R^{15} are independently selected from the group consisting of: H, C_{1-4} alkyl and halo;

R^{12} and R^{14} are independently selected from the group consisting of: H, halo, C_{1-4} alkyl and C_{1-4} alkoxy; and

R^{13} is independently selected from the group consisting of: H, halo, C_{1-4} alkyl substituted with 0-1 R^i, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, $-(CH_2)_m-C_{3-4}$ cycloalkyl, CN, NR^fR^j, SR^j, $NHCO_2(C_{1-4}$ alkyl), $NHSO_2(C_{1-4}$ alkyl), and a 4- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S.

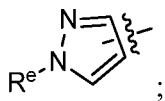
[0016] In a fourth aspect, the present invention provides a compound of Formula (II):



(II)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof; within the scope of any of the above aspects.

[0017] In a fifth aspect, the present invention includes a compound of Formula (I) or (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of any of the above aspects, wherein:

R^1 is independently selected from the group consisting of: C_{1-6} alkyl, C_{3-6} cycloalkyl, $-CONHC_{4-18}$ alkyl, $-CONHC_{2-8}$ haloalkyl, $-CONH(CH_2)_{1-8}$ Ph, $-(CH_2)_m-$(phenyl substituted with 1 R^b and 0-2 R^g), and a 5- to 6-membered heteroaryl substituted with 0-1 R^b and 0-2 R^g, wherein said heteroaryl is selected from: pyridyl, oxazolyl, thiazolyl and  ;

R^2 is independently selected from the group consisting of: C_{1-4} alkyl and C_{1-4} haloalkyl;

R^3 is independently selected from the group consisting of: H and F;

R^4 is independently selected from the group consisting of: H and F;

R^6 is independently selected from the group consisting of: CN, NH_2,

-CONH(C_{1-6} alkyl), R^c, -$(CH_2)_n$-$(X)_t$-$(CH_2)_m R^c$, -NHCO$(CH_2)SO_2(C_{1-4}$ alkyl), -$NHCOCH_2PO(OEt)_2$, -NHCOCO(C_{1-4} alkyl), -NHCOCH(OH)(C_{1-4} alkyl), -$NHCOCH_2CO(C_{1-4}$ alkyl), -NHCONH(C_{1-4} alkyl), and -OCONH(C_{1-4} alkyl);

R^{11} and R^{15} are independently selected from the group consisting of: H, C_{1-4} alkyl and halo;

R^{12} and R^{14} are independently selected from the group consisting of: H, halo, C_{1-4} alkyl and C_{1-4} alkoxy;

R^{13} is independently selected from the group consisting of: H, halo, C_{1-4} alkyl substituted with 0-1 C_{1-4} alkoxy, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, -$(CH_2)_m$-C_{3-4} cycloalkyl, CN, N(C_{1-4} alkyl)$_2$, NHCO$_2$(C_{1-4} alkyl), NHSO$_2$(C_{1-4} alkyl), pyrazolyl, and morpholinyl;

alternatively, R^{12} and R^{13}, together with the carbon atoms to which they are attached, combine to form a 5 to 6-membered carbocyclic ring or a 5 to 6-membered heterocyclic ring comprising: carbon atoms and 1-3 heteroatoms selected from N, NR^e, O, and S;

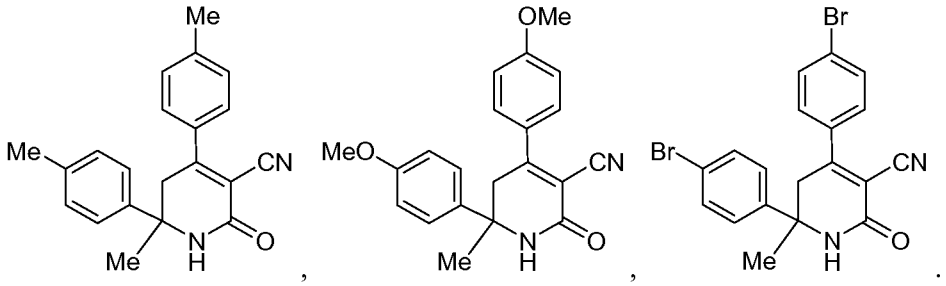
R^b is, at each occurrence, independently selected from the group consisting of: halo, OH, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkyl, C_{1-10} haloalkoxy, -$O(CH_2)_s O(C_{1-6}$ alkyl), N(C_{1-4} alkyl)$_2$, -$CONH(CH_2)_{6-20}H$, -$(CH_2)_m(C_{3-6}$ cycloalkyl), -$(CH_2)_m(C_{4-6}$ cycloalkenyl), -$O(CH_2)_m(C_{3-6}$ cycloalkyl), 4-C_{1-4} alkoxy-Ph, -$O(CH_2)_m$Ph, morpholinyl, pyridyl, 2-C_{1-4} alkoxy-pyridin-5-yl, pyrimidinyl, pyrazinyl, and -O-pyrimidinyl;

R^g is, at each occurrence, independently selected from the group consisting of: halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

m, at each occurrence, is independently 0, 1, 2 or 3; and

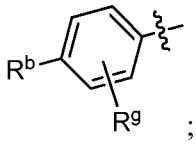
s, at each occurrence, is independently 1, 2, or 3;

provided that the following compounds are excluded:



[0018] In a sixth aspect, the present invention includes a compound of Formula (I) or (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of any of the above aspects, wherein:

R^1 is independently selected from the group consisting of: C_{1-6} alkyl,



$-CONHC_{4-18}$ alkyl, $-CONH(CH_2)_{1-8}Ph$, and ;

R^6 is independently selected from the group consisting of: CN, NH_2, $-CONH(C_{1-6}$ alkyl), $-NHCOCH_2PO(OEt)_2$, $-NHCO(CH_2)SO_2(C_{1-4}$ alkyl), R^c, OR^c, $-CONHR^c$, and $-NHCOR^c$;

R^{12} is independently selected from the group consisting of: H, halo, C_{1-4} alkyl and C_{1-4} alkoxy;

R^{13} is independently selected from the group consisting of: H, halo, C_{1-4} alkyl substituted with 0-1 C_{1-4} alkoxy, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, $-(CH_2)_m$-C_{3-4} cycloalkyl, CN, $N(C_{1-4}$ alkyl$)_2$, $NHCO_2(C_{1-4}$ alkyl), $NHSO_2(C_{1-4}$ alkyl), pyrazolyl, and morpholinyl;

alternatively, R^{12} and R^{13}, together with the carbon atoms to which they are attached, combine to form a 5 to 6-membered carbocyclic ring or a 5 to 6-membered saturated heterocyclic ring comprising: carbon atoms and 1-2 oxygen atoms;

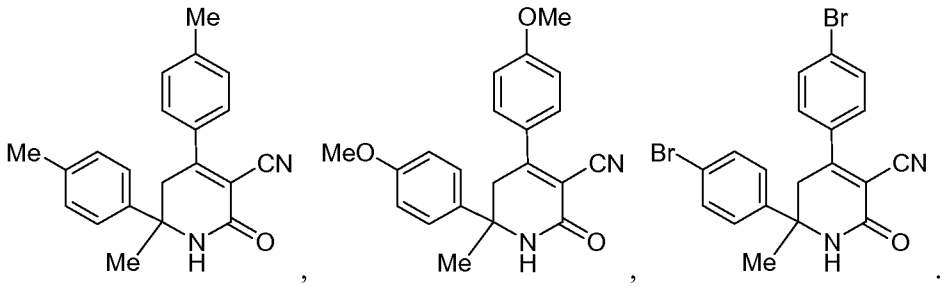
R^{14} is independently selected from the group consisting of: H and C_{1-4} alkoxy;

R^b is, at each occurrence, independently selected from the group consisting of: halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-10} haloalkoxy, $-O(CH_2)_sO(C_{1-6}$ alkyl), $-CONH(CH_2)_{6-20}H$, $-(CH_2)_m(C_{3-6}$ cycloalkyl), $-(CH_2)_m(C_{4-6}$ cycloalkenyl),

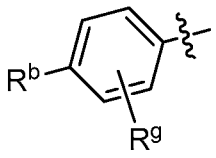
-O(CH_2)$_m$(C_{3-6} cycloalkyl), phenoxy, benzoxy, morpholinyl, 2-C_{1-4} alkoxy-pyridin-5-yl, pyrimidin-5-yl, pyrazin-2-yl and -O-pyrimidinyl; and

R^c is, at each occurrence, independently selected from the group consisting of: C_{3-6} cycloalkyl substituted with 0-2 R^d, -(CH_2)$_m$-(phenyl substituted with 0-3 R^d), and a heteroaryl selected from: oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, and pyrazinyl; wherein said heteroaryl is substituted with 0-2 R^d; and

provided that the following compounds are excluded:



[0019] In a seventh aspect, the present invention includes a compound of Formula (I) or (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of any of the above aspects, wherein:

R^1 is 

;

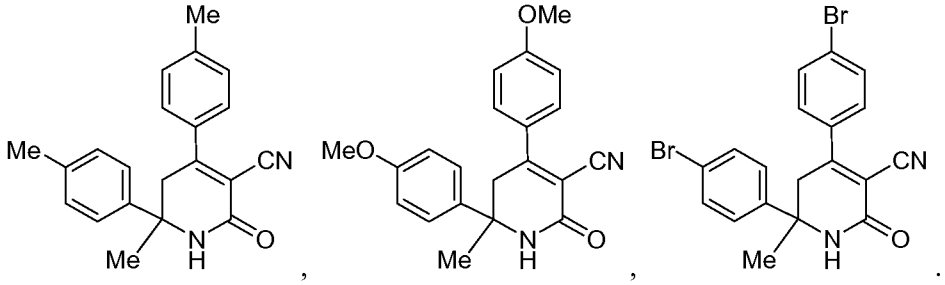
R^6 is independently selected from the group consisting of: NH_2, CN, -CONH(C_{1-4} alkyl), OPh, -CONH(C_{3-6} cycloalkyl), -CONHPh, -CONH-(2-halo-Ph), -CONH-(3-halo-Ph), -CONH-(4-halo-Ph), -CONH-(4-C_{1-4} alkyl-Ph), -CONH(4-OH-Ph), -CONH-(3-C_{1-4} alkoxy-Ph), -CONH-(4-C_{1-4} alkoxy-Ph), -CONH-(4-C_{1-4} haloalkyl-Ph), -CONH-(4-C_{1-4} haloalkoxy-Ph), -CONH-(4-CN-Ph), -CONH-(4-tetrazolyl-Ph), -CONH-(3-halo-4-C_{1-4} alkyl-Ph), -CONH-(3-halo-4-C_{1-4} alkoxy-Ph), -CONH(CH_2)$_2$Ph, -CONH(4-(4-C_{1-4} alkoxy-Ph)-thiazol-2-yl), -CONH(1-C_{1-4} alkyl-pyrazol-3-yl), -CONH(5-C_{1-4} alkoxy-pyrid-2-yl), -CONH(6-C_{1-4} alkoxy-pyrid-3-yl), -CONH(5-C_{1-4} alkoxy-pyrazin-2-yl), -CONH(6-C_{1-4} alkoxy-pyridazin-3-yl), -NHCO(CH_2)SO_2(C_{1-4} alkyl), -NHCOPh,

-NHCO(2-C_{1-4} alkyl-Ph), -NHCO(3-C_{1-4} alkyl-Ph), -NHCO(4-C_{1-4} alkyl-Ph), -NHCO(2-halo-Ph), -NHCO(3-halo-Ph), -NHCO(2-C_{1-4} haloalkyl-Ph), -NHCO(2-C_{1-4} haloalkoxy-Ph), -NHCO(2-halo-4-halo-Ph), -NHCO(2-halo-5-halo-Ph), -NHCO(oxazolyl), -NHCO(isoxazolyl), -NHCO(3-C_{1-4} alkyl-isoxazol-5-yl), -NHCO(4-C_{1-4} alkyl-isoxazol-5-yl), -NHCO(3-C_{1-4} alkoxy-isoxazol-5-yl), -NHCO(4-C_{1-4} alkoxy-isoxazol-5-yl), -NHCO(3-halo-isoxazol-5-yl), -NHCO(3-OBn-isoxazol-5-yl), -NHCO(3-(2-halo-Ph)-isoxazol-5-yl), -NHCO(3-(3-halo-Ph)-isoxazol-5-yl), -NHCO(5-C_{1-4} alkyl-1*H*-pyrazol-3-yl), imidazolyl, -NHCO(5-C_{1-4} alkyl-1,3,4-oxadiazol-2-yl), -NHCO(1-C_{1-4} alkyl-1,2,3-triazol-4-yl), -NHCO(6-C_{1-4} alkoxy-pyrid-3-yl), -NHCO(pyrazinyl), -NHCO(6-halo-pyridazin-3-yl), 5-C_{1-4} haloalkyl-1,3,4-oxadiazol-2-yl, 3-NO_2-1*H*-1,2,4-triazol-1-yl, tetrazolyl and 5-C_{1-4} alkyl-tetrazol-1-yl;

R^b is independently selected from the group consisting of: halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-8} haloalkoxy, -CONH$(CH_2)_{6-20}$H, C_{3-6} cycloalkyl, C_{4-6} cycloalkenyl, -O$(CH_2)_m$(C_{3-6} cycloalkyl), phenoxy, benzoxy, pyrimidinyl, pyrazinyl and -O-pyrimidinyl; and

R^g is independently selected from the group consisting of: halo and C_{1-4} alkyl;

provided that the following compounds are excluded:



[0020] In an eighth aspect, the present invention includes a compound of Formula (I) or (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of any of the above aspects, wherein:

R^2 is independently selected from the group consisting of: CF_3 and Me;

R^3 is independently selected from the group consisting of: H and F;

R^4 is independently selected from the group consisting of: H and F;

R^6 is independently selected from the group consisting of: NH_2, CN, -CONHMe, OPh, -CONH(cyclopropyl), -CONH(cyclobutyl), -CONH(cyclopentyl), -CONH(cyclohexyl), -CONHPh, -CONH(4-F-Ph), -CONH(2-Cl-Ph), -CONH(4-Cl-Ph), -CONH(4-Me-Ph), -CONH(4-OH-Ph), -CONH(3-OMe-Ph), -CONH(4-OMe-Ph), -CONH(4-CF_3-Ph), -CONH(4-OCF_3-Ph), -CONH(1-Me-pyrazol-3-yl), -CONH(4-(1*H*-tetrazol-2-yl)-Ph), -CONH(4-(2*H*-tetrazol-5-yl)-Ph), -CONH(3-F-4-Me-Ph), -CONH(3-F-4-OMe-Ph), -CONH$(CH_2)_2$Ph, -CONH(5-OMe-pyrid-2-yl), -CONH(6-OMe-pyrid-3-yl), -CONH(5-OMe-pyrazin-2-yl), -CONH(6-OMe-pyridazin-3-yl), -NHCO$(CH_2)SO_2$Me, -NHCOPh, -NHCO(2-Me-Ph), -NHCO(3-Me-Ph), -NHCO(4-Me-Ph), -NHCO(2-Cl-Ph), -NHCO(3-Cl-Ph), -NHCO(2-Cl-4-F-Ph), -NHCO(2-Cl-5-F-Ph), -NHCO(isoxazol-5-yl), -NHCO(3-Me-isoxazol-5-yl), -NHCO(4-Me-isoxazol-5-yl), -NHCO(3-OMe-isoxazol-5-yl), -NHCO(3-Br-isoxazol-5-yl), -NHCO(3-(2-Cl-Ph)-isoxazol-5-yl), -NHCO(3-(3-F-Ph)-isoxazol-5-yl), -NHCO(3-OBn-isoxazol-5-yl), 1*H*-imidazol-1-yl, -NHCO(5-Me-1,3,4-oxadiazol-2-yl), -NHCO(1-Me-1,2,3-triazol-4-yl), -NHCO(6-OMe-pyrid-3-yl), -NHCO(6-Cl-pyridazin-3-yl), 5-CF_3-1,3,4-oxadiazol-2-yl, 1*H*-tetrazol-1-yl, 1*H*-tetrazol-3-yl, and 2*H*-tetrazol-5-yl;

R^{11} and R^{15} are independently selected from the group consisting of: H, Me, F, and Cl;

R^{12} is independently selected from the group consisting of: H, F, Cl, Me and OMe;

R^{13} is independently selected from the group consisting of: H, F, Cl, Br, Me, OMe, OEt, CH_2OMe, CF_3, CH_2CF_3, $OCHF_2$, OCF_3, CN, $N(Me)_2$, cyclopropyl and cyclopropylmethyl;

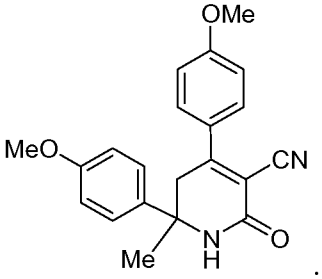
alternatively, R^{12} and R^{13}, together with the carbon atoms to which they are attached, combine to form a 5 to 6-membered carbocyclic ring or a 5 to 6-membered saturated heterocyclic ring comprising: carbon atoms and 1-2 oxygen atoms;

R^{14} is H;

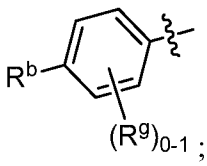
R^b is, at each occurrence, independently selected from the group consisting of: n-pentyl, methoxy, n-butoxy, i-butoxy, i-pentoxy, $-O(CH_2)_{1-6}CF_3$, $-O(CH_2)_{1-4}CF_2CF_3$, $-CONH(CH_2)_{6-20}H$, cyclopropyl, cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, $-O(CH_2)_2$(cyclopentyl), phenoxy, benzoxy, pyrimidin-5-yl, pyrazin-2-yl and -O-pyrimidin-2-yl; and

R^g is F;

provided that the following compound is excluded:



[0021] In a ninth aspect, the present invention includes a compound of Formula (I) or (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of any of the first, second, third, fourth, fifth and sixth apsects, wherein:

R^1 is 

;

R^2 is independently selected from CF_3 and CH_3;

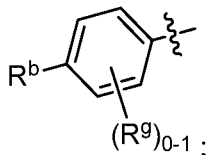
R^6 is independently selected from: CN, R^c, $-CONHR^c$, $-NHCOR^c$, and $-NHCOCH_2SO_2$ (C_{1-4} alkyl);

R^b is independently selected from: $-O(CH_2)_{1-6}CF_3$, $-O(CH_2)_{1-4}CF_2CF_3$, $-CONH(CH_2)_{6-20}H$, cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, $-O(CH_2)_2$(cyclopentyl), phenoxy, benzoxy, pyrimidin-5-yl, pyrazin-2-yl and -O-pyrimidin-2-yl;

R^c is, at each occurrence, independently selected from the group consisting of: $-(CH_2)_m$-(phenyl substituted with 0-3 R^d), and a heteroaryl selected from: oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, and pyrazinyl; wherein said heteroaryl is substituted with 0-2 R^d; and

R^d is, at each occurrence, independently selected from the group consisting of: halo, OH, CN, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, tetrazolyl and OBn.

[0022] In another aspect, the present invention includes a compound of Formula (I) or (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of any of the first, second, third, fourth, fifth, sixth and ninth apsects, wherein:

R^1 is  ;

R^2 is independently selected from CF_3 and CH_3;

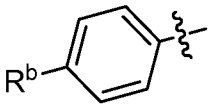
R^6 is independently selected from: CN, R^c, -CONHR^c, -NHCOR^c, and -NHCOCH$_2$SO$_2$ (C_{1-4} alkyl);

R^{11}, R^{12}, R^{14} and R^{15} are H;

R^{13} is independently selected from the group consisting of: H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy; and

R^b is independently selected from: -O(CH$_2$)$_{1-6}$CF$_3$ and -O(CH$_2$)$_{1-4}$CF$_2$CF$_3$.

[0023] In another aspect, the present invention includes a compound of Formula (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of the fourth or fifth aspect, wherein:

R^1 is  ;

R^2 is independently selected from CF_3 and CH_3;

R^3 and R^4 are H;

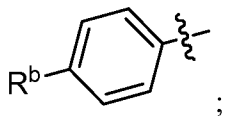
R^6 is independently 5-membered nitrogen heteroaryl;

R^{11}, R^{12}, R^{14} and R^{15} are H;

R^{13} is independently selected from the group consisting of: H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy; and

R^b is independently selected from: $-O(CH_2)_{1-6}CF_3$ and $-O(CH_2)_{1-4}CF_2CF_3$.

[0024] In another aspect, the present invention includes a compound of Formula (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of the fourth or ffith aspect, wherein:

R^1 is  ;

R^2 is independently selected from CF_3 and CH_3;

R^3 and R^4 are H;

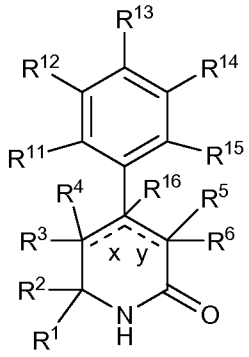
R^6 is independently selected from: 1*H*-imidazol-1-yl, 1*H*-tetrazol-1-yl, 1*H*-tetrazol-3-yl, and 2*H*-tetrazol-5-yl;

R^{11}, R^{12}, R^{14} and R^{15} are H;

R^{13} is independently selected from the group consisting of: H, Me, OMe, and $OCHF_2$; and

R^b is independently selected from: $-O(CH_2)_{1-6}CF_3$ and $-O(CH_2)_{1-4}CF_2CF_3$.

[0025] In a tenth aspect, the present invention provides, *inter alia*, a compound of Formula (I):



(I)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, wherein:

$\overline{---}$ designates a single or double bond;

x and y can be both a single bond; when x is a double bond, then y is a single bond and R^4 and R^{16} are absent; when y is a double bond, then x is a single bond and R^5 and R^{16} are absent;

R^1 is independently selected from the group consisting of: $-(CH_2)_m-(C_{3-10}$ carbocycle substituted with 0-3 $R^b)$ or a C_{1-12} hydrocarbon chain substituted with 0-3 R^a; wherein said hydrocarbon chain may be straight or branched, saturated or unsaturated;

R^2 is independently selected from the group consisting of: C_{1-4} alkyl and C_{1-4} haloalkyl;

R^3 is independently selected from the group consisting of: H, halo, C_{1-4} alkyl and CN;

R^4 and R^5 are independently selected from the group consisting of: H, halo and C_{1-4} alkyl;

when x is a single bond, R^3 and R^4 may be combined with the carbon atom to which they are attached to form a 3- to 6-membered carbocycle;

R^6 is independently selected from the group consisting of: H, halo, C_{1-4} alkyl, CN, NO_2, and $-(CH_2)_n-(X)_t-(CH_2)_mR^c$;

X is independently selected from the group consisting of: O, S, NH, CONH and NHCO;

when y is a single bond, R^5 and R^6 may be combined with the carbon atom to which they are attached to form a 3- to 6-membered carbocycle;

R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are independently selected from the group consisting of: H, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CN and a 5- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S;

R^{16} is independently selected from the group consisting of: H and C_{1-4} alkyl;

R^a is, at each occurrence, independently selected from the group consisting of: halo, OH, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $N(C_{1-4}$ alkyl$)_2$, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$, and $-(CH_2)_n-(CH_2O)_m-(CH_2)_nR^f$;

R^b is, at each occurrence, independently selected from the group consisting of: halo, OH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$, and $-(CH_2)_n-(CH_2O)_m-(CH_2)_nR^f$;

R^c is independently selected from the group consisting of: C_{3-6} cycloalkyl substituted with 0-2 R^d, phenyl substituted with 0-3 R^d, and a 5- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S; wherein said heterocycle is substituted with 0-2 R^d;

R^d is, at each occurrence, independently selected from the group consisting of: halo, OH, CN, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

R^e is independently selected from the group consisting of: H, C_{1-4} alkyl, benzyl, $CO(C_{1-4}$ alkyl) and COBn;

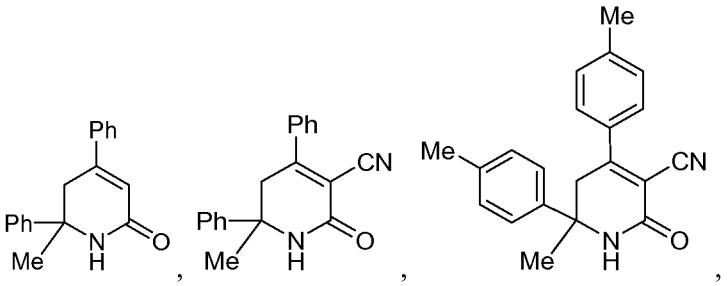
R^f is independently selected from the group consisting of: H and C_{1-4} alkyl;

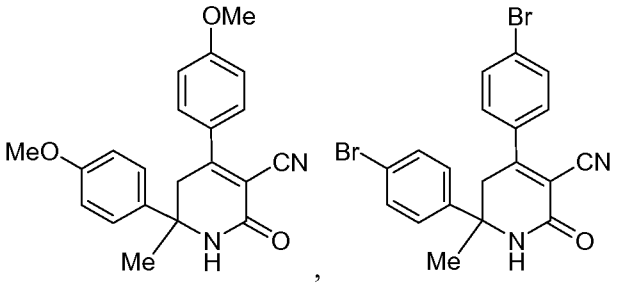
n, at each occurrence, is independently 0 or 1;

m, at each occurrence, is independently 0, 1, 2, 3 or 4; and

t, at each occurrence, is independently 0 or 1;

provided that the following compounds are excluded:





[0026] In an eleventh tenth aspect, the present invention includes a compound of Formula (I), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of the tenth aspect, wherein:

R^1 is independently selected from the group consisting of: C_{1-6} alkyl substituted with 0-2 R^a, $-(CH_2)_m$-(phenyl substituted with 0-3 R^b), and $-(CH_2)_m$-(C_{3-6} cycloalkyl substituted with 0-2 R^b).

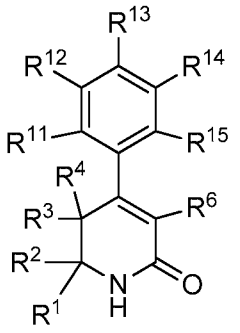
[0027] In a twelfth aspect, the present invention includes a compound of Formula (I), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of the tenth or eleventh aspect, wherein:

R^{11} and R^{15} are independently selected from the group consisting of: H and halo;

R^{12} and R^{14} are independently selected from the group consisting of: H, C_{1-4} alkyl and C_{1-4} alkoxy; and

R^{13} is independently selected from the group consisting of: H, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CN and morpholinyl.

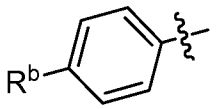
[0028] In a thirteenth aspect, the present invention provides a compound of Formula (II):



(II)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof; within the scope of any of the tenth, eleventh and twelfth aspects.

[0029] In a fourteenth aspect, the present invention includes a compound of Formula (I) or (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of any of the tenth, eleventh, twelfth and thirteenth aspects, wherein:

R^1 is independently selected from the group consisting of: C_{1-6} alkyl, C_{3-6} cycloalkyl, $-(CH_2)_mPh$ and  ;

R^2 is independently selected from the group consisting of: C_{1-4} alkyl and C_{1-4} haloalkyl;

R^3 is H;

R^4 is H;

R^6 is independently selected from the group consisting of: CN, NO_2, $-CONH(C_{1-6}$ alkyl), -CONHPh, -CONH-(3-halo-Ph), -CONH-(4-halo-Ph), $-CONH-(4-C_{1-4}$ alkyl -Ph), $-CONH-(3-C_{1-4}$ alkoxy-Ph), $-CONH-(4-C_{1-4}$ alkoxy-Ph), $-CONH-(4-C_{1-4}$ haloalkyl-Ph), $-CONH-(4-C_{1-4}$ haloalkoxy-Ph), $-CONH-(3\text{-halo-}4-C_{1-4}$ alkyl-Ph), $-CONH-(3\text{-halo-}4-C_{1-4}$ alkoxy-Ph), $-CONH(CH_2)_2Ph$, and 2H-tetrazol-5-yl;

R^{11} and R^{15} are independently selected from the group consisting of: H and halo;

R^{12} and R^{14} are independently selected from the group consisting of: H, C_{1-4} alkyl and C_{1-4} alkoxy;

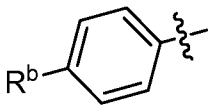
R^{13} is independently selected from the group consisting of: H, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CN and morpholinyl;

R^b is independently selected from the group consisting of: halo, OH, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $-O(CH_2)_mO(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl$)_2$, $-O(CH_2)_m(C_{3-6}$ cycloalkyl), $4-C_{1-4}$ alkoxy-Ph, $-O(CH_2)_mPh$, pyridin-2-yl, $2-C_{1-4}$ alkoxy-pyridin-5-yl, pyrimidin-5-yl, pyrazin-2-yl and -O-pyrimidin-2-yl; and

m, at each occurrence, is independently 0, 1, 2 or 3.

[0030] In a fifteenth aspect, the present invention includes a compound of Formula (I) or (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of any of the tenth, eleventh, twelfth, thirteenth and fourteenth aspects, wherein:

R^1 is independently selected from the group consisting of: C_{1-6} alkyl and



;

R^6 is independently selected from the group consisting of: CN, -CONH(C_{1-6} alkyl), -CONHPh, -CONH-(3-halo-Ph), -CONH-(4-halo-Ph), -CONH-(4-C_{1-4} alkyl -Ph), -CONH-(3-C_{1-4} alkoxy-Ph), -CONH-(4-C_{1-4} alkoxy-Ph), -CONH-(4-C_{1-4} haloalkyl-Ph), -CONH-(4-C_{1-4} haloalkoxy-Ph), -CONH-(3-halo-4-C_{1-4} alkoxy-Ph), -CONH$(CH_2)_2$Ph, and 2*H*-tetrazol-5-yl;

R^{12} is independently selected from the group consisting of: H, C_{1-4} alkyl and C_{1-4} alkoxy;

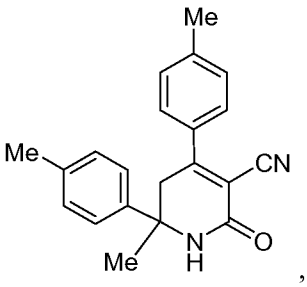
R^{14} is independently selected from the group consisting of: H and C_{1-4} alkoxy;

R^{13} is independently selected from the group consisting of: H, halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy and CN;

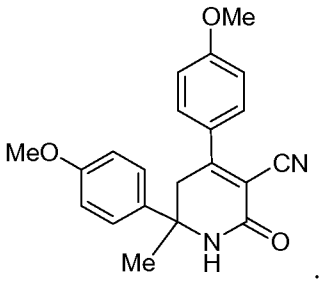
R^b is independently selected from the group consisting of: C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, -O$(CH_2)_m$O(C_{1-4} alkyl), -O$(CH_2)_m$(C_{3-6} cycloalkyl), phenoxy, benzoxy, 2-C_{1-4} alkoxy-pyridin-5-yl, pyrimidin-5-yl, pyrazin-2-yl and -O-pyrimidin-2-yl; and

m, at each occurrence, is independently 0, 1, 2 or 3;

provided that the following compounds are excluded:



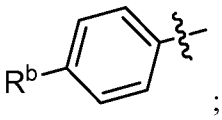
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[0031] In a sixteenth aspect, the present invention includes a compound of Formula (I) or (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate

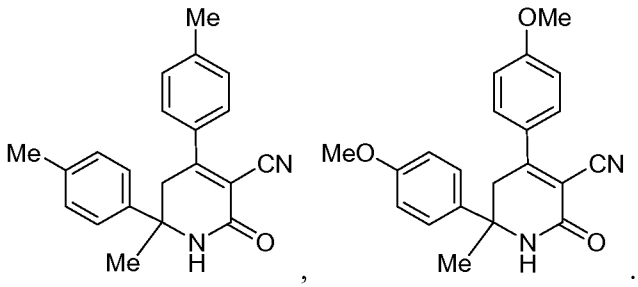
thereof, within the scope of any of the ninth, tenth, eleventh, twelfth, thirteenth, fourteenth and fifteenth aspects, wherein:

R^1 is  ;

R^6 is independently selected from the group consisting of: CN, -CONHPh, -CONH-(4-halo-Ph), -CONH-(4-C_{1-4} alkyl -Ph), -CONH-(3-C_{1-4} alkoxy-Ph), -CONH-(4-C_{1-4} alkoxy-Ph), -CONH-(4-C_{1-4} haloalkyl-Ph), -CONH-(4-C_{1-4} haloalkoxy-Ph), -CONH-(3-halo-4-C_{1-4} alkoxy-Ph), -CONH$(CH_2)_2$Ph, and 2*H*-tetrazol-5-yl; and

R^b is independently selected from the group consisting of: C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, -O$(CH_2)_m$(C_{3-6} cycloalkyl), phenoxy, benzoxy, pyrimidin-5-yl, pyrazin-2-yl and -O-pyrimidin-2-yl;

provided that the following compounds are excluded:



[0032] In a seventeenth aspect, the present invention includes a compound of Formula (I) or (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of any of the ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth and sixteenth aspects, wherein:

R^2 is independently selected from the group consisting of: CF_3 and Me;

R^6 is independently selected from the group consisting of: CN, -CONHPh, -CONH-(4-F-Ph), -CONH-(4-Cl-Ph), -CONH-(4-Me-Ph), -CONH-(3-OMe-Ph), -CONH-(4-OMe-Ph), -CONH-(4-CF_3-Ph), -CONH-(4-OCF_3-Ph), -CONH-(3-F-4-OMe-Ph), -CONH$(CH_2)_2$Ph, and 2*H*-tetrazol-5-yl;

R^{11} and R^{15} are independently selected from the group consisting of: H and F;

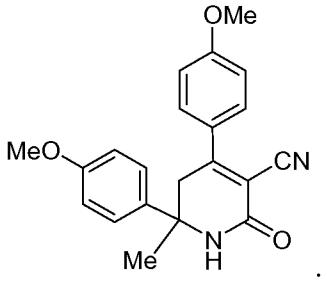
R^{12} is independently selected from the group consisting of: H, Me and OMe;

R^{13} is independently selected from the group consisting of: H, F, Cl, Me, OMe, OEt, CF_3, $OCHF_2$, OCF_3 and CN;

R^{14} is H; and

R^b is independently selected from the group consisting of: n-pentyl, methoxy, n-butoxy, i-butoxy, $-O(CH_2)_{1-3}CF_3$, $-O(CH_2)_2$(cyclopentyl), phenoxy, benzoxy, pyrimidin-5-yl, pyrazin-2-yl and -O-pyrimidin-2-yl;

provided that the following compounds are excluded:



[0033] In an eighteenth aspect, the present invention provides a compound selected from the exemplified examples or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

[0034] In another aspect, the present invention provides a compound selected from any subset list of compounds or a single compound from the exemplified examples within the scope of any of the above aspects.

[0035] In another aspect, the present disclosure provides a compound selected from:

(*S*)-3-(1*H*-tetrazol-5-yl)-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one,

(*S*)-N-(4-methoxyphenyl)-2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxamide,

(*S*)-3-(2*H*-tetrazol-5-yl)-4-(p-tolyl)-6-(4-((6,6,6-trifluorohexyl)oxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one,

(*S*)-2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile,

(*S*)-2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-N-(4-(trifluoromethoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxamide,

(*S*)-N-(6-methoxypyridin-3-yl)-2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxamide,

(*S*)-N-cyclopropyl-2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxamide,

(*S*)-N-(4-hydroxyphenyl)-2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxamide,

(*S*)-4-(4-(difluoromethoxy)phenyl)-2-oxo-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile,

(*S*)-2-oxo-4-(p-tolyl)-6-(trifluoromethyl)-6-(4-(3,3,3-trifluoropropoxy)phenyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile,

(*S*)-4-(4-(difluoromethoxy)phenyl)-3-(1*H*-tetrazol-1-yl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one,

(*S*)-3-methyl-N-(2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridin-3-yl)isoxazole-5-carboxamide,

(*S*)-5-methyl-N-(2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridin-3-yl)-1,3,4-oxadiazole-2-carboxamide,

N^2-heptyl-N^5-(4-methoxyphenyl)-2-methyl-6-oxo-4-(p-tolyl)-1,2,3,6-tetrahydropyridine-2,5-dicarboxamide,

(*S*)-3-(1*H*-tetrazol-1-yl)-4-(p-tolyl)-6-(4-((6,6,6-trifluorohexyl)oxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one,

(*S*)-2-oxo-4-(p-tolyl)-6-(4-((6,6,6-trifluorohexyl)oxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile,

(*S*)-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one,

(*S*)-2-(methylsulfonyl)-N-(2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridin-3-yl)acetamide,

(*S*)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-4-(4-(2,2,2-trifluoroethyl)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one, and

(*S*)-N-(5-methoxypyrazin-2-yl)-2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxamide; or a pharmaceutically acceptable salt thereof.

[0036] In another embodiment, R^1 is independently -CONH(C_{4-18} alkyl), -CONHC_{2-8} haloalkyl, or -CONH$(CH_2)_{1-8}$Ph.

[0037] In another embodiment, R^1 is -$(CH_2)_m$-(C_{3-10} carbocycle substituted with 0-2 R^b and 0-2 R^g), or -$(CH_2)_m$-(5- to 6-membered heteroaryl comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O and S; wherein said heteroaryl is substituted with 0-1 R^b and 0-2 R^g).

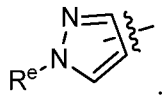
[0038] In another embodiment, R^1 is -$(CH_2)_m$-(C_{3-10} carbocycle substituted with 0-2 R^b and 0-2 R^g).

[0039] In another embodiment, R^1 is -$(CH_2)_m$-(phenyl substituted with 0-2 R^b and 0-2 R^g).

[0040] In another embodiment, R^1 is -$(CH_2)_m$-(5- to 6-membered heteroaryl comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O and S; wherein said heteroaryl is substituted with 0-1 R^b and 0-2 R^g).

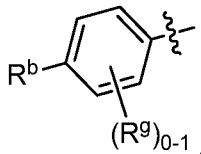
[0041] In another embodiment, R^1 is a C_{1-12} hydrocarbon chain substituted with 0-3 R^a; wherein said hydrocarbon chain may be straight or branched, saturated or unsaturated.

[0042] In another embodiment, R^1 is independently: C_{1-6} alkyl, C_{3-6} cycloalkyl, -CONHC_{4-18} alkyl, -CONHC_{2-8} haloalkyl, -CONH$(CH_2)_{1-8}$ Ph, -$(CH_2)_m$-(phenyl substituted with 1 R^b and 0-2 R^g), or a 5- to 6-membered heteroaryl substituted with 0-1 R^b and 0-2 R^g, wherein said heteroaryl is selected from: pyridyl, oxazolyl, thiazolyl and



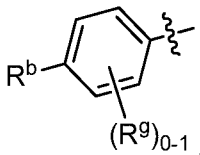
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[0043] In another embodiment, R^1 is independently: C_{1-6} alkyl, -CONHC_{4-18} alkyl, -CONH$(CH_2)_{1-8}$Ph, or

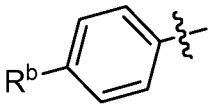


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[0044] In another embodiment, R^1 is



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[0045] In another embodiment, R^1 is independently  .

[0046] In another embodiment, R^2 is independently C_{1-4} alkyl or C_{1-4} haloalkyl.

[0047] In another embodiment, R^2 is C_{1-4} alkyl.

[0048] In another embodiment, R^2 is C_{1-4} haloalkyl.

[0049] In another embodiment, R^2 is independently CF_3 or Me.

[0050] In another embodiment, R^2 is CF_3.

[0051] In another embodiment, R^2 is Me.

[0052] In another embodiment, R^3 is independently H or F.

[0053] In another embodiment, R^3 is H.

[0054] In another embodiment, R^3 is F.

[0055] In another embodiment, R^4 is independently H or F.

[0056] In another embodiment, R^4 is H.

[0057] In another embodiment, R^4 is F.

[0058] In another embodiment, R^5 is independently H or F.

[0059] In another embodiment, R^5 is H.

[0060] In another embodiment, R^5 is F.

[0061] In another embodiment, R^6 is independently C_{1-4} alkyl, CN, R^c, or $-(CH_2)_n-(X)_t-(CH_2)_mR^c$.

[0062] In another embodiment, R^6 is independently $-CONH(C_{1-6}$ alkyl), $-NHCOX_1SO_2R^j$, $-NHCOCOR^j$, $-NHCOCH(OH)R^j$, $-NHCOCH_2COR^j$, $-NHCONHR^j$, or $-OCONR^fR^j$.

[0063] In another embodiment, R^6 is independently CN, NH_2, $-CONH(C_{1-6}$ alkyl),

R^c, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$, $-NHCO(CH_2)SO_2(C_{1-4}$ alkyl), $-NHCOCO(C_{1-4}$ alkyl), $-NHCOCH(OH)(C_{1-4}$ alkyl), $-NHCOCH_2CO(C_{1-4}$ alkyl), $-NHCONH(C_{1-4}$ alkyl), or $-OCONH(C_{1-4}$ alkyl).

[0064] In another embodiment, R^6 is independently CN, NH_2, $-CONH(C_{1-6}$ alkyl), $-NHCO(CH_2)SO_2(C_{1-4}$ alkyl), R^c, OR^c, $-CONHR^c$, or $-NHCOR^c$.

[0065] In another embodiment, R^6 is independently CN, NH_2, $-CONH(C_{1-6}$ alkyl), $-NHCO(CH_2)SO_2(C_{1-4}$ alkyl), R^c, OR^c, $-CONHR^c$, or $-NHCOR^c$.

[0066] In another embodiment, R^6 is independently CN, R^c, $-CONHR^c$, $-NHCOR^c$, or $-NHCOCH_2SO_2$ (C_{1-4} alkyl).

[0067] In another embodiment, R^6 is independently 5-membered nitrogen heteroaryl.

[0068] In another embodiment, R^6 is independently: 1*H*-imidazol-1-yl, 1*H*-tetrazol-1-yl, 1*H*-tetrazol-3-yl, or 2*H*-tetrazol-5-yl.

[0069] In another embodiment, R^{11} is independently H, C_{1-4} alkyl or halo.

[0070] In another embodiment, R^{11} is independently H, Me, F, or Cl.

[0071] In another embodiment, R^{11} is H.

[0072] In another embodiment, R^{11} is C_{1-4} alkyl.

[0073] In another embodiment, R^{11} is Me.

[0074] In another embodiment, R^{11} is halo.

[0075] In another embodiment, R^{11} is independently F or Cl.

[0076] In another embodiment, R^{12} is independently H, halo, C_{1-4} alkyl or C_{1-4} alkoxy.

[0077] In another embodiment, R^{12} is independently H, F, Cl, Me and OMe.

[0078] In another embodiment, R^{12} is H.

[0079] In another embodiment, R^{12} is C_{1-4} alkyl.

[0080] In another embodiment, R^{12} is Me.

[0081] In another embodiment, R^{12} is C_{1-4} alkoxy.

[0082] In another embodiment, R^{12} is OMe.

[0083] In another embodiment, R^{12} is halo.

[0084] In another embodiment, R^{12} is independently F or Cl.

[0085] In another embodiment, R^{13} is independently: H, halo, C_{1-4} alkyl substituted with 0-1 R^i, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{3-4} cycloalkyl, CN, NR^fR^j, SR^j, $NHCO_2(C_{1-4}$ alkyl), $NHSO_2(C_{1-4}$ alkyl), or a 4- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S.

[0086] In another embodiment, R^{13} is independently: H, halo, C_{1-4} alkyl substituted with 0-1 C_{1-4} alkoxy, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CN, C_{3-4} cycloalkyl, $N(C_{1-4}$ alkyl$)_2$, $NHCO_2(C_{1-4}$ alkyl), $NHSO_2(C_{1-4}$ alkyl), pyrazolyl, or morpholinyl.

[0087] In another embodiment, R^{13} is independently: H, halo, C_{1-4} alkyl substituted with 0-1 C_{1-4} alkoxy, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CN or C_{3-4} cycloalkyl.

[0088] In another embodiment, R^{13} is independently: NR^fR^j, $NHCO_2(C_{1-4}$ alkyl), $NHSO_2(C_{1-4}$ alkyl), or a 4- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S.

[0089] In another embodiment, R^{14} is independently H, halo, C_{1-4} alkyl or C_{1-4} alkoxy.

[0090] In another embodiment, R^{14} is independently H, F, Cl, Me and OMe.

[0091] In another embodiment, R^{14} is H.

[0092] In another embodiment, R^{14} is C_{1-4} alkyl.

[0093] In another embodiment, R^{14} is Me.

[0094] In another embodiment, R^{14} is C_{1-4} alkoxy.

[0095] In another embodiment, R^{14} is OMe.

[0096] In another embodiment, R^{14} is halo.

[0097] In another embodiment, R^{14} is independently F or Cl.

[0098] In another embodiment, R^{15} is independently H, C_{1-4} alkyl or halo.

[0099] In another embodiment, R^{15} is independently H, Me, F, or Cl.

[00100] In another embodiment, R^{15} is H.

[00101] In another embodiment, R^{15} is C_{1-4} alkyl.

[00102] In another embodiment, R^{15} is Me.

[00103] In another embodiment, R^{15} is halo.

[00104] In another embodiment, R^{15} is independently F or Cl.

[00105] In another embodiment, R^{16} is H.

[00106] In another embodiment, R^{16} is C_{1-4} alkyl.

[00107] In another embodiment, X is independently O, S, or NH.

[00108] In another embodiment, X is independently O or S.

[00109] In another embodiment, X is O.

[00110] In another embodiment, X is independently CONH or NHCO.

[00111] In another embodiment, X is CONH.

[00112] In another embodiment, X is NHCO.

[00113] In another embodiment, R^b is, at each occurrence, independently: C_{1-10} alkyl, C_{1-10} alkoxy, C_{1-10} haloalkyl, C_{1-10} haloalkoxy, C_{1-10} alkylthio, C_{1-10} haloalkyltho, $-CONH(CH_2)_{4-20}H$, $-O(CH_2)_sO(C_{1-6}$ alkyl), R^c, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$, or $-(CH_2)_n-(CH_2O)_m-(CH_2)_nR^f$.

[00114] In another embodiment, R^b is, at each occurrence, independently: halo, OH, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkyl, C_{1-10} haloalkoxy, $-O(CH_2)_sO(C_{1-6}$ alkyl), $N(C_{1-4}$ alkyl$)_2$, $-CONH(CH_2)_{6-20}H$, $-(CH_2)_m(C_{3-6}$ cycloalkyl), $-(CH_2)_m(C_{4-6}$ cycloalkenyl), $-O(CH_2)_m(C_{3-6}$ cycloalkyl), 4-C_{1-4} alkoxy-Ph, $-O(CH_2)_mPh$, morpholinyl, pyridyl, 2-C_{1-4} alkoxy-pyridin-5-yl, pyrimidinyl, pyrazinyl, or -O-pyrimidinyl.

[00115] In another embodiment, R^b is, at each occurrence, independently: halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-10} haloalkoxy, $-O(CH_2)_sO(C_{1-6}$ alkyl), $-CONH(CH_2)_{6-20}H$, $-(CH_2)_m(C_{3-6}$ cycloalkyl), $-(CH_2)_m(C_{4-6}$ cycloalkenyl),

-O$(CH_2)_m$(C_{3-6} cycloalkyl), phenoxy, benzoxy, morpholinyl, 2-C_{1-4} alkoxy-pyridin-5-yl, pyrimidin-5-yl, pyrazin-2-yl or -O-pyrimidinyl.

[00116] In another embodiment, R^b is, at each occurrence, independently: halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-8} haloalkoxy, -CONH$(CH_2)_{6-20}$H, C_{3-6} cycloalkyl, C_{4-6} cycloalkenyl, -O$(CH_2)_m$(C_{3-6} cycloalkyl), phenoxy, benzoxy, pyrimidinyl, pyrazinyl and -O-pyrimidinyl.

[00117] In another embodiment, R^b is, at each occurrence, independently: -O$(CH_2)_{1-6}CF_3$ and -O$(CH_2)_{1-4}CF_2CF_3$.

[00118] In another embodiment, R^c is, at each occurrence, independently: C_{3-6} cycloalkyl substituted with 0-2 R^d, C_{3-6} cycloalkenyl substituted with 0-2 R^d, or -$(CH_2)_m$-(phenyl substituted with 0-3 R^d).

[00119] In another embodiment, R^c is, at each occurrence, independently: C_{3-6} cycloalkyl substituted with 0-2 R^d or C_{3-6} cycloalkenyl substituted with 0-2 R^d.

[00120] In another embodiment, R^c is, at each occurrence, independently -$(CH_2)_m$-(phenyl substituted with 0-3 R^d),.

[00121] In another embodiment, R^c is, at each occurrence, independently C_{3-6} cycloalkyl substituted with 0-2 R^d.

[00122] In another embodiment, R^c is, at each occurrence, independently C_{3-6} cycloalkenyl substituted with 0-2 R^d.

[00123] In another embodiment, R^c is, at each occurrence, independently a 5- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S; wherein said heterocycle is substituted with 0-2 R^d.

[00124] In another embodiment, R^c is, at each occurrence, independently -$(CH_2)_m$-(phenyl substituted with 0-3 R^d), or a heteroaryl selected from: oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, and pyrazinyl; wherein said heteroaryl is substituted with 0-2 R^d.

[00125] In another embodiment, R^c is, at each occurrence, independently a heteroaryl selected from: oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, and pyrazinyl; wherein said heteroaryl is substituted with 0-2 R^d.

[00126] In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 10 μM, using the MGAT2 SPA assay.

[00127] In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 5 μM, using the MGAT2 SPA assay.

[00128] In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 1 μM, using the MGAT2 SPA assay.

[00129] In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 0.5 μM, using the MGAT2 SPA assay.

[00130] In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 10 μM, using the MGAT2 LCMS assay.

[00131] In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 5 μM, using the MGAT2 LCMS assay.

[00132] In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 2.5 μM, using the MGAT2 LCMS assay.

[00133] In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 1 μM, using the MGAT2 LCMS assay.

[00134] In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 0.5 μM, using the MGAT2 LCMS assay.

[00135] In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 0.1 μM, using the MGAT2 LCMS assay.

II. OTHER EMBODIMENTS OF THE INVENTION

[00136] In another embodiment, the present invention provides a composition comprising at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

[00137] In another embodiment, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one of the

compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

[00138] In another embodiment, the present invention provides a pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

[00139] In another embodiment, the present invention provides a process for making a compound of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

[00140] In another embodiment, the present invention provides an intermediate for making a compound of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

[00141] In another embodiment, the present invention provides a pharmaceutical composition further comprising additional therapeutic agent(s). In a preferred embodiment, the present invention provides pharmaceutical composition, wherein the additional therapeutic agent is, for example, a dipeptidyl peptidase-IV (DPP4) inhibitor (for example a member selected from saxagliptin, sitagliptin, vildagliptin and alogliptin).

[00142] In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2, comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

[00143] Examples of diseases or disorders associated with the activity of the MGAT2 that can be prevented, modulated, or treated according to the present invention include, but are not limited to, diabetes, hyperglycemia, impaired glucose tolerance, gestational diabetes, insulin resistance, hyperinsulinemia, nonalcoholic fatty liver disease (NAFLD) including nonalcoholic steatohepatitis (NASH), retinopathy, neuropathy, nephropathy, delayed wound healing, atherosclerosis and its sequelae, abnormal heart function, myocardial ischemia, stroke, Metabolic Syndrome, hypertension, obesity, dyslipidemia, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low high-

density lipoprotein (HDL), high low-density lipoprotein (LDL), non-cardiac ischemia, lipid disorders, and glaucoma.

[00144] In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of diabetes, hyperglycemia, gestational diabetes, obesity, dyslipidemia, and hypertension, comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

[00145] In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of diabetes, comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

[00146] In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of hyperglycemia, comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

[00147] In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of obesity, comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

[00148] In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of dyslipidemia, comprising administering to a patient in need of such treatment and/or prophylaxis a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

[00149] In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of hypertension, comprising administering to a patient in

need of such treatment and/or prophylaxis a therapeutically effective amount of at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent.

[00150] In another embodiment, the present invention provides a compound of the present invention for use in therapy.

[00151] In another embodiment, the present invention provides a compound of the present invention for use in therapy for the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2.

[00152] In another embodiment, the present invention also provides the use of a compound of the present invention for the manufacture of a medicament for the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2.

[00153] In another embodiment, the present invention provides a method for the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2, comprising: administering to a patient in need thereof a therapeutically effective amount of a first and second therapeutic agent, wherein the first therapeutic agent is a compound of the present invention. Preferably, the second therapeutic agent, for example, dipeptidyl peptidase-IV (DPP4) inhibitor (for example a member selected from saxagliptin, sitagliptin, vildagliptin, linagliptin and alogliptin).

[00154] In another embodiment, the present invention provides a combined preparation of a compound of the present invention and additional therapeutic agent(s) for simultaneous, separate or sequential use in therapy.

[00155] In another embodiment, the present invention provides a combined preparation of a compound of the present invention and additional therapeutic agent(s) for simultaneous, separate or sequential use in the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2.

[00156] Where desired, the compound of the present invention may be used in combination with one or more other types of antidiabetic agents and/or one or more other types of therapeutic agents which may be administered orally in the same dosage form, in a separate oral dosage form or by injection. The other type of antidiabetic agent that may be optionally employed in combination with the MGAT2 inhibitor of the present invention may be one, two, three or more antidiabetic agents or antihyperglycemic agents

which may be administered orally in the same dosage form, in a separate oral dosage form, or by injection to produce an additional pharmacological benefit.

[00157] The antidiabetic agents used in the combination with the MGAT2 inhibitor of the present invention include, but are not limited to, insulin secretagogues or insulin sensitizers, other MGAT2 inhibitors, or other antidiabetic agents. These agents include, but are not limited to, dipeptidyl peptidase IV (DP4) inhibitors (for example, sitagliptin, saxagliptin, alogliptin, linagliptin and vildagliptin), biguanides (for example, metformin and phenformin), sulfonyl ureas (for example, glyburide, glimepiride and glipizide), glucosidase inhibitors (for example, acarbose, miglitol), PPARγ agonists such as thiazolidinediones (for example, rosiglitazone and pioglitazone), PPAR α/γ dual agonists (for example, muraglitazar, tesaglitazar and aleglitazar), glucokinase activators, GPR40 receptor modulators (e.g. TAK-875), GPR119 receptor modulators (for example, MBX-2952, PSN821, and APD597), sodium-glucose transporter-2 (SGLT2) inhibitors (for example, dapagliflozin, canagliflozin and remagliflozin), 11b-HSD-1 inhibitors (for example MK-0736, BI35585, BMS-823778, and LY2523199), amylin analogs such as pramlintide, and/or insulin.

[00158] The MGAT2 inhibitor of the present invention may also be optionally employed in combination with one or more hypophagic and/or weight-loss agents such as diethylpropion, phendimetrazine, phentermine, orlistat, sibutramine, lorcaserin, pramlintide, topiramate, MCHR1 receptor antagonists, oxyntomodulin, naltrexone, Amylin peptide, NPY Y5 receptor modulators, NPY Y2 receptor modulators, NPY Y4 receptor modulators, cetilistat, 5HT2c receptor modulators, and the like. The compounds of the present invention may also be employed in combination with an agonist of the glucagon-like peptide-1 receptor (GLP-1 R), such as exenatide, liraglutide, GPR-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37), which may be administered via injection, intranasal, or by transdermal or buccal devices.

[00159] The MGAT2 inhibitor of the present invention may also be optionally employed in combination with one or more other types of therapeutic agents, such as DGAT inhibitors, LDL lowering drugs such as statins (inhibitors of HMG CoA reductase) or inhibitors of cholesterol absorption, modulators of PCSK9, drugs that increase HDL such as CETP inhibitors.

[00160] The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of preferred aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional embodiments. It is also understood that each individual element of the embodiments is its own independent embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

III. CHEMISTRY

[00161] Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof where such isomers exist. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are within the scope of the invention. Many geometric isomers of C=C double bonds, C=N double bonds, ring systems, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. Cis- and trans- (or *E*- and *Z*-) geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. The present compounds can be isolated in optically active or racemic forms. Optically active forms may be prepared by resolution of racemic forms or by synthesis from optically active starting materials. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. When enantiomeric or diastereomeric products are prepared, they may be separated by conventional methods, for example, by chromatography or fractional crystallization. Depending on the process conditions the end products of the present invention are obtained either in free (neutral) or salt form. Both the free form and the salts of these end products are within the scope of the invention. If so desired, one form of a compound may be converted into another form. A free base or acid may be converted into a salt; a salt may be converted into the free compound or another salt; a mixture of isomeric compounds of the present invention may be separated into the individual isomers. Compounds of the present invention, free form and salts thereof, may exist in multiple tautomeric forms, in which hydrogen atoms are

transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that all tautomeric forms, insofar as they may exist, are included within the invention.

[00162] As used herein, the term "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For examples, "C_1 to C_{12} alkyl" or "C_{1-12} alkyl" (or alkylene), is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11} and C_{12} alkyl groups; "C_4 to C_{18} alkyl" or "C_{4-18} alkyl" (or alkylene), is intended to include C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, and C_{18} alkyl groups. Additionally, for example, "C_1 to C_6 alkyl" or "C_{1-6} alkyl" denotes alkyl having 1 to 6 carbon atoms. Alkyl group can be unsubstituted or substituted with at least one hydrogen being replaced by another chemical group. Example alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (*e.g.*, n-propyl and isopropyl), butyl (*e.g.*, n-butyl, isobutyl, *t*-butyl), and pentyl (*e.g.*, n-pentyl, isopentyl, neopentyl). When "C_0 alkyl" or "C_0 alkylene" is used, it is intended to denote a direct bond.

[00163] Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either straight or branched configuration having the specified number of carbon atoms and one or more, preferably one to two, carbon-carbon double bonds that may occur in any stable point along the chain. For example, "C_2 to C_6 alkenyl" or "C_{2-6} alkenyl" (or alkenylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. Examples of alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3, pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, and 4-methyl-3-pentenyl.

[00164] "Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either straight or branched configuration having one or more, preferably one to three, carbon-carbon triple bonds that may occur in any stable point along the chain. For example, "C_2 to C_6 alkynyl" or "C_{2-6} alkynyl" (or alkynylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups; such as ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

[00165] When the term "hydrocarbon chain" is used, it is intended to include "alkyl", "alkenyl" and "alkynyl", unless otherwise specified.

[00166] The term "alkoxy" or "alkyloxy" refers to an -O-alkyl group. For example, "C_1 to C_6 alkoxy" or "C_{1-6} alkoxy" (or alkyloxy), is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkoxy groups. Example alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy (*e.g.*, n-propoxy and isopropoxy), and *t*-butoxy. Similarly, "alkylthio" or "thioalkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example methyl-S- and ethyl-S-.

[00167] "Halo" or "halogen" includes fluoro, chloro, bromo, and iodo. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogens. Examples of haloalkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, heptafluoropropyl, and heptachloropropyl. Examples of haloalkyl also include "fluoroalkyl" that is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more fluorine atoms.

[00168] "Haloalkoxy" or "haloalkyloxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. For example, "C_{1-6} haloalkoxy", is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 haloalkoxy groups. Examples of haloalkoxy include, but are not limited to, trifluoromethoxy, 2,2,2-trifluoroethoxy, and pentafluorothoxy. Similarly, "haloalkylthio" or "thiohaloalkoxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example trifluoromethyl-S-, and pentafluoroethyl-S-.

[00169] The term "cycloalkyl" refers to cyclized alkyl groups, including mono-, bi- or poly-cyclic ring systems. For example, "C_3 to C_6 cycloalkyl" or "C_{3-6} cycloalkyl" is intended to include C_3, C_4, C_5, and C_6 cycloalkyl groups. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and norbornyl. Branched cycloalkyl groups such as 1-methylcyclopropyl and 2-methylcyclopropyl are included in the definition of "cycloalkyl". The term "cycloalkenyl" refers to cyclized alkenyl groups. C_{4-6} cycloalkenyl is intended to include

C_4, C_5, and C_6 cycloalkenyl groups. Example cycloalkenyl groups include, but are not limited to, cyclobutenyl, cyclopentenyl, and cyclohexenyl.

[00170] As used herein, "carbocycle," "carbocyclyl," or "carbocyclic residue" is intended to mean any stable 3-, 4-, 5-, 6-, 7-, or 8-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, or 13-membered bicyclic or tricyclic ring, any of which may be saturated, partially unsaturated, unsaturated or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, anthracenyl, and tetrahydronaphthyl (tetralin). As shown above, bridged rings are also included in the definition of carbocycle (*e.g.*, [2.2.2]bicyclooctane). Preferred carbocycles, unless otherwise specified, are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, indanyl, and tetrahydronaphthyl. When the term "carbocycle" is used, it is intended to include "aryl." A bridged ring occurs when one or more, preferably one to three, carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

[00171] As used herein, the term "bicyclic carbocycle" or "bicyclic carbocyclic group" is intended to mean a stable 9- or 10-membered carbocyclic ring system that contains two fused rings and consists of carbon atoms. Of the two fused rings, one ring is a benzo ring fused to a second ring; and the second ring is a 5- or 6-membered carbon ring which is saturated, partially unsaturated, or unsaturated. The bicyclic carbocyclic group may be attached to its pendant group at any carbon atom which results in a stable structure. The bicyclic carbocyclic group described herein may be substituted on any carbon if the resulting compound is stable. Examples of a bicyclic carbocyclic group are, but not limited to, naphthyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, and indanyl.

[00172] "Aryl" groups refer to monocyclic or bicyclic aromatic hydrocarbons, including, for example, phenyl, and naphthyl. Aryl moieties are well known and described, for example, in *Hawley's Condensed Chemical Dictionary* (15th ed.), R.J.

Lewis, ed., J. Wiley & Sons, Inc., New York, 2007. "C_{6-10} aryl" refers to phenyl and naphthyl.

[00173] The term "benzyl," as used herein, refers to a methyl group on which one of the hydrogen atoms is replaced by a phenyl group.

[00174] As used herein, the term "heterocycle," "heterocyclyl," or "heterocyclic group" is intended to mean a stable 3-, 4-, 5-, 6-, or 7-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, 13-, or 14-membered polycyclic heterocyclic ring that is saturated, partially unsaturated, or fully unsaturated, and that contains carbon atoms and 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O and S; and including any polycyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and $S(O)_p$, wherein p is 0, 1 or 2). The nitrogen atom may be substituted or unsubstituted (*i.e.*, N or NR wherein R is H or another substituent, if defined). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. When the term "heterocycle" is used, it is intended to include heteroaryl.

[00175] Examples of heterocycles include, but are not limited to, acridinyl, azetidinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, imidazolopyridinyl, indolenyl, indolinyl, indolizinyl, indolyl, 3*H*-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolopyridinyl, isoxazolyl, isoxazolopyridinyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl,

1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolopyridinyl, oxazolidinylperimidinyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolopyridinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2-pyrrolidonyl, 2*H*-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrazolyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thiazolopyridinyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

[00176] Examples of 5- to 10-membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxadiazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benztetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl, quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl.

[00177] Examples of 5- to 6-membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxadiazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

[00178] As used herein, the term "bicyclic heterocycle" or "bicyclic heterocyclic group" is intended to mean a stable 9- or 10-membered heterocyclic ring system which contains two fused rings and consists of carbon atoms and 1, 2, 3, or 4 heteroatoms

independently selected from the group consisting of N, O and S. Of the two fused rings, one ring is a 5- or 6-membered monocyclic aromatic ring comprising a 5-membered heteroaryl ring, a 6-membered heteroaryl ring or a benzo ring, each fused to a second ring. The second ring is a 5- or 6-membered monocyclic ring which is saturated, partially unsaturated, or unsaturated, and comprises a 5-membered heterocycle, a 6-membered heterocycle or a carbocycle (provided the first ring is not benzo when the second ring is a carbocycle).

[00179] The bicyclic heterocyclic group may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The bicyclic heterocyclic group described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1.

[00180] Examples of a bicyclic heterocyclic group are, but not limited to, quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, indolyl, isoindolyl, indolinyl, 1*H*-indazolyl, benzimidazolyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydro-quinolinyl, 2,3-dihydro-benzofuranyl, chromanyl, 1,2,3,4-tetrahydro-quinoxalinyl, and 1,2,3,4-tetrahydro-quinazolinyl.

[00181] As used herein, the term "aromatic heterocyclic group" or "heteroaryl" is intended to mean stable monocyclic and polycyclic aromatic hydrocarbons that include at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl groups include, without limitation, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrroyl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, benzodioxolanyl, and benzodioxane. Heteroaryl groups are substituted or unsubstituted. The nitrogen atom is substituted or unsubstituted (*i.e.*, N or NR wherein R is H or another substituent, if defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and $S(O)_p$, wherein p is 0, 1 or 2).

[00182] Examples of 5- to 6-membered heteroaryls include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, imidazolyl, imidazolidinyl,

tetrazolyl, isoxazolyl, oxazolyl, oxadiazolyl, oxazolidinyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl.

[00183] Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more, preferably one to three, atoms (*i.e.*, C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Examples of bridged rings include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon-nitrogen group. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

[00184] The term "counter ion" is used to represent a negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate or a positively charged species such as sodium (Na+), potassium (K+), ammonium (R_nNH_m+ where n=0-4 and m=0-4) and the like.

[00185] When a dotted ring is used within a ring structure, this indicates that the ring structure may be saturated, partially saturated or unsaturated.

[00186] As used herein, the term "amine protecting group" means any group known in the art of organic synthesis for the protection of amine groups which is stable to an ester reducing agent, a disubstituted hydrazine, R4-M and R7-M, a nucleophile, a hydrazine reducing agent, an activator, a strong base, a hindered amine base and a cyclizing agent. Such amine protecting groups fitting these criteria include those listed in Wuts, P. G. M. and Greene, T.W. *Protecting Groups in Organic Synthesis*, 4th Edition, Wiley (2007) and *The Peptides: Analysis, Synthesis, Biology*, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference. Examples of amine protecting groups include, but are not limited to, the following: (1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; (2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); (3) aliphatic carbamate types such as *tert*-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; (4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; (5) alkyl types such as triphenylmethyl and benzyl; (6) trialkylsilane such as trimethylsilane; (7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl; and (8) alkyl types such as

triphenylmethyl, methyl, and benzyl; and substituted alkyl types such as 2,2,2-trichloroethyl, 2-phenylethyl, and *t*-butyl; and trialkylsilane types such as trimethylsilane.

[00187] As referred to herein, the term "substituted" means that at least one hydrogen atom is replaced with a non-hydrogen group, provided that normal valencies are maintained and that the substitution results in a stable compound. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N, or N=N).

[00188] In cases wherein there are nitrogen atoms (*e.g.*, amines) on compounds of the present invention, these may be converted to N-oxides by treatment with an oxidizing agent (*e.g.*, mCPBA and/or hydrogen peroxides) to afford other compounds of this invention. Thus, shown and claimed nitrogen atoms are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative.

[00189] When any variable occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R, then said group may optionally be substituted with up to three R groups, and at each occurrence R is selected independently from the definition of R.

[00190] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom in which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent.

[00191] Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[00192] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, and/or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00193] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base

salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic, and the like.

[00194] The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington: The Science and Practice of Pharmacy*, 22nd Edition, Allen, L. V. Jr., Ed.; Pharmaceutical Press, London, UK (2012), the disclosure of which is hereby incorporated by reference.

[00195] In addition, compounds of formula I may have prodrug forms. Any compound that will be converted *in vivo* to provide the bioactive agent (*i.e.*, a compound of formula I) is a prodrug within the scope and spirit of the invention. Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

a) Bundgaard, H., ed., *Design of Prodrugs*, Elsevier (1985), and Widder, K. et al., eds., *Methods in Enzymology*, 112:309-396, Academic Press (1985);

b) Bundgaard, H., Chapter 5, "Design and Application of Prodrugs," *A Textbook of Drug Design and Development*, pp. 113-191, Krosgaard-Larsen, P. et al., eds., Harwood Academic Publishers (1991);

c) Bundgaard, H., *Adv. Drug Deliv. Rev.*, 8:1-38 (1992);

d) Bundgaard, H. et al., *J. Pharm. Sci.*, 77:285 (1988);

e) Kakeya, N. et al., *Chem. Pharm. Bull.*, 32:692 (1984); and

f) Rautio, J (Editor). *Prodrugs and Targeted Delivery (Methods and Principles in Medicinal Chemistry)*, Vol 47, Wiley-VCH, 2011.

[00196] Compounds containing a carboxy group can form physiologically hydrolyzable esters that serve as prodrugs by being hydrolyzed in the body to yield formula I compounds *per se*. Such prodrugs are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester *per se* is active, or in those instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of formula I include C_{1-6}alkyl, C_{1-6}alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C_{1-6} alkanoyloxy-C_{1-6}alkyl (*e.g.*, acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl), C_{1-6}alkoxycarbonyloxy-C_{1-6}alkyl (*e.g.*, methoxycarbonyl-oxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl), and other well known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared by conventional techniques known in the art.

[00197] Preparation of prodrugs is well known in the art and described in, for example, King, F.D., ed., *Medicinal Chemistry: Principles and Practice*, The Royal Society of Chemistry, Cambridge, UK (2nd edition, reproduced, 2006); Testa, B. et al., *Hydrolysis in Drug and Prodrug Metabolism. Chemistry, Biochemistry and Enzymology*, VCHA and Wiley-VCH, Zurich, Switzerland (2003); Wermuth, C.G., ed., *The Practice of Medicinal Chemistry*, 3rd edition, Academic Press, San Diego, CA (2008).

[00198] The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include ^{13}C and ^{14}C. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

[00199] The term "solvate" means a physical association of a compound of this invention with one or more solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The solvent molecules in the solvate may be present in a regular arrangement and/or a non-ordered arrangement. The solvate may comprise either a stoichiometric or nonstoichiometric amount of the solvent molecules. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include, but are not limited to, hydrates, ethanolates, methanolates, and isopropanolates. Methods of solvation are generally known in the art.

[00200] Abbreviations as used herein, are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "L" for liter or liters, "mL" for milliliter or milliliters, "μL" for microliter or microliters, "N" for normal, "M" for molar, "mmol" for millimole or millimoles, "min" for minute or min, "h" for hour or h, "rt" for room temperature, "RT" for retention time, "atm" for atmosphere, "psi" for pounds per square inch, "conc." for concentrate, "aq" for "aqueous", "sat" or "sat'd " for saturated, "MW" for molecular weight, "mp" for melting point, "MS" or "Mass Spec" for mass spectrometry, "ESI" for electrospray ionization mass spectroscopy, "HR" for high resolution, "HRMS" for high resolution mass spectrometry, "LCMS" for liquid chromatography mass spectrometry, "HPLC" for high pressure liquid chromatography, "RP HPLC" for reverse phase HPLC, "TLC" or "tlc" for thin layer chromatography, "NMR" for nuclear magnetic resonance spectroscopy, "nOe" for nuclear Overhauser effect spectroscopy, "^{1}H" for proton, "δ" for delta, "s" for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "m" for multiplet, "br" for broad, "Hz" for hertz, and "α", "β", "R", "S", "E", "Z" and "ee" are stereochemical designations familiar to one skilled in the art.

Me	methyl
Et	ethyl
Pr	propyl
i-Pr	isopropyl
Bu	butyl

i-Bu	isobutyl
t-Bu	*tert*-butyl
Ph	phenyl
Bn	benzyl
Hex	hexanes
MeOH	methanol
EtOH	ethanol
i-PrOH or IPA	isopropanol
AcOH or HOAc	acetic acid
Ag_2CO_3	silver carbonate
AgOAc	silver acetate
$CDCl_3$	deutero-chloroform
$CHCl_3$	chloroform
cDNA	complimentary DNA
DCC	*N,N'*-dicyclohexylcarbodiimide
DIAD	diisopropyl azodicarboxylate
DMA	dimethylamine
DME	dimethylether
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
DMAP	4-dimethylaminopyridine
EDTA	ethylenediaminetetraacetic acid
EtOAc	ethyl acetate
Et_2O	diethyl ether
$AlCl_3$	aluminum chloride
Boc	*tert*-butyloxycarbonyl
CH_2Cl_2	dichloromethane
CH_3CN or ACN	acetonitrile
Cs_2CO_3	cesium carbonate
HCl	hydrochloric acid
H_2SO_4	sulfuric acid

K_2CO_3	potassium carbonate
KCN	potassium cyanide
mCPBA or m-CPBA	*meta*-chloroperbenzoic acid
Pd/C	palladium on carbon
$PhSO_2Cl$	benzenesulfonyl chloride
i-Pr_2NEt	diisopropylethylamine
PS	polystyrene
SFC	Supercritical Fluid Chromatography
SiO_2	silica oxide
$SnCl_2$	tin(II) chloride
TBAT	tetrabutylammonium triphenydifluorosilicate
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
KOAc	potassium acetate
$MgSO_4$	magnesium sulfate
NaCl	sodium chloride
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
NaOH	sodium hydroxide
Na_2SO_3	sodium sulfite
Na_2SO_4	sodium sulfate
NH_3	ammonia
NH_4Cl	ammonium chloride
NH_4OH	ammonium hydroxide
LG	leaving group
Pd_2dba_3	tris(dibenzylideneacetone)dipalladium(0)
selectFluor	*N*-fluoro-*N'*-methyl-triethylenediamine bis(tetrafluoroborate)

[00201] The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present

invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent or solvent mixture appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

[00202] The novel compounds of this invention may be prepared using the reactions and techniques described in this section. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. Restrictions to the substituents that are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

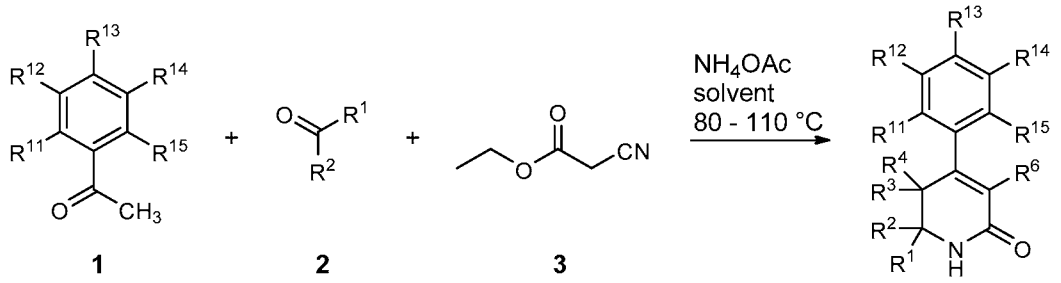
SYNTHESIS

[00203] The compounds of Formula (I) may be prepared by the exemplary processes described in the following schemes and working examples, as well as relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter and in the working examples. Protection and de-protection in the processes below may be carried out by procedures generally known in the art (see, for example, Wuts, P. G. M. and Greene, T.W. *Protecting Groups in Organic Synthesis*, 4th Edition, Wiley (2007)). General methods of organic synthesis and functional group transformations are found in: Trost, B.M. and Fleming, I., eds., *Comprehensive Organic Synthesis: Selectivity, Strategy & Efficiency in Modern Organic Chemistry*, Pergamon Press, New York, NY (1991); Smith, M. B. and March, J., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*. 6th Edition, Wiley & Sons, New York, NY (2007); Katritzky, A.R. and Taylor, R. J. K., eds.,

Comprehensive Organic Functional Groups Transformations II, 2nd Edition, Elsevier Science Inc., Tarrytown, NY (2004); Larock, R.C., *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, NY (1999), and references therein.

[00204] For example, compounds of Formula (II), where $R^3 = R^4 = H$ and $R^6 = CN$, can be made according to Scheme 1. Ketones **1** and **2** and 2-cyanoethyl acetate (**3**) are heated to between 80 °C and 110 °C with ammonium acetate in a solvent such as DMF or DMSO. Ketones **1** and **2** may be different or the same.

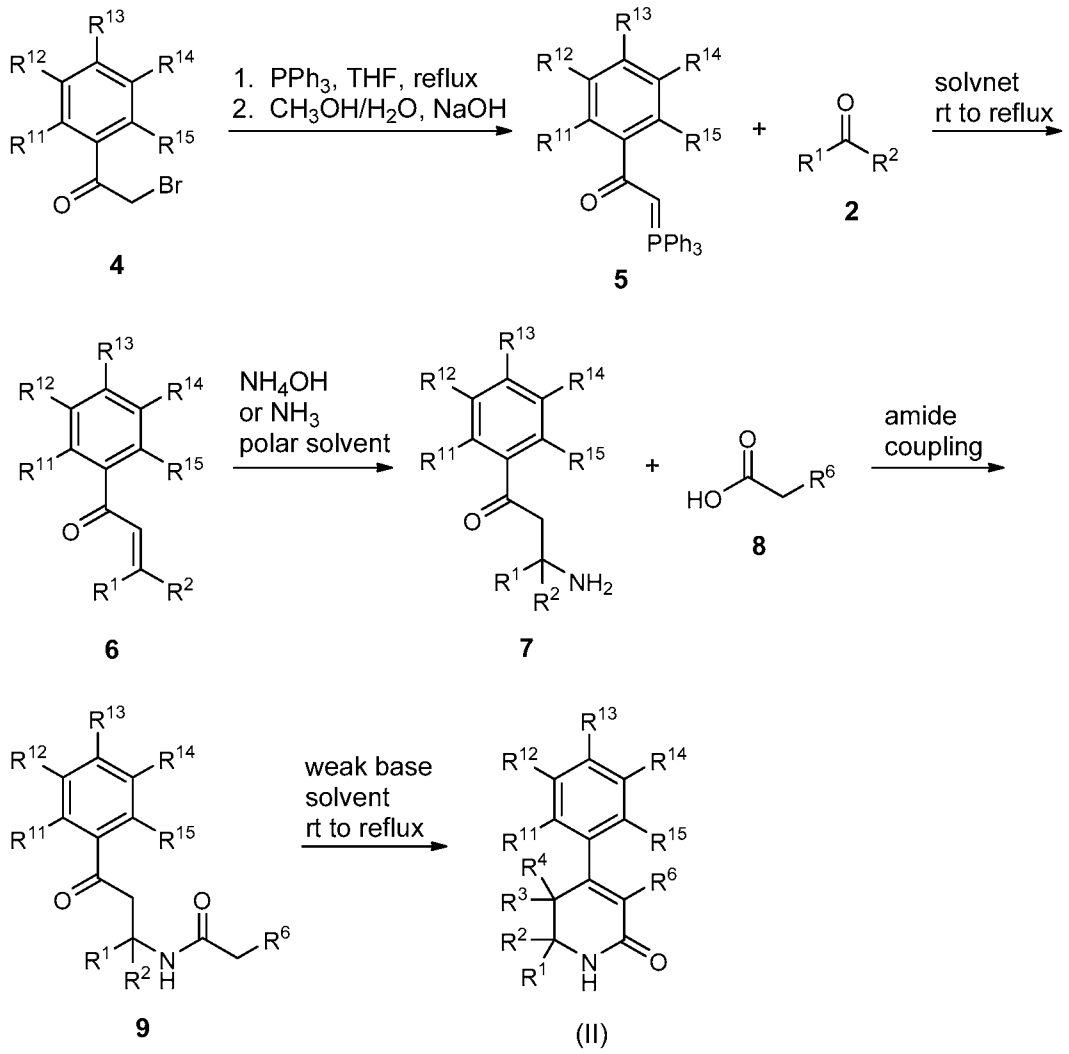
Scheme 1



[00205] Alternatively, compounds of Formula (II), where $R^3 = R^4 = H$, may be made according to Scheme 2. α-Bromoketone **4** is combined with triphenylphosphine in a solvent such as THF, CH_2Cl_2 or 1,4-dioxane at temperatures between room temperature and reflux. The intermediate triphenylphosphonium bromide is treated with base, such as NaOH, in a solvent such as methanol and water to form the phosphorous ylide **5**. The phosphorous ylide **5** is heated to 80 °C with ketone **2** in a suitable solvent such as THF or DMSO to give α,β-unsat'd ketone **6**, which may exist as a mixture of E/Z isomers. Microwave irradiation may be employed to shorten the reaction time. α,β-Unsat'd ketone **6** is treated with concentrated aq NH_4OH in a solvent such as DMSO in a sealed vessel to provide amine **7**. Alternatively, alkene **6** may be treated with NH_3 in a solvent such as DMSO or DMSO and methanol in a sealed vessel to provide amine **7**. Amine **7** is couple with carboxylic acid **8** using a variety of amide bond forming reactions. For example, carboxylic acid **8** may be converted to the corresponding acid chloride using oxalyl chloride in a solvent such as CH_2Cl_2 and catalytic DMF. Alternatively, when R^6 is an amide or a heterocycle, the carboxylic acid **8** may be activated using triphenylphosphine

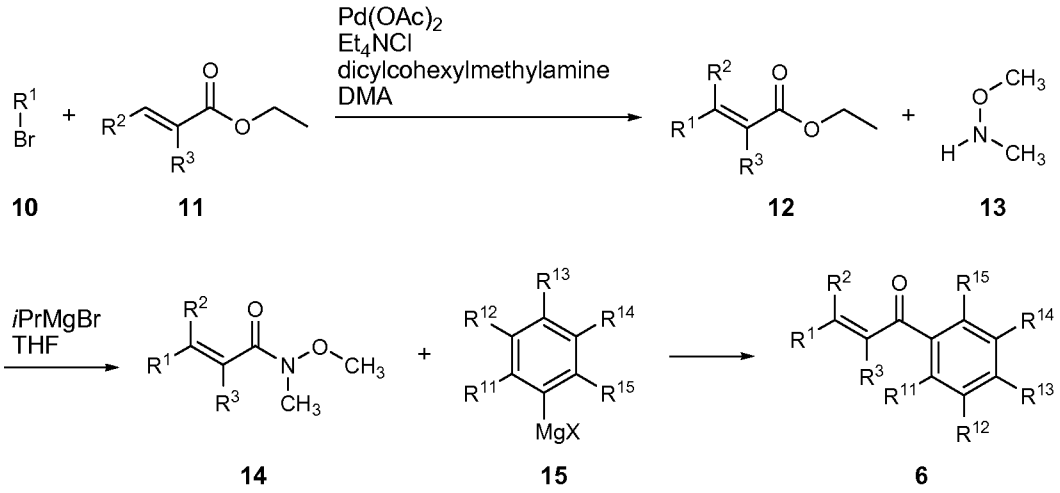
and trichloroacetonitrile in a suitable solvent such as CH_2Cl_2. The acid chlorides thus formed are combined with amine **7** in a suitable solvent such as CH_2Cl_2 or CH_2Cl_2 and DMF in the presence of a base, preferably pyridine. When R^2 is CF_3, cyclization of amide **9** to a compound of Formula (I) typically occurs during the work-up procedure for amide **9**; for example, when an EtOAc solution of amide **9** is washed with sat'd aq $NaHCO_3$. When cyclization does not occur under these conditions, cyclization may be affected by stirring amide **9** in the presence of a weak base such as piperidine in a suitable solvent such as EtOH at a temperature between room temperature and reflux.

Scheme 2



[00206] An alternate synthesis to α,β-unsaturated ketone **6**, where R^1 is $-(CH_2)_m-$ (phenyl substituted with 0-3 R^b) and m = 0, is shown in Scheme 3. Aryl bromide **10** and α,β-unsat'd ester **11** are coupled using palladium (II) acetate, tetrabutylammonium chloride and dicyclohexylamine in DMA at 110 °C. α,β-Unsat'd ester **12** is combined with *O,N*-dimethylhydroxyl-amine **13** in the presence of a strong base such as *iso*-propylmagnesium bromide in an aprotic solvent such as THF. α,β-Unsat'd amide **14** is combined with aryl magnesium halide **15** to provide α,β-unsat'd ketone **6**. The identity of the halide in the aryl magnesium halide is dependent upon availability of the aryl halide used to make the Grignard reagent; typically the halide is chloride or bromide.

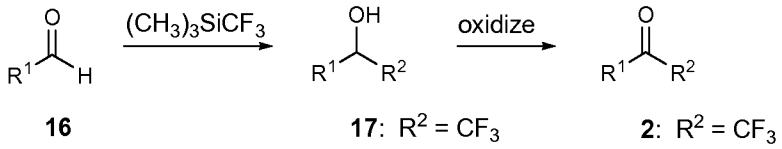
Scheme 3



10 **11** **12** **13** **14** **15** **6**

[00207] Non-commercial α,α,α-trifluoroketones **2**, where $R^2 = CF_3$, may be made from the corresponding aldehyde **16** as shown in Scheme 4. Aldehyde **16** is reacted with trimethyl-(trifluoromethyl)silane in the presence of a fluoride source, for example cesium fluoride, using a suitable solvent such dimethoxyethane at room temperature. Other fluoride sources, such as potassium hydrogen fluoride or tetrabutylammonium difluorotriphenylsilicate, and other solvents, such as THF or acetonitrile and methanol, may also be employed. Trifluoromethyl alcohol **17** is oxidized using, for example, Dess-Martin periodinane in a suitable solvent such as CH_2Cl_2.

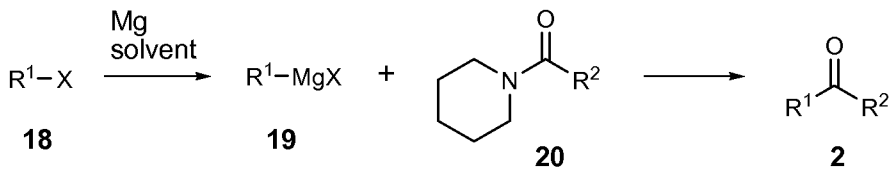
Scheme 4



16 **17**: $R^2 = CF_3$ **2**: $R^2 = CF_3$

[00208] Ketones of formula **2** may be made according to Scheme 5. For example, aryl halide **18**, where X = bromine and the aryl group is a suitable chemical moiety to form a Grignard reagent, is combined with magnesium metal in the presence of an initiator such as iodine in a suitable solvent such as THF. Other alkyl halides having a chemical moiety suitable for formation of Grignard reagents, other halides such as chlorine or iodine, other solvents such as diethyl ether or 1,4-dioxane, and other initiators such as 1,2-dibromoethene, may be employed as determined by one skilled in the art. Grignard reagent **19** is combined with amide **20** in a suitable solvent such as THF to provide ketone **2**. Other solvents such as 1,4-dioxane or diethyl ether may be employed as determined by one skilled in the art.

Scheme 5

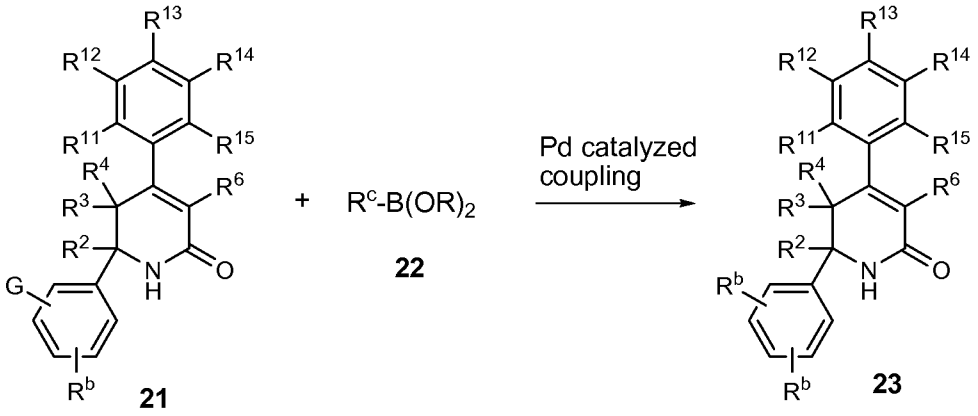


18 **19** **20** **2**

[00209] Compounds of Formula **23** having $R^3 = R^4 = H$, $R^1 = -(CH_2)_m$-(phenyl substituted with 0-3 R^b) where m = 0, and at least one $R^b = -(CH_2)_n-(X)_t-(CH_2)_m-R^c$ where n = m = t = 0, or n = m = 0 and t = 1 when X = O or NH, and R^c is a suitable chemical moiety to participate in palladium cross coupling reactions, may be made according to Scheme 6. Compound **21** is heated with boronic acid **22**, where R = H, in the presence of a palladium catalyst and base using a suitable solvent such as 1,4-dioxane, toluene, DMF with or without water. Boronic acid **22** may be substituted with alternative boronic acid analogs such as boronate esters, trifluoroborates, and others known to those skilled in the art. Palladium catalyst commonly employed include, but are not restricted to, $Pd(PPh_3)_4$ and $PdCl_2(dppf)$. Other palladium catalyst known to those skilled in the art

may be employed. Bases commonly employed include, but are not restricted to, K_3PO_4 and K_2CO_3. Other bases known to those skilled in the art may also be employed. When n = m = 0 and t = 1 when X = O or NH, biarylethers or biarylamines such as **23** can be obtained from **21** when G = OH. Alternatively, biaryl ethers and amines can also be obtained from **21**, when G = boronic acid or equivalent, via metal-catalyzed coupling with suitable phenols or amines.

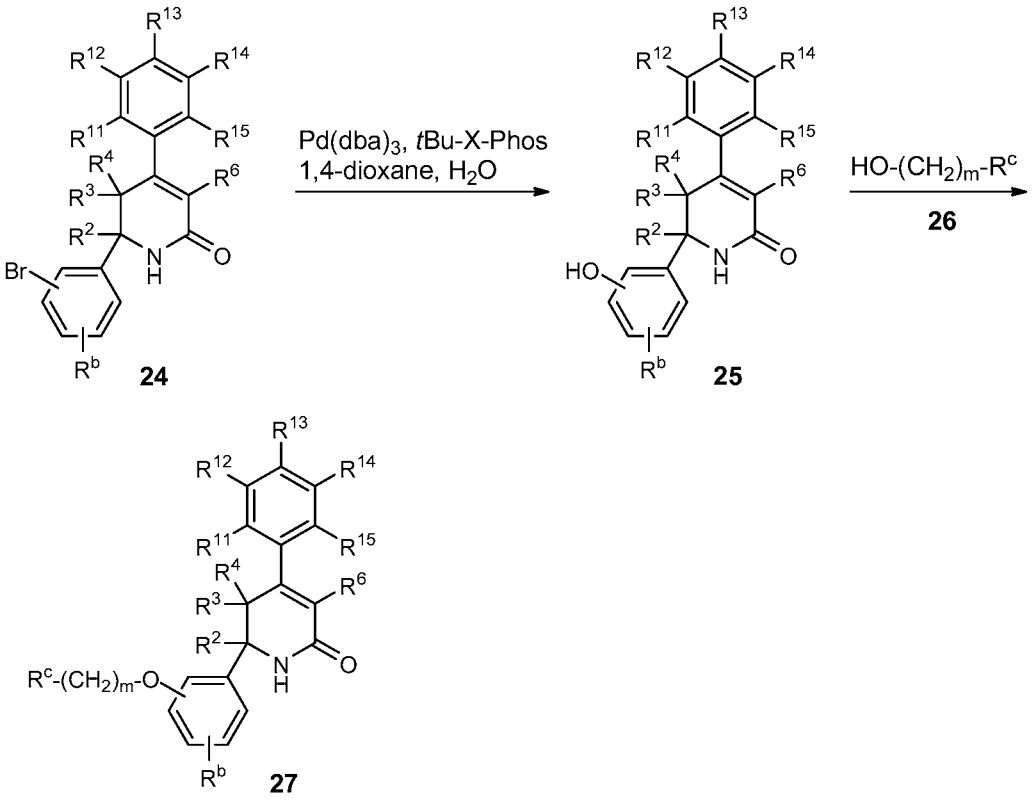
Scheme 6



G = Cl, Br, I, OMs, OTs, OTf, OH, NH_2

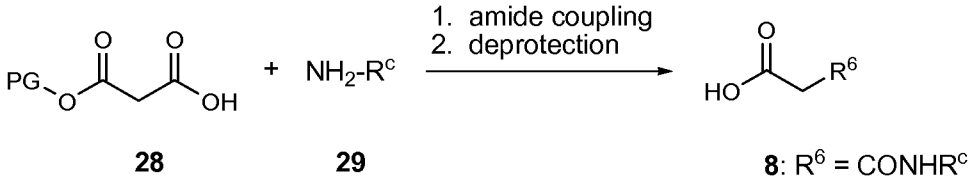
[00210] Compounds of Formula **27** having $R^3 = R^4 = H$, $R^1 = -(CH_2)_m$-(phenyl substituted with 0-3 R^b) where m = 0, and at least one $R^b = -(CH_2)_n-(X)_t-(CH_2)_m-R^c$ where n = 0, t = 1, m = 1-4 and X = O, may be made according to Scheme 7. Bromide **24** is treated with tris(dibenzylideneacetone)palladium (0) in the presence of bis(1,1-dimethylethyl)[2′,4′,6′-tris(1-methylethyl)[1,1′-biphenyl]-2-yl]- phosphine (*t*-butyl-Xphos) using 1,4-dioxane and water as solvent and KOH as base. Phenol **25** and alcohol **26** were stirred in the presence of triphenylphosphine and DIAD in a suitable solvent such as CH_2Cl_2.

Scheme 7



[00211] Carboxylic acid **8**, where R^6 = $CONHR^c$, may be made according to Scheme 8. The mono-ester of malonic acid **28**, where PG = benzyl group, and amine **29** are coupled together using standard amide bond forming conditions. For example, treatment of carboxylic acid **28** with oxalyl chloride in CH_2Cl_2 and DMF provides the acid chloride. The acid chloride is then combined with amine **29** in the presence of pyridine in a suitable solvent such as CH_2Cl_2. Other amide bond forming reaction known to those skilled in the art may be employed. The benzyl group is removed using a combination of hydrogen gas and 10% palladium on carbon in a suitable solvent such as methanol or methanol and EtOAc. Other PG moieties and methods for their removal known to those skilled in the art may be employed.

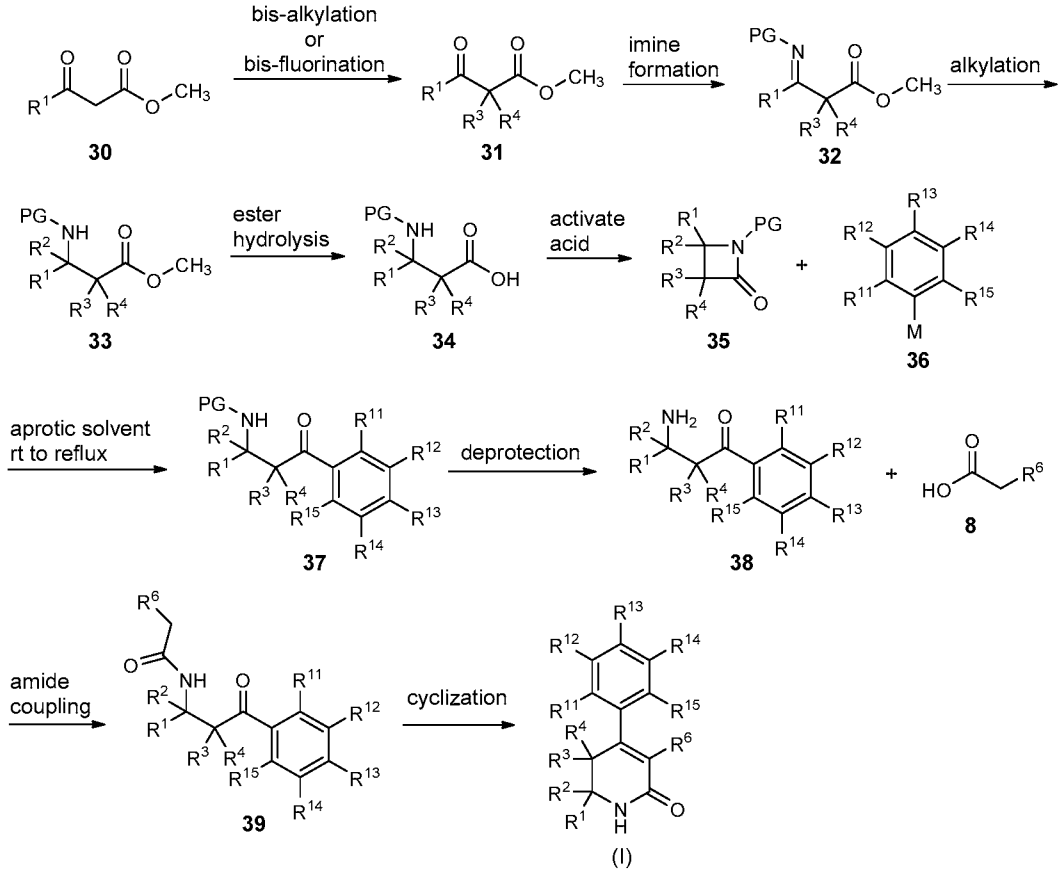
Scheme 8



[00212] Compounds of Formula (I), where R^3 and R^4 are combined with the carbon atom to which they are attached to form a 3-6 membered carbocycle, or $R^3 = R^4 = F$, may be made according to Scheme 9. For example, to synthesize compounds for Formula (I) where R^3 and R^4 are combined with the carbon atom to which they are attached to form a 3-membered ring (*i.e.*, cyclopropyl), β-ketoester **30** is stirred at room temperature with 1,2-dibromoethane in the presence of a base, for example K_2CO_3, in a suitable solvent such as DMF to provide the cyclopropyl β-ketoester **31**. Cyclopropyl β-ketoester **31** is stirred with a suitable amine, such as benzyl amine, in the presence of a suitable Lewis acid, such as $TiCl_4$, in a solvent such as CH_2Cl_2 starting at 0 °C then warming to room temperature. Other amines, Lewis acids, solvents and temperatures may be used as determined by those skilled in the art. The use of benzylamine provides imine **32**, where PG = benzyl. Imine **32** is alkylated with, for example, trimethyl(trifluoromethyl)silane in the presence of a fluoride source such as potassium hydrogen fluoride and TFA, using acetonitrile and DMF. Other fluoride sources, such as tetrabutylammonium difluorotriphenylsilicate or cesium fluoride, other acids such as HOAc or HCl, and other solvents may be employed as determined by those skilled in the art. Use of trimethyl(trifluoromethyl)silane provides amino ester **33**, where $R^2 = CF_3$. Ester hydrolysis of amino ester **33** was done in the presence of lithium iodide in refluxing pyridine to provide amino acid **34**. Use of other hydrolysis conditions known to those skilled in the art may be employed. Cyclization of amino acid **34** to β-lactam **35** was affected by activating the carboxylic acid of amino acid **34** with oxalyl chloride in a suitable solvent such as CH_2Cl_2 containing catalytic DMF. The cyclization occurred spontaneously at room temperature to provide β-lactam **35**. Other methods for activating the carboxylic acid may be employed as determined by those skilled in the art. β-Lactam **35** is arylated using an organometallic reagent. Organometallic reagents may include, for example, Grignard reagents or organolithium reagents, formed from a suitably

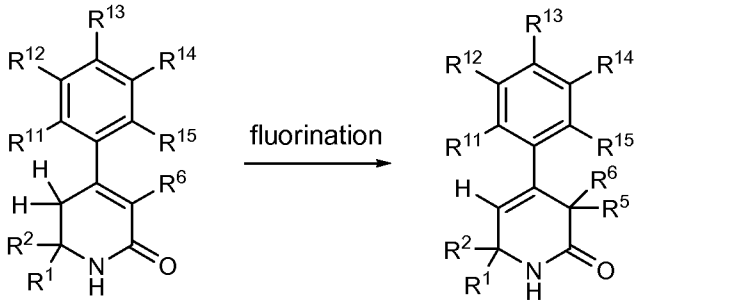
substituted phenyl ring containing a halide atom able to react with either elemental magnesium to form a Grignard reagent or with an alkyl lithium reagent to form an phenyl lithium reagent via transmetallation. Exact conditions required to form these phenyl organometallic species must determined by those skilled in the art. A suitable aprotic solvent is used, for example, THF. Other suitable solvents may be employed as determined by those skilled in the art. The reaction is carried out between room temperature and reflux depending upon the identity of the organometallic reagent employed and the substitution pattern on β-lactam **35**. The β-amino ketone **37** thus formed is deprotected using hydrogen gas and 10% palladium on carbon in a suitable solvent such as methanol containing 4.4% formic acid to provide β-amino ketone **38**. Other conditions to remove the benzyl group may be employed as determined by those skilled in the art. β-Amino ketone **38** is acylated with carboxylic acid **8** using conditions described in Scheme 2 to give the β-keto amide **39**. Stirring β-keto amide **39** with a base such as sodium ethoxide in a suitable solvent such as ethanol at room temperature provides compounds having Formula (I).

Scheme 9



[00213] Compounds of Formula (I), where y is a single bond and R^5 = F may be made according to Scheme 10. This synthesis is exemplified for a compound of Formula (I) where R^6 = CN. Thus, a compound of Formula (I), where x is a single bond and R^6 = CN, was heated to 80 °C in the presence of a fluorinating reagent, 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2,2,2]octane bis(tetrafluoroborate), in a suitable solvent such as DMF in the presence of a base such as Na_2CO_3 to provide compounds of Formula (I), where y is a single bond, R^5 = F and R^6 = CN. Other fluorinating reagents, solvents and bases may be employed as determined by one skilled in the art.

Scheme 10

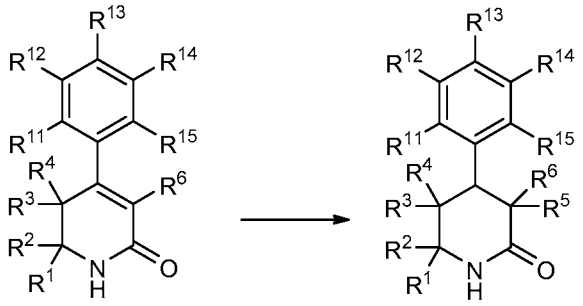


(I): x = single bond

(I): y = single bond
R^6 = F

[00214] Compounds of Formula (I), where x and y are both single bonds and R^5 = H, can be made according to Scheme 11. Reduction of compounds of Formula (I), where x equals a single bond and y equals a double bond, is carried out using a suitable catalyst such as palladium on carbon under an atmosphere of hydrogen gas at suitable pressure, such as 50 psi, to effect reduction of the double bond y to a single bond. Suitable solvents include, but are not restricted to, methanol.

Scheme 11



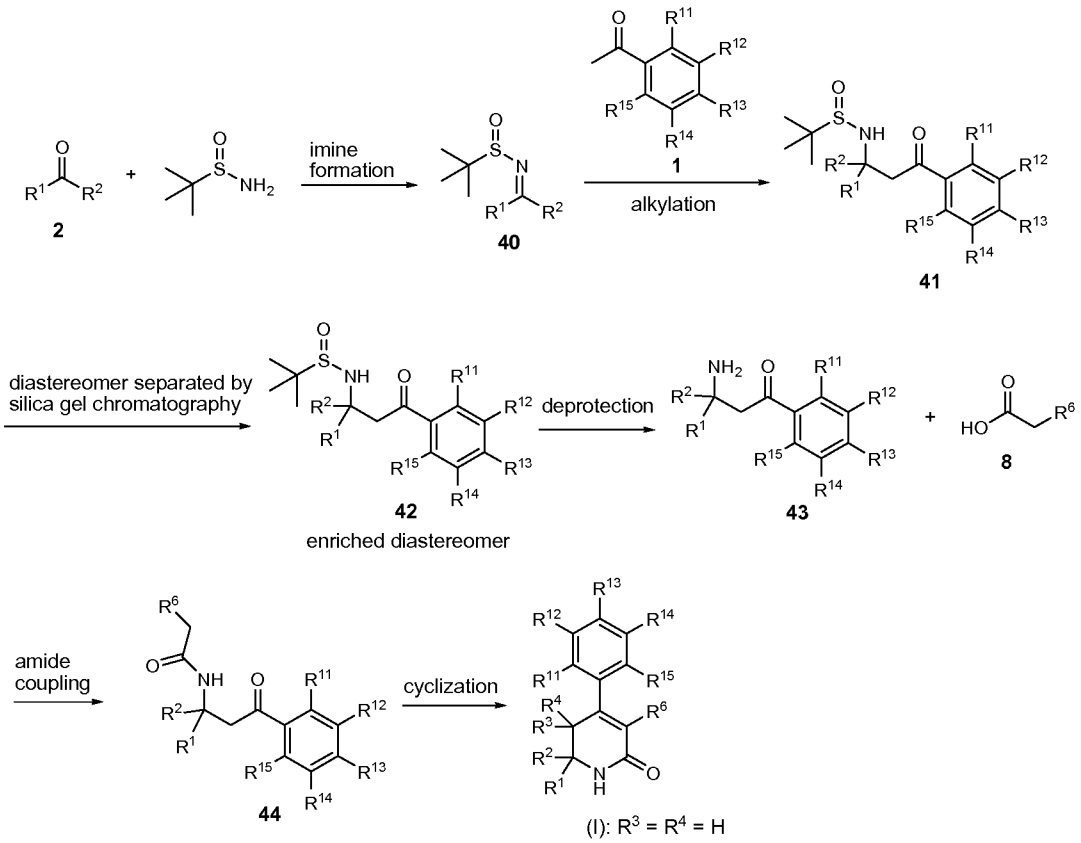
(I): x = single bond
y = double bond

(I): x = y = single bond
R^5 = H

[00215] Compounds of Formula (II), single enantiomer, where R^3 = R^4 =H, can be made according to Scheme 12. Ketone **2** was stirred with 2-methylpropane-2-sulfinamide in the presence of a suitable Lewis acid, such as $Ti(OEt)_4$, in a solvent such as THF at refluxed tempereature provides imine **40**. Other Lewis acids, solvents and temperatures may be used as determined by those skilled in the art. Imine **40** is alkylated with ketone **1**

in the presence of a base, such as LiHMDS, KHMDS, NaHMDS, or LDA in an aprotic solvent such as THF or ether at a temperature ranging from -78 °C to ambient to provide β-amino ketone **41** as a mixture of two diastereomers, which can be separated by silica gel chromatography to give the desired isomer **42**. Other metal enolates (such as titanium enolate), solvents, and temperatures may be used as determined by those skilled in the art (T. P. Tang, J. A Ellman, J. Org. Chem. 1999, 64, 12-13, J. Org. Chem. 2002, 67, 7819-7832). Preferably, chiral *S*- or *R*-2-methylpropane-2-sulfinamide can be optionally used to generate each of the optically pure enantiomers of imine **40** that can allow for chiral induction to prepare diastereomerically enriched ketone **42**. In these cases, the product mixture can be further purified by silica gel chromatography to obtain desired products with diaseteromeric excess of >97%. β-amino ketone **42** thus formed is deprotected using HCl in a suitable solvent such as MeOH to provide β-amino ketone **43**. Other conditions to remove the *t*-butylsulfinyl group may be employed as determined by those skilled in the art. β-Amino ketone **43** is acylated with carboxylic acid **8** using conditions described in Scheme 2 to give the β-keto amide **44**. Stirring β-keto amide **44** with a base such as sodium ethoxide in a suitable solvent such as ethanol at room temperature provides compounds having Formula (II).

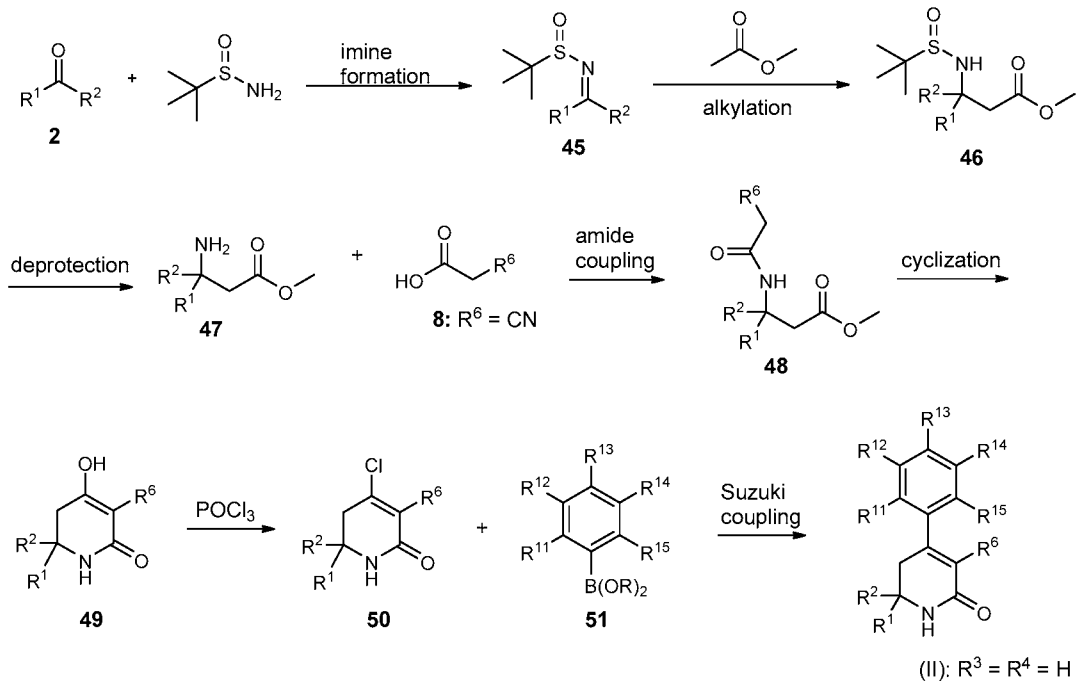
Scheme 12



[00216] Alternatively, compounds of Formula (II), where $R^3 = R^4 = H$, may be made according to Scheme 13. Ketone **2** can be reacted with 2-methylpropane-2-sulfinamide in the presence of a suitable Lewis acid, such as $Ti(OEt)_4$, in a solvent such as THF at a temperature ranging from ambient to reflux to provide imine **45**. Other Lewis acids, solvents and temperatures may be used as determined by those skilled in the art. Imine **45** is alkylated with the enolate of an ester in a suitable aprotic solvent such as THF or ether starting at -78 °C then warming to 0 °C or room temperature to provide protected β-amino ketone **46** as a mixture of two diastereomers, which can be separated by silica gel chromatography to give each individual chiral compound. The generation of the ester enolate is achieved by treating the ester, such as methyl acetate, with a suitable base such as LHMDS, KHMDS, NaHMDS, or LDA in an aprotic solvent such as THF or ether at a temperature ranging from -78 °C to ambient. Other metal enolates (such as titanium enolate), solvents, and temperatures may be used as determined by those skilled in the art (T. P. Tang, J. A Ellman, J. Org. Chem. 1999, 64, 12-13, J. Org. Chem. 2002, 67, 7819-

7832). Preferably, chiral *S*- or *R*-2-methylpropane-2-sulfinamide can be optionally used to generate each of the optically pure enantiomers of imine **45** that can allow for chiral induction to prepare diastereomerically enriched ester **46**. In these cases, the product mixture can be further purified by silica gel chromatography to obtain desired products with diaseteromeric excess of >97%. The tert-butyl sulfinyl group of **46** is removed using acids such as HCl and TFA in a suitable solvent such as MeOH or dioxane to generate amino ester **47**. Other conditions to remove the *t*-butylsulfinyl group may be employed as determined by those skilled in the art. β-Amino ketone **47** is acylated with carboxylic acid **8** using conditions described in Scheme 2 to give the β-keto amide **48**. Stirring β-keto amide **48** with a base such as sodium ethoxide in a suitable solvent such as ethanol at room temperature to 80 °C provides cyclic enol **49**. Other conditions can also by used to effect the cyclization as determined by those skilled in the art. Compound **49**, when treated with stoichiometric amount of a chlorinating agent, such as $POCl_3$, at elevated temperature in an inert solvent such as toluene, is converted to mono-chloride **50**. Chloride **50** can then react with various boronic reagents through a Suzuki-type of cross coupling reaction to generate compounds of Formula (II). The choices of boronic reagents, catalysts, ligands, bases, solvents and temperatures are well documented in the literature and can be selected appropriately by those skilled in the art.

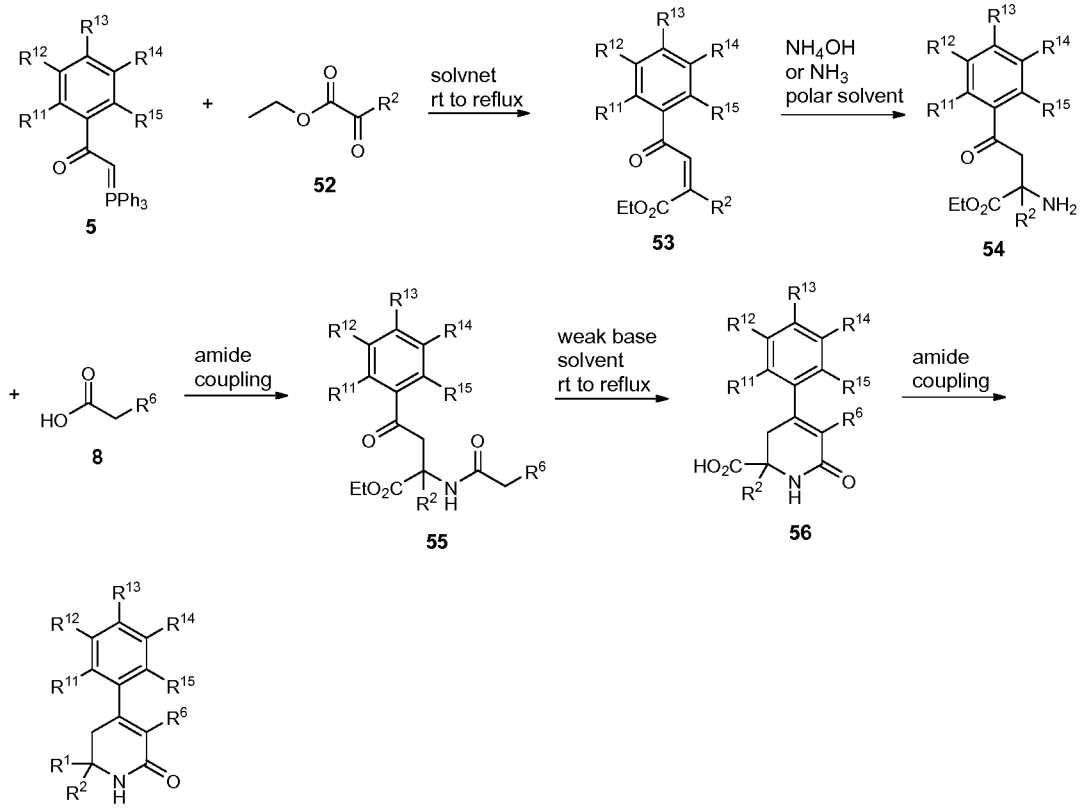
Scheme 13



[00217] Compounds of Formula (II), where $R^3 = R^4 = H$ and $R^1 = CONHC_{4\text{-}18}$ alkyl or $CONH(CH_2)_{1\text{-}8}Ph$ can be made according to Scheme 14. The phosphorous ylide **5** is heated, using microwave irradiation, to 150 °C with α-ketoester **52** in a suitable solvent such as THF or DMSO to give α,β-unsat'd ketone **53**. α,β-Unsat'd ketone **53** is treated with concentrated aq NH_4OH in a solvent such as DMSO in a sealed vessel to provide amine **54**. Alternatively, alkene **53** may be treated with NH_3 in a solvent such as DMSO or DMSO and methanol in a sealed vessel to provide amine **54**. Amine **54** is couple with carboxylic acid **8** using a variety of amide bond forming reactions. For example, carboxylic acid **8** may be converted to the corresponding acid chloride using oxalyl chloride in a solvent such as CH_2Cl_2 and catalytic DMF. Alternatively, the carboxylic acid **8** may be activated using 1-chloro-N,N,2-trimethylprop-en-1-amine in a suitable solvent such as CH_2Cl_2. The acid chlorides thus formed are combined with amine **54** in a suitable solvent such as CH_2Cl_2 or CH_2Cl_2 and DMF in the presence of a base, preferably pyridine. Other amide bond forming reaction known to those skilled in the art may be employed. Cyclization of amide **55** and susequent hydrolysis to a the carboxylic acid **56** typically occurs by stirring amide **55** in the presence of a weak base such as

piperidine in a suitable solvent such as EtOH at a temperature between room temperature and reflux or a base such as litium hydroxide in a suitable solvent such as THF and water at room temperature. Alternatively, when R^6 is a nitrile, cyclization of amide **55** typically occurs by stirring amide **55** in the presence of a base such as lithium hydroxide in a suitable solvent such as THF and water at room temperature. Hydrolysis is then carried out under acidic conditions using a strong acid such as HCl in a suitable solvent such as acetic acid at temperatures between room temperature and 50 °C. Carboxylic acid **56** and an amine are coupled together using standard amide bond forming conditions. For example, treatment of carboxylic acid **56** and an amine with HOBt, EDC and DIEA in the presence of pyridine in a suitable solvent such as DCM at room temperature provides compounds having Formula (II). Other amide bond forming reaction known to those skilled in the art may be employed.

Scheme 14

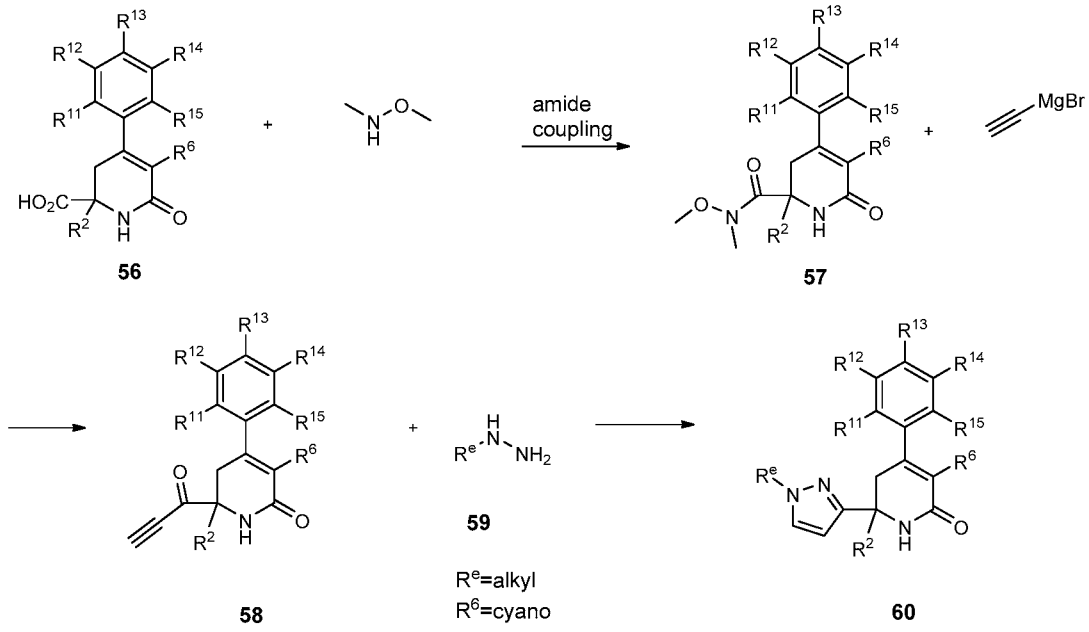


(II): R^1 = $CONHC_{4\text{-}18}$ alkyl, $CONH(CH_2)_{2\text{-}8}Ph$

$R^3 = R^4 = H$

[00218] Compounds of formula **60** having R^e = alkyl and R^6 = cyano can be synthesized by coupling acid **56** with N, O-dimethylhydroxylamine using typical amide bond forming reactions. For example, carboxylic acid **56** is coupled to N, O-dimethylhydroxylamine using EDC in the presence of base, preferably N-methylmopholine, in a suitable solvent, such as CH_2Cl_2, to provide the Weinreb amide **57**. Other amide forming reactions known to those skilled in the art may also be employed. The intermediate Weinreb amide **57** is reacted with ethynylmagnesium bromide in an aprotic solvent such as THF at 0-35 °C to provide the acylacetylide intermediate **58**. Compounds of formula **60** are obtained when acylacetylide intermediate **58** is reacted with hydrazine **59** in the presence of a base such as TEA in a suitable solvent such as EtOH.

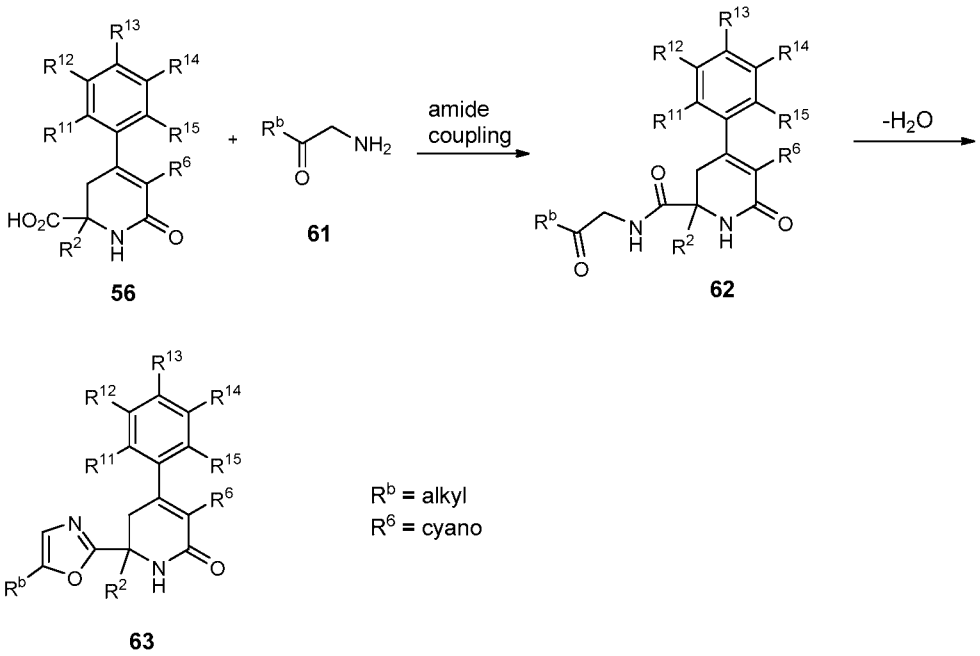
Scheme 15



[00219] Compounds of formula **63** having R^b = alkyl and R^6 = cyano can be synthesized by first coupling acid **56** with β–ketoamine **61** using typical amide bond forming reactions. For example, carboxylic acid **56** is coupled to α–ketoamine **61** using EDC and HOBt in the presence of base, preferably DIEA, in a suitable solvent, such as CH_2Cl_2, to provide β-ketoamide **62**. Other amide forming reactions known to those skilled in the art may also be employed. 5-Alkyl substituted oxazole **63** is then obtained

via the dehydrative cyclization of β-ketoamide **62** using a dehydrating agent, preferably $POCl_3$, in the presence of a suitable base, such as DIEA, in a suitable solvent such as dichloroethane at a temperature of 80-120 °C.

Scheme 16



56 61 62 63

IV. BIOLOGY

[00220] In mammals, there are two triglyceride synthesis pathways: glycerol-3-phosphate pathway and monoacylglycerol pathway. The former is mainly responsible for energy storage in the peripheral tissues such as fat, liver, skeletal muscle; the latter is essential for the dietary fat absorption which takes place in the small intestine. When dietary fat is ingested, pancreatic lipase digests triglycerides into free fatty acids and 2-monoacylglycerol, which are absorbed by intestinal epithelial enterocytes. Once inside enterocytes, free fatty acids and 2-monoacylglycerol are used as building blocks to resynthesize triglycerides by two sequential acylation steps; first by MGAT and then by DGAT enzyme reactions. Triglycerides are then incorporated into chylomicrons and secreted into lymph to be utilized as an energy supply for the body.

[00221] Monoacylglycerol acyltransferase 2 (MGAT2) is a membrane bound acyltransferase that belongs to diacylglycerol acyltransferase 2 (DGAT2) gene family. It

is highly and selectively expressed in the small intestine. Genetic deletion of MGAT2 in mice decreased the rate of absorption for the orally ingested triglycerides, indicating that MGAT2 plays an important role for the intestinal MGAT/DGAT pathway [Yen, C.L. et al, *Nat. Med.*, 15(4):442-446 (2009); Okawa, M. et al., *Biochem. Biophys. Res. Commun.*, 390(3):377-381 (2009)]. When chronically challenged with a high fat diet, in contrast to wild type mice that became obese, MGAT2 knockout mice resisted the impact of high-fat feeding and demonstrated with a lower body weight, less adiposity, and less hepatic fat accumulation. In contrast to hyperinsulinemic wild type mice after high-fat challenge, MGAT2 deletion normalizes the insulin level and decreased fasting glucose. In the glucose tolerance test, they also had an improved glucose excursion. Consistent with their improved glycemic profile, MGAT2 knockout mice also had an increased level of GLP1, an incretin gut hormone that profoundly impacts glucose metabolism[Yen, C.L. et al., *Nat. Med.*, 15(4):442-446 (2009)]. Taken together, it is expected that inhibition of MGAT2 through pharmacological intervention would provide the same benefit as demonstrated in the knock-out mice, *e.g.*, resistance to weight gain, or conversely, reduction in fat body mass. In addition, MGAT2 inhibition would lead to an improved insulin sensitivity and glucose metabolism which either leads to a decrease in the incidence of Type II diabetes, or a treatment of diabetic condition.

[00222] It is also desirable and preferable to find compounds with advantageous and improved characteristics compared with known anti-diabetic agents, in one or more of the following categories that are given as examples, and are not intended to be limiting: (a) pharmacokinetic properties, including oral bioavailability, half life, and clearance; (b) pharmaceutical properties; (c) dosage requirements; (d) factors that decrease blood drug concentration peak-to-trough characteristics; (e) factors that increase the concentration of active drug at the receptor; (f) factors that decrease the liability for clinical drug-drug interactions; (g) factors that decrease the potential for adverse side-effects, including selectivity versus other biological targets; and (h) improved therapeutic index with less propensity for hypoglycemia.

[00223] As used herein, the term "patient" encompasses all mammalian species.

[00224] As used herein, the term "subject" refers to any human or non-human organism that could potentially benefit from treatment with a MGAT2 inhibitor. Exemplary subjects include human beings of any age with risk factors for metabolic

disease. Common risk factors include, but are not limited to, age, sex, weight, family history, or signs of insulin resistance such as acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovary syndrome (PCOS).

[00225] As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) inhibiting the disease-state, *i.e.*, arresting it development; and/or (b) relieving the disease-state, *i.e.*, causing regression of the disease state.

[00226] As used herein, "prophylaxis" or "prevention" cover the preventive treatment of a subclinical disease-state in a mammal, particularly in a human, aimed at reducing the probability of the occurrence of a clinical disease-state. Patients are selected for preventative therapy based on factors that are known to increase risk of suffering a clinical disease state compared to the general population. "Prophylaxis" therapies can be divided into (a) primary prevention and (b) secondary prevention. Primary prevention is defined as treatment in a subject that has not yet presented with a clinical disease state, whereas secondary prevention is defined as preventing a second occurrence of the same or similar clinical disease state.

[00227] As used herein, "risk reduction" covers therapies that lower the incidence of development of a clinical disease state. As such, primary and secondary prevention therapies are examples of risk reduction.

[00228] "Therapeutically effective amount" is intended to include an amount of a compound of the present invention that is effective when administered alone or in combination to inhibit MGAT2 and/or to prevent or treat the disorders listed herein. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the preventive or therapeutic effect, whether administered in combination, serially, or simultaneously.

A. ASSAY METHODS

MGAT SPA Assay

[00229] MGAT2 enzyme was assayed using membranes isolated from Sf9 cells expressing the recombinant human MGAT2 cDNA with 2-monooleoylglycerol and [^{3}H]-oleoyl-CoA as substrates as described by Seethala et al. [*Anal. Biochem.*, 383(2):144-150 (Dec. 15, 2008)]. Briefly, the assays were conducted in 384-well plates in a total volume

of 30 µL at 25 °C. In each assay, 200 ng of recombinant human MGAT2 membrane was incubated with 10 µM of 2-monooleoylglycerol and 15 µM of [^{3}H]-oleoyl-CoA in 100 mM potassium phosphate (pH 7.4) for 20 min with various concentrations of compounds delivered in DMSO. The assay was terminated by the addition of 20 µl of Stopping Solution (7.5 mg/ml Yittrium Oxide Polylysine beads, 3.3 mg/ml Fraction V BSA and 200 µM Mercuric chloride in 50 mM HEPES, pH 7.4). The signal was measured 1 h after quenching the reaction using LEADSEEKER^{SM} for 5 minutes. To calculate the degree of inhibition, the zero level of enzyme activity (blank) was defined by the above assay procedure using membrane form Sf9 cell uninfected with baculovirus (Naive) and the 100% level of MGAT2 enzyme activity was defined by human MGAT2 assay with the vehicle DMSO. The IC_{50}s of inhibitors were determined by logistic 4 parameter equation in XL-fit.

MGAT LCMS Assay

[00230] The MGAT enzyme reactions were performed in CORNING® Falcon 96-well Polypropylene plates, in a total volume of 60 µL of 50 mM Potassium Phosphate buffer pH 7.4, containing a final concentration of 100 µM 2-oleoylglycerol, 15 µM oleoyl-Coenzyme A and 0.0013 µg/µL Human or Mouse MGAT-2 or 0.0026 µg/µL Rat recombinant MGAT-2 membranes expressed in Sf9 cells. Assay plates were run through a fully automated robotics system and shaken for 5 seconds every minute for a total 10 minutes. The reactions were then quenched with 120 µL of ice cold methanol containing 1 µg/mL 1,2-distearoyl-*rac*-glycerol as the internal standard. Plates were shaken for 2 minutes and spun down to remove protein precipitation. After the spin, samples were transferred to LC/MS compatible PCR plates. For LC/MS analysis, a ThermoFisher Surveyor pump, utilizing a Waters Symmetry C8, 50 x 2.1 mm column, was used for the chromatography of enzyme products. The buffer system consists of 0.1% formic acid in water with a mobile phase consisting 0.1% formic acid in methanol. The shallow gradient is 90-100% mobile phase in 0.2 min with a total run time of 2.3 min. The first 0.5 minutes of each injection was diverted to waste to eliminate the presence of Phosphate buffer in the enzymatic reaction. The column was run at 0.6 mL/min and a temperature of 65 °C. Mass spectrometry analysis of the samples was performed on a ThermoFisher Quantum Triple quad utilizing APCI (+) as the mode of ionization. Data

was acquired in Single Ion Monitoring (SIM) mode analyzing Diolein =*m/z* 603.6 (PRODUCT) and 1,2- distearoyl-*rac*-glycerol (IS)= *m/z* 607.6. The ratio of Diolein to internal standard (Peak Area Ratio) is utilized to calculate IC_{50} values.

[00231] The exemplified Examples disclosed below were tested in the MGAT2 *in vitro* assays described above and were found having MGAT2 inhibitory activity. Table 1 below lists human MGAT2 IC_{50} values measured for the following examples. "NT" denotes "Not tested".

Table 1

Example No.	h-MGAT2 IC_{50} (nM)	
	SPA Assay	LCMS Assay
1	651	2049
2	85	5
2-1	35	8
2-2	1400	261
3	1804	NT
4	5871	NT
5	309	21
6	15	7
6-1	1435	NT
6-2	14	2
7	818	NT
8	NT	7
9	33330	121
10	2716	138
11	48	13
12	NT	374
13	3333	35
14	NT	2050
15-1	3306	12

15-2	33330	431
15-3	33330	756
15-4	33330	2049
16-1	25	7
16-2	8430	416
17	1931	NT
18	5762	NT
19	2905	NT
20	3456	NT
21	913	NT
22	801	NT
23	1292	NT
24	1731	NT
25	4569	NT
26	6428	NT
27	2519	NT
28	564	NT
29	7602	NT
30	774	NT
31	1510	NT
32	9956	NT
33	167	12
34	656	126
35	5199	13
36	396	57
37	263	15
38	2143	NT
39	401	20
40	2546	164
41	170	15
42	403	77
43	5387	60

44	1458	NT
45	569	NT
46	871	NT
47	756	NT
48	226	7
49	127	64
50	242	95
51	63	13
52	477	99
53	111	3
54	258	20
55	846	20
56	6550	NA
57	412	16
58	275	29
59	53	4
60	441	12
61	709	NT
62	156	24
63	116	28
64	761	280
65	96	3
66	731	265
67	1935	253
68	7523	1282
69	9230	983
70	3404	NA
71	2931	1917
72	3519	214
73	684	15
74	2476	697
75	873	209

76	5073	370
77	89	27
78	151	4
79	1856	45
80	310	5
81	55	4
82	133	2
83	89	1
84	115	2
85	1465	7
86	201	1
87	NT	1215
88	28	5
89	731	20
90	815	18
91	916	2
92	NT	136
93	37	30
94	32	4
95	95	43
96	NT	1431
97	NT	1199
98	154	69
99	NT	795
100	NT	1575
101	379	108
102	NT	1088
103	NT	645
104	NT	103
105	672	24
106	NT	552
107	NT	93

108	NT	189
109	NT	39
110	11	5
111	9	7
112	1297	204
113	158	8
114	NT	704
115	NT	40
116	48	4
117	22	18
118	32	4
119	94	21
120	58	6
121	231	20
122	14	1
123	743	5
124	4264	55
125	NT	282
126	1874	33
127	655	10
128	NT	328
129	NT	222
130	20	1
131	NT	1050
132	NT	163
133	1518	127
134	NT	168
135	NT	778
136	NT	328
137	NT	252
138	NT	5799
140	NT	356

141	NT	459
142	93	10
143	156	4
144	175	16
145	130	25
146	397	25
147	91	14
148	102	9
149	53	6
150	11	3
151	NT	5115
152	NT	252
153	NT	247
154	34	8
155	NT	484
156	NT	254
157	168	84
158	302	75
159	NT	16710
160	NT	5401
161	NT	1261
162	NT	214
163	1176	47
164	NT	162
165	60	8
166	237	102
167	8	2
168	NT	113
169	NT	421
170	NT	210
171	724	57
172	16	3

173	43	63
174	237	60
175	NT	264
176	NT	3
177	NT	399
178	47	78
179	24	2
180	36	30
181	NT	2049
182	NT	2049
183	NT	50
184	NT	76
185	NT	121
186	NT	229
187	NT	4
188	NT	1524
189	NT	1159
190	NT	155
191	NT	797
192	NT	433
193	NT	46
194	NT	6
195	NT	33
196	NT	826
197	NT	178
198	NT	16
199	NT	16
200	NT	37
201	NT	24
202	NT	89
203	NT	59
204	NT	41

205	NT	13
206	NT	78
207	NT	11
208	NT	30
209	NT	37
210	NT	2
211	NT	97
212	NT	416
213	NT	1096
214	NT	12
215	NT	11
216	NT	440
217	NT	118
218	NT	166
219	NT	172
220	NT	13
221	NT	152
222	NT	733
223	NT	112
224	NT	414
225	NT	889
226	NT	206
227	NT	63
228	NT	7
229	NT	25
230	NT	1532
231	NT	34
232	NT	6
233	NT	639
234	NT	40
235	NT	22
236	NT	489

237	NT	130
238	NT	7
239	NT	15
240	NT	7
242	NT	44
243	NT	14
244	NT	61
245	NT	46
246	NT	36
247	NT	51
248	NT	8
249	NT	185
250	NT	243
251	NT	3
252	NT	7
253	NT	411
254	NT	170
255	NT	702
256	NT	22
257	NT	421
258	NT	1147
259	NT	15
260	NT	56
261	NT	1222
262	NT	96
263	NT	103
264	NT	46
265	NT	40
266	NT	10
267	NT	796
268	NT	8
269	NT	171

270	NT	407
271	NT	12
272	NT	112
273	21	10
274	NT	1
275	NT	2
276	NT	2
277	NT	2
278	NT	2
279	NT	2
280	NT	2
281	NT	3
282	NT	3
283	NT	3
284	NT	4
285	NT	4
286	NT	4
287	NT	13
288	NT	19
289	NT	19
290	NT	56
291	NT	178
292	NT	304
293	NT	7
294	NT	84
295	NT	183
296	NT	2
297	NT	639
298	NT	2
299	NT	11
300	NT	11
301	NT	19

302	NT	105
303	NT	28
304	NT	6
305	NT	94
306	NT	3
307	NT	3
308	NT	61
309	NT	1
310	NT	4
311	NT	3
312	NT	21
313	NT	4
314	NT	109

[00232] The compounds of the present invention possess activity as inhibitors of MGAT2, and, therefore, may be used in the treatment of diseases associated with MGAT2 activity. Via modulation of MGAT2, the compounds of the present invention may preferably be employed to modulate, either enhance or decrease the production/secretion of insulin and/or gut hormones, such as GLP1, GIP, CCK, PYY, PP, Amylin.

[00233] Accordingly, the compounds of the present invention can be administered to mammals, preferably humans, for the treatment of a variety of conditions and disorders, including, but not limited to, treating, preventing, or slowing the progression of diabetes and related conditions, microvascular complications associated with diabetes, macrovascular complications associated with diabetes, cardiovascular diseases, Metabolic Syndrome and its component conditions, inflammatory diseases and other maladies. Consequently, it is believed that the compounds of the present invention may be used in preventing, inhibiting, or treating diabetes, hyperglycemia, impaired glucose tolerance, gestational diabetes, insulin resistance, hyperinsulinemia, retinopathy, neuropathy, nephropathy, wound healing, atherosclerosis and its sequelae (acute coronary syndrome, myocardial infarction, angina pectoris, peripheral vascular disease, intermittent claudication, myocardial ischemia, stroke, heart failure), Metabolic Syndrome,

hypertension, obesity, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, high LDL, lipid disorders, PCOS, and glaucoma.

[00234] Metabolic Syndrome or "Syndrome X" is described in Ford et al., *J. Am. Med. Assoc.,* 287:356-359 (2002) and Arbeeny et al., *Curr. Med. Chem. - Imm., Endoc. & Metab. Agents,* 1:1-24 (2001).

V. PHARMACEUTICAL COMPOSITIONS, FORMULATIONS AND COMBINATIONS

[00235] The compounds of this invention can be administered for any of the uses described herein by any suitable means, for example, orally, such as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions (including nanosuspensions, microsuspensions, spray-dried dispersions), syrups, and emulsions; sublingually; bucally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection, or infusion techniques (*e.g.*, as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally, including administration to the nasal membranes, such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

[00236] The term "pharmaceutical composition" means a composition comprising a compound of the invention in combination with at least one additional pharmaceutically acceptable carrier. A "pharmaceutically acceptable carrier" refers to media generally accepted in the art for the delivery of biologically active agents to animals, in particular, mammals, including, *i.e.*, adjuvant, excipient or vehicle, such as diluents, preserving agents, fillers, flow regulating agents, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispensing agents, depending on the nature of the mode of administration and dosage forms.

[00237] Pharmaceutically acceptable carriers are formulated according to a number of factors well within the purview of those of ordinary skill in the art. These include, without limitation: the type and nature of the active agent being formulated; the subject to

which the agent-containing composition is to be administered; the intended route of administration of the composition; and the therapeutic indication being targeted. Pharmaceutically acceptable carriers include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi-solid dosage forms. Such carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in the formulation for a variety of reasons, *e.g.*, stabilization of the active agent, binders, etc., well known to those of ordinary skill in the art. Descriptions of suitable pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources such as, for example, Allen, L. V. Jr. *et al. Remington: The Science and Practice of Pharmacy (2 Volumes)*, 22nd Edition (2012), Pharmaceutical Press.

[00238] The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired.

[00239] By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to about 5000 mg per day, preferably between about 0.01 to about 1000 mg per day, and most preferably between about 0.1 to about 250 mg per day. Intravenously, the most preferred doses will range from about 0.01 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

[00240] The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, *e.g.*, oral tablets, capsules, elixirs, and syrups, and consistent with conventional pharmaceutical practices.

[00241] Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 2000 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be

present in an amount of about 0.1-95% by weight based on the total weight of the composition.

[00242] A typical capsule for oral administration contains at least one of the compounds of the present invention (250 mg), lactose (75 mg), and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule.

[00243] A typical injectable preparation is produced by aseptically placing at least one of the compounds of the present invention (250 mg) into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of physiological saline, to produce an injectable preparation.

[00244] The present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, a therapeutically effective amount of at least one of the compounds of the present invention, alone or in combination with a pharmaceutical carrier. Optionally, compounds of the present invention can be used alone, in combination with other compounds of the invention, or in combination with one or more other therapeutic agent(s), *e.g.*, an antidiabetic agent or other pharmaceutically active material.

[00245] The compounds of the present invention may be employed in combination with other MGAT2 inhibitors or one or more other suitable therapeutic agents useful in the treatment of the aforementioned disorders including: anti-diabetic agents, anti-hyperglycemic agents, anti-hyperinsulinemic agents, anti-retinopathic agents, anti-neuropathic agents, anti-nephropathic agents, anti-atherosclerotic agents, anti-ischemic agents, anti-hypertensive agents, anti-obesity agents, anti-dyslipidemic agents, anti-dyslipidemic agents, anti-hyperlipidemic agents, anti-hypertriglyceridemic agents, anti-hypercholesterolemic agents, anti-restenotic agents, anti-pancreatic agents, lipid lowering agents, anorectic agents, memory enhancing agents, anti-dementia agents, or cognition promoting agents, appetite suppressants, treatments for heart failure, treatments for peripheral arterial disease and anti-inflammatory agents.

[00246] Where desired, the compound of the present invention may be used in combination with one or more other types of antidiabetic agents and/or one or more other types of therapeutic agents which may be administered orally in the same dosage form, in a separate oral dosage form or by injection. The other type of antidiabetic agent that may

be optionally employed in combination with the MGAT2 inhibitor of the present invention may be one, two, three or more antidiabetic agents or antihyperglycemic agents which may be administered orally in the same dosage form, in a separate oral dosage form, or by injection to produce an additional pharmacological benefit.

[00247] The antidiabetic agents used in the combination with the compound of the present invention include, but are not limited to, insulin secretagogues or insulin sensitizers, other MGAT2 inhibitors, or other antidiabetic agents. These agents include, but are not limited to, dipeptidyl peptidase IV (DP4) inhibitors (for example, sitagliptin, saxagliptin, alogliptin, vildagliptin and the like), biguanides (for example, metformin, phenformin and the like), sulfonyl ureas (for example, glyburide, glimepiride, glipizide and the like), glucosidase inhibitors (for example, acarbose, miglitol, and the like), PPARγ agonists such as thiazolidinediones (for example, rosiglitazone, pioglitazone, and the like), PPAR α/γ dual agonists (for example, muraglitazar, tesaglitazar, aleglitazar, and the like), glucokinase activators (as described in Fyfe, M.C.T. et al., *Drugs of the Future*, 34(8):641-653 (2009) and incorporated herein by reference), GPR40 receptor modulators, GPR119 receptor modulators (MBX-2952, PSN821, APD597 and the like), SGLT2 inhibitors (dapagliflozin, canagliflozin, remagliflozin and the like), amylin analogs such as pramlintide, and/or insulin. Reviews of current and emerging therapies for the treatment of diabetes can be found in: Mohler, M.L. et al., *Medicinal Research Reviews*, 29(1):125-195 (2009), and Mizuno, C.S. et al., *Current Medicinal Chemistry*, 15:61-74 (2008).

[00248] The compounds of the present invention may also be optionally employed in combination with agents for treating complication of diabetes. These agents include PKC inhibitors and/or AGE inhibitors.

[00249] The compounds of the present invention may also be optionally employed in combination with one or more hypophagic agents such as diethylpropion, phendimetrazine, phentermine, orlistat, sibutramine, lorcaserin, pramlintide, topiramate, MCHR1 receptor antagonists, oxyntomodulin, naltrexone, Amylin peptide, NPY Y5 receptor modulators, NPY Y2 receptor modulators, NPY Y4 receptor modulators, cetilistat, 5HT2c receptor modulators, and the like. The compound of structure I may also be employed in combination with an agonist of the glucagon-like peptide-1 receptor (GLP-1 R), such as exenatide, liraglutide, GPR-1(1-36) amide, GLP-1(7-36) amide,

GLP-1(7-37) (as disclosed in U.S. Patent No. 5,614,492 to Habener, the disclosure of which is incorporated herein by reference), which may be administered via injection, intranasal, or by transdermal or buccal devices. Reviews of current and emerging therapies for the treatment of obesity can be found in: Melnikova, I. et al., *Nature Reviews Drug Discovery*, 5:369-370 (2006); Jones, D., *Nature Reviews: Drug Discovery*, 8:833-834 (2009); Obici, S., *Endocrinology*, 150(6):2512-2517 (2009); and Elangbam, C.S., *Vet. Pathol.*, 46(1):10-24 (2009).

[00250] The compounds of the present invention may also be optionally employed in combination with one or more other types of therapeutic agents, such as DGAT inhibitors, LDL lowering drugs such as statins (inhibitors of HMG CoA reductase) or inhibitors of cholesterol absorption, modulators of PCSK9, drugs increase HDL such as CETP inhibitors.

[00251] The above other therapeutic agents, when employed in combination with the compounds of the present invention may be used, for example, in those amounts indicated in the *Physicians' Desk Reference*, as in the patents set out above, or as otherwise determined by one of ordinary skill in the art.

[00252] Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of the present invention and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material that affects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer,

and the other component is also coated with a polymer such as a low viscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

[00253] These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

[00254] The compounds of the present invention can be administered alone or in combination with one or more additional therapeutic agents. By "administered in combination" or "combination therapy" it is meant that the compound of the present invention and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination, each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect.

[00255] The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the MGAT2 enzyme. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving MGAT2 or anti-diabetic activity. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an unknown activity. This would ensure the experimentor that the assay was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness.

[00256] The compounds of the present invention may also be used in diagnostic assays involving MGAT2.

[00257] The present invention also encompasses an article of manufacture. As used herein, article of manufacture is intended to include, but not be limited to, kits and packages. The article of manufacture of the present invention, comprises: (a) a first container; (b) a pharmaceutical composition located within the first container, wherein

the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention or a pharmaceutically acceptable salt form thereof; and, (c) a package insert stating that the pharmaceutical composition can be used for the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2 (as defined previously). In another embodiment, the package insert states that the pharmaceutical composition can be used in combination (as defined previously) with a second therapeutic agent for the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2. The article of manufacture can further comprise: (d) a second container, wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container. Located within the first and second containers means that the respective container holds the item within its boundaries.

[00258] The first container is a receptacle used to hold a pharmaceutical composition. This container can be for manufacturing, storing, shipping, and/or individual/bulk selling. First container is intended to cover a bottle, jar, vial, flask, syringe, tube (*e.g.*, for a cream preparation), or any other container used to manufacture, hold, store, or distribute a pharmaceutical product.

[00259] The second container is one used to hold the first container and, optionally, the package insert. Examples of the second container include, but are not limited to, boxes (*e.g.*, cardboard or plastic), crates, cartons, bags (*e.g.*, paper or plastic bags), pouches, and sacks. The package insert can be physically attached to the outside of the first container via tape, glue, staple, or another method of attachment, or it can rest inside the second container without any physical means of attachment to the first container. Alternatively, the package insert is located on the outside of the second container. When located on the outside of the second container, it is preferable that the package insert is physically attached via tape, glue, staple, or another method of attachment. Alternatively, it can be adjacent to or touching the outside of the second container without being physically attached.

[00260] The package insert is a label, tag, marker, etc. that recites information relating to the pharmaceutical composition located within the first container. The information recited will usually be determined by the regulatory agency governing the area in which the article of manufacture is to be sold (*e.g.*, the United States Food and Drug

Administration). Preferably, the package insert specifically recites the indications for which the pharmaceutical composition has been approved. The package insert may be made of any material on which a person can read information contained therein or thereon. Preferably, the package insert is a printable material (*e.g.*, paper, plastic, cardboard, foil, adhesive-backed paper or plastic, etc.) on which the desired information has been formed (*e.g.*, printed or applied).

[00261] Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

VI. EXAMPLES

[00262] The following Examples are offered as illustrative, as a partial scope and particular embodiments of the invention and are not meant to be limiting of the scope of the invention. Abbreviations and chemical symbols have their usual and customary meanings unless otherwise indicated. Unless otherwise indicated, the compounds described herein have been prepared, isolated and characterized using the schemes and other methods disclosed herein or may be prepared using the same.

HPLC/MS, PREPARATORY/ANALYTICAL HPLC, AND CHIRAL SEPARATION METHODS EMPLOYED IN CHARACTERIZATION OR PURIFICATION OF EXAMPLES

[00263] Analytical HPLC/MS (unless otherwise noted) was performed on Shimadzu SCL-10A liquid chromatographs and Waters MICROMASS® ZQ Mass Spectrometers (Desolvation Gas: Nitrogen; Desolvation Temp. 250 °C; Ion Source Temp: 120 °C; Positive Electrospray conditions) using the following methods:

Linear Gradient of 0% to100% solvent B over 2 min, with 1 minute hold at 100% B, or

Linear Gradient of 0% to100% solvent B over 4 min, with 1 minute hold at 100% B; UV visualization at 220 nm;

Column: PHENOMENEX® Luna C18 (2) 30mm × 4.6 mm; 5μ particle (heated to Temp. 40 °C);

Flow rate: 1.0 mL/min (2 min gradient) or 0.8 ml/min (4 min gradient);

Solvent A: 10% ACN, 90% water, 0.1% TFA; or, 10% MeOH, 90% water, 0.1% TFA and

Solvent B: 90% ACN, 10% water, 0.1% TFA; or, 90% MeOH, 10% water, 0.1% TFA.

[00264] Preparatory HPLC (unless otherwise noted) was performed on a Shimadzu SCL-10A liquid chromatograph with a linear gradient of 20-100% Solvent B over 10 to 30 min, with either a 2 to 5 min hold at 100% Solvent B as determined by on skilled in the art;

UV visualization at 220 nm;

Column: PHENOMENEX® Luna Axia 5μ C18 30 × 100 mm;

Flow rate: 20 mL/min;

Solvent A: 10% ACN, 90% water, 0.1% TFA; or 10% MeOH, 90% water, 0.1% TFA; and

Solvent B: 90% ACN, 10% water, 0.1% TFA; or 90% MeOH, 10% water, 0.1% TFA.

[00265] Preparatory chiral SFC chromatography (unless otherwise noted) was performed on a Berger Multigram II SFC chromatograph using one of the following methods:

Preparative chiral SFC method A:

Column: CHIRALCEL® OD-H, 30 × 250mm ID, 5 μ

Flow rate: 90 mL/min, 100 bar BP, 40 °C

Mobile Phase: 15% Methanol /85% CO_2

Detector Wavelength: 254 nm

Injection Vol and Sample Solution: 0.5 mL of 4.65 g in 35 mL Methanol (133 mg/mL)

Preparative chiral SFC method B:

Instrument: Berger SFC MGII (HPW-2501)

Column: CHIRALPAK® IA 25 × 3 cm ID, 5 μm

Flow rate: 85.0 mL/min

Mobile Phase: 85/15/0.1,CO_2/IPA/DEA, 150 bar

Detector Wavelength: 225 nm (Lamda max)

Sample Prep and Inj. Volume: 300 µL of ~13 mg / 0.5 mL IPA (~26 mg/mL)
Preparative chiral SFC method C
Column: CHIRALPAK® IA 25 × 3 cm ID, 5 µm
Flow rate: 90 mL/min
Mobile Phase: 85/15/0.1,CO_2/MeOH/DEA, 150 bar
Detector Wavelength: 270 nm (Lambda max)
Sample Prep and Inj. Volume: 300 µL of ~90 mg / 2 mL MeOH (~45 mg/mL)
Preparative chiral SFC method D
Flow rate: 40 mL/min, 100 Bar, 35 °C
Mobile Phase: 20% Methanol/80% CO_2
Detector Wavelength: 224 nm (Lambda max)
Injection Volume: 300 µL
Sample Preparation: 10 mg dissolved in 0.5 mL MeCN (20 mg/mL);
17 mg dissolved in 0.5 mL MeCN (34 mg/mL)

[00266] Analytical chiral SFC chromatography (unless otherwise noted) was performed on an Aurora Analytical SFC or Berger Analytical SFC using one of the following methods:

Analytical chiral SFC method A:
Column: CHIRALCEL® OD-H, 4.6 × 250mm ID, 5 µm
Flow rate: 3.0 mL/min, 100 bar BP, 35 °C.
Mobile Phase: 15% Methanol/85% CO_2
Detector Wavelength: 220 nm
Sample Solution: 1 mg/mL in methanol (concentrated/reconstituted)
Injection Volume: 10 µL
Analytical chiral SFC method B:
Column: CHIRALPAK® IA 250 × 4.6 mm ID, 5µm
Flow rate: 2.0 mL/min
Mobile Phase: 85/15/0.1, CO_2/IPA/DEA, 150 bar
Detector Wavelength: 225 nm (Lamda max)
Injection Volume: 10 µL
Analytical chiral SFC method C:

Column: CHIRALPAK® IA 250 × 4.6 mm ID, 5 μm
Flow rate: 3.0 mL/min
Mobile Phase: 65/35/0.1, CO_2/MeOH/DEA, 150 bar
Detector Wavelength: 270 nm (Lambda max)
Injection Volume: 10 μL
Analytical chiral SFC method D:
Column: CHIRALCEL® OD, 250 × 4.6 mm ID, 10 μm
Flow rate: 2.0 mL/min, 100 bar, 35 °C
Mobile Phase: 20% Methanol/80% CO_2
Detector Wavelength: 223 nm
Injection Volume: 10 μL

NMR EMPLOYED IN CHARACTERIZATION OF EXAMPLES

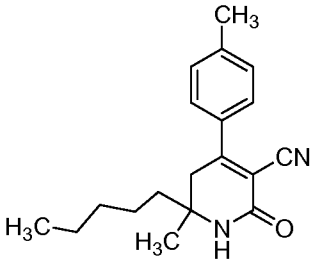
[00267] ^{1}H NMR spectra (unless otherwise noted) were obtained with JEOL or Bruker FOURIER® transform spectrometers operating at 400 MHz or 500 MHz. ^{1}H-nOe experiments were performed in some cases for regiochemistry elucidation with a 400 MHz Bruker FOURIER® Transform spectrometer.

[00268] Spectral data are reported as chemical shift (multiplicity, number of hydrogens, coupling constants in Hz) and are reported in ppm (δ units) relative to either an internal standard (tetramethyl silane = 0 ppm) for ^{1}H NMR spectra, or are referenced to the residual solvent peak (2.49 ppm for CD_3SOCD_2H, 3.30 ppm for CD_2HOD, 1.94 for CHD_2CN, 7.26 ppm for $CHCl_3$, 5.32 ppm for $CDHCl_2$).

[00269] Microwave instrumentation employed in heating reactions.

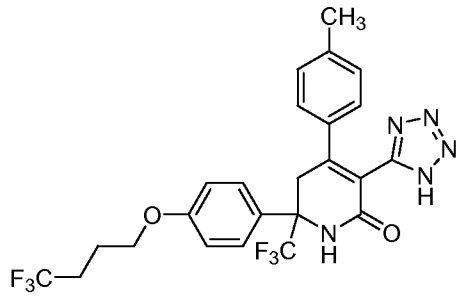
[00270] BIOTAGE® Initiator 2.5, maximum power 400 W, reaction volume range 0.2 - 10 mL. Reactions are run in sealed pressure vessels specially manufactured for this instrument.

Example 1. 6-Methyl-2-oxo-6-phenyl-4-*p*-tolyl-1,2,5,6-tetrahydropyridine-3-carbonitrile

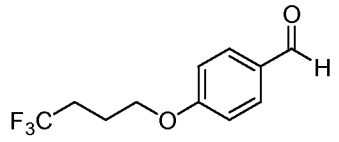


[00271] A solution of heptan-2-one (51 mg, 0.45 mmol), 1-*p*-tolylethanone (60 mg, 0.45 mmol), ethyl-2-cyanoacetate (51 mg, 0.45 mmol) and ammonium acetate (42 mg, 0.55 mmol) in anhydrous DMF (0.6 mL) was heated with stirring at 100 °C for 16 h. The reaction was diluted with EtOAc and washed with water. The solvent was removed *in vacuo* and the product was purified by preparative HPLC ($MeOH/H_2O/TFA$) to provide the desired product (8 mg, 6%) as a white solid. LCMS Anal. Calc'd for $C_{19}H_{24}N_2O$ 297.41, found [M+H] 297.2. ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 6.87 Hz, 3 H), 1.24 - 1.40 (m, 9 H), 1.51 - 1.71 (m, 2 H) 2.42 (s, 3 H), 2.73 - 2.97 (m, 2 H), 6.09 (s, 1 H), 7.30 (d, J = 7.70 Hz, 2 H), 7.52 (d, J = 7.70 Hz, 2 H).

Example 2. 3-(1*H*-Tetrazol-5-yl)-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one



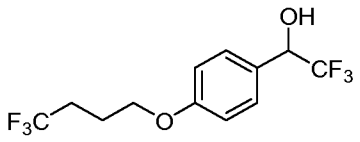
Intermediate 2A. 4-(4,4,4-Trifluorobutoxy)benzaldehyde



[00272] To a solution of 4-hydroxybenzaldehyde (20 g, 164 mmol) and 4,4,4-trifluorobutan-1-ol (25 g, 195 mmol) in anhydrous CH_2Cl_2 (500 mL) at 0 °C under Ar was added a solution of PPh_3 (51.5 g, 196 mmol) in CH_2Cl_2 (200 mL) over 15 min, and

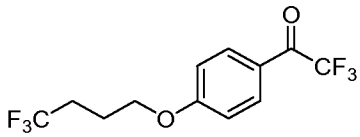
then DIAD (36.4 g, 180 mmol) in anhydrous CH_2Cl_2 (150 mL) was added dropwise. The mixture was stirred at 0 °C for 0.5 h. The reaction was warmed to rt and stirred for another 3 h. The solvent was removed *in vacuo* and the residue was triturated with CH_2Cl_2 three times to remove insoluble solids. The combined CH_2Cl_2 washings were concentrated and the residue was purified by silica gel chromatography (330 g silica gel, eluted with EtOAc in hexanes) to provide Intermediate 2A (27 g, 71%) as a light brown oil. LCMS Anal. Calc'd for $C_{11}H_{11}F_3O_2$ 232.20, found [M+H] 233.0.

Intermediate 2B. 2,2,2-Trifluoro-1-(4-(4,4,4-trifluorobutoxy)phenyl)ethanol



[00273] To the solution of Intermediate 2A (26.7 g, 114 mmol) and trimethyl(trifluoromethyl)silane (16.9 g, 119 mmol) in anhydrous DME (112 mL) was added CsF (500 mg, 3.29 mmol). The reaction was stirred at rt for 16 h. To the mixture was added 4 N aq HCl (114 mL) and the reaction was stirred at rt for 2.5 h. The reaction was diluted with EtOAc (300 mL) and washed with water, sat'd aq $NaHCO_3$, sat'd aq NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated to provide Intermediate 2B (42.5 g, 122%) as an oil. The crude product was used without further purification. LCMS Anal. Calc'd for $C_{12}H_{12}F_6O_2$ 302.21, found [M-H] 301.2.

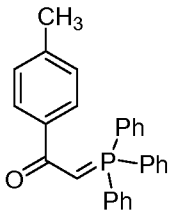
Intermediate 2C. 2,2,2-Trifluoro-1-(4-(4,4,4-trifluorobutoxy)phenyl)ethanone



[00274] To a solution of Intermediate 2B (115 mmol) in anhydrous CH_2Cl_2 (320 mL) was added Dess-Martin periodinane (50.2 g, 118 mmol) portionwise at 0 °C. The reaction was stirred at 0 °C for 0.5 h then at rt for 3 h. To the reaction was added 100 mL of sat'd aq Na_2CO_3 and 250 mL of EtOAc. The reaction was stirred for another 2 h. The insoluble material was removed by filtration. The layers were separated. The organic layer was washed with sat'd aq Na_2CO_3. Additional solids that formed upon standing overnight were removed. The organic solution was washed with sat'd aq NaCl, dried

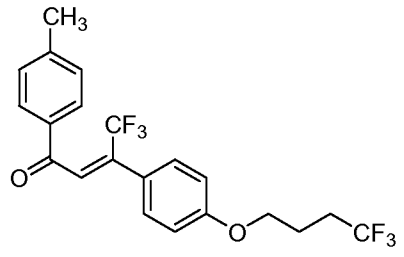
over anhydrous $MgSO_4$, filtered and concentrated to provide a dark brown liquid, which was purified by silica gel chromatography (220 g silica gel, elute with EtOAc in hexanes to provide Intermediate 2C (26 g, 76%) as a colorless oil.

Intermediate 2D. Triphenylphosphonium *p*-tolylcarbonylylide



[00275] To a refluxing solution of PPh_3 (6.15 g, 23.47 mmol) in anhydrous THF (220 mL) under argon was added dropwise a solution of 2-bromo-1-*p*-tolylethanone (5 g, 23.47 mmol) in THF (60 mL). The reaction was refluxed for 2.5 h and then cooled to rt. The precipitate was collected by filtration and rinsed with diethyl ether. The solids were suspended in 1:1 MeOH and H_2O (500 mL), and then 2 N aq NaOH (55 mL) was added. The reaction was stirred at rt for 16 h. MeOH was removed *in vacuo* and the aq solution was extracted with $CHCl_3$. The combined organic extracts were washed with sat'd aq NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated to provide Intermediate 2D (9 g, 97%) as a white solid. LCMS Anal. Calc'd for $C_{27}H_{23}OP$ 394.44, found [M+H] 395.2.

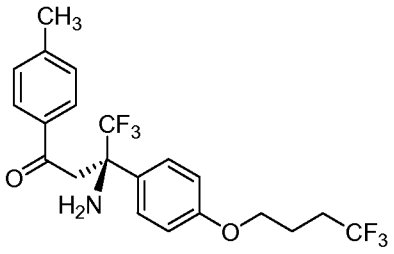
Intermediate 2E. (*Z*)-4,4,4-Trifluoro-1-*p*-tolyl-3-(4-(4,4,4-trifluorobutoxy)phenyl)but-2-en-1-one



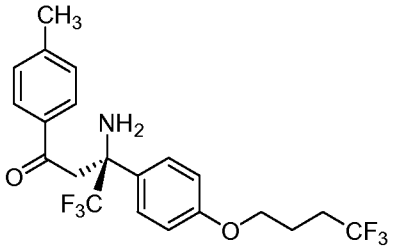
[00276] Intermediate 2D (5.13 g, 13 mmol) and Intermediate 2C (3.90 g, 13 mmol) were suspended in DMSO (15 mL). The reaction was heated to 160 °C for 1000 s under microwave conditions. The reaction was cooled to rt and diluted with EtOAc (60 mL). The mixture was washed with water and sat'd aq NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography

(120 g silica gel, elute with EtOAc in hexanes to provide Intermediate 2E (5.9 g, 98%) as a light brown oil.

Intermediate 2F, isomer 1. (*R*)-3-Amino-4,4,4-trifluoro-1-*p*-tolyl-3-(4-(4,4,4-trifluorobutoxy)phenyl)-butan-1-one



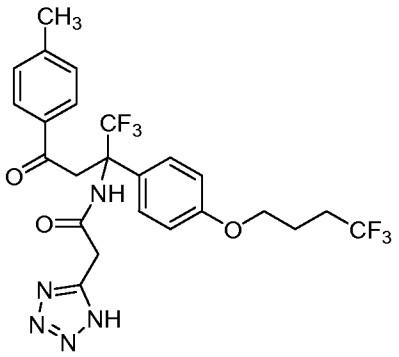
Intermediate 2F, isomer 2. (*S*)-3-Amino-4,4,4-trifluoro-1-*p*-tolyl-3-(4-(4,4,4-trifluorobutoxy)phenyl)-butan-1-one



[00277] To a solution of Intermediate 2E (2.1 g, 5.04 mmol) in DMSO (50 mL) was added 15 N aq NH_4OH (25 mL). The mixture was stirred in sealed pressure vessel for 2 days. The reaction was diluted with EtOAc (60 mL), washed with water and sat'd aq NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography column (eluted with EtOAc in hexanes to provide racemic Intermediate 2F (2.2 g, 101%) as a white solid. LCMS Anal. Calc'd for $C_{21}H_{21}F_6NO_2$ 433.39, found [M+H] 434.2. Separation of the individual enantiomers of Intermediate 2F was carried out using preparative chiral SFC method A: Racemic Intermediate 2F (2200 mg) provided Intermediate 2F, isomer 1 (817 mg) and Intermediate 2F, isomer 2 (790 mg). Enantiomeric purity determination of Intermediate 2F, isomer 1 and 2 was carried out using analytical SFC method A. Intermediate 2F, isomer 1: RT = 2.2 min, 99% ee. Intermediate 2F, isomer 2: RT = 2.8 min, 99% ee. X-ray crystal data collected for the camphorsulfonic acid salt of Intermediate 2F, isomer 1 showed the chiral center to have

the *R*-configuration; therefore, the chiral center for Intermediate 2F, isomer 2 has the *S*-configuration.

Intermediate 2G. 2-(1*H*-Tetrazol-5-yl)-*N*-(1,1,1-trifluoro-4-oxo-4-*p*-tolyl-2-(4-(4,4,4-trifluorobutoxy)-phenyl)butan-2-yl)acetamide



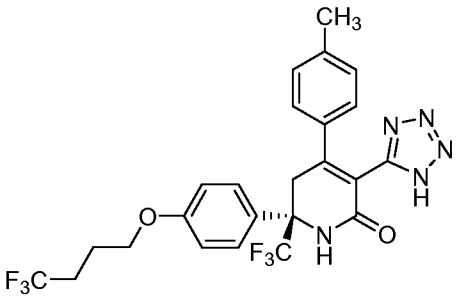
[00278] To a solution of Intermediate 2F (789 mg, 1.82 mmol) in anhydrous THF (9 ml) at 0 °C was added DCC (1.13 g, 5.46 mmol). 2-Tetrazole acetic acid (700 mg, 5.46 mmol) was added dropwise as a suspension in anhydrous THF (8 mL). The reaction was stirred at 0 °C for 1 h and then at rt overnight. The reaction was filtered and solids were rinsed with THF. The filtrate was diluted with EtOAc (40 mL), washed with sat'd Na_2CO_3 and sat'd aq NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated to provide Intermediate 2G (1.5 g, 152%) as a reddish brown solid. Intermediate 2G was used in the next step without further purification. LCMS Anal. Calc'd for $C_{24}H_{23}F_6N_5O_3$ 543.46, found [M+H] 543.9.

Example 2

[00279] To a solution of Intermediate 2G (1.5 g) in EtOH (11 mL) was added piperidine (0.33 mL). The reaction was heated to 78 °C for 16 h in a sealed vial. The reaction was cooled to rt and the solvent was removed *in vacuo*. The residue was purified by preparative HPLC ($MeOH/H_2O$/TFA). Fractions containing the product were dried *in vacuo* and the product was re-dissolved in MeOH and concentrated again. The oily brown product was re-dissolved in CH_2Cl_2 (5 mL) and concentrated *in vacuo* to provide Example 2 (552 mg, 57% over 2 steps) as a reddish foam. LCMS Anal. Calc'd for $C_{24}H_{21}F_6N_5O_2$ 525.45, found [M+H] 526.2. ^1H NMR (500 MHz, CD_3OD) δ 7.61 (d, J = 9.1 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 7.07 - 7.01 (m, 2H), 6.90 (d, J = 8.3 Hz, 2H), 4.10

(t, J = 6.1 Hz, 2H), 3.84 - 3.64 (m, 2H), 2.48 - 2.35 (m, 2H), 2.30 (s, 3H), 2.14 - 2.00 (m, 2H).

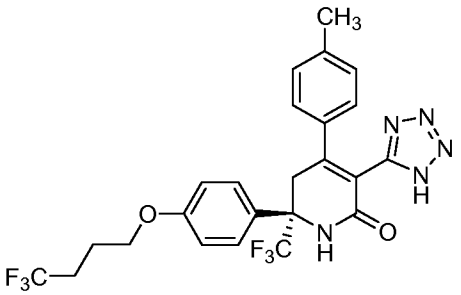
Example 2-1. (*S*)-3-(1*H*-Tetrazol-5-yl)-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one



[00280] Separation of the individual enantiomers of Example 2 was carried out using preparative chiral SFC method C: Racemic Example 2 (89 mg) provided Example 2-1 (21 mg). Enantiomeric purity determination of Example 2-1 was carried out using analytical SFC method C. RT = 6.0 min, 99% ee.

[00281] Example 2-1 can be alternatively obtained from Intermediate 2F, isomer 2 using a sequence similar to one used for the conversion of Intermediate 2F to Example 2.

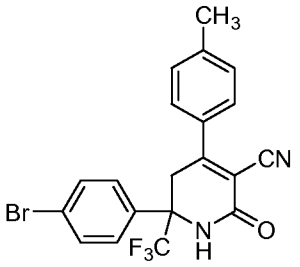
Example 2-2. (*R*)-3-(1*H*-Tetrazol-5-yl)-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one



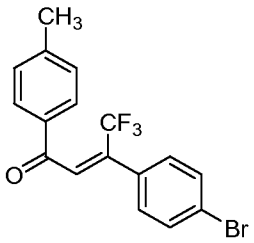
[00282] Separation of the individual enantiomers of Example 2 was carried out using preparative chiral SFC method C: Racemic Example 2 (89 mg) provided Example 2-2 (22 mg). Enantiomeric purity determination of Example 2-2 was carried out using analytical SFC method C. RT = 15.1 min, 99% ee.

[00283] Example 2-2 can be alternatively obtained from Intermediate 2F, isomer 1 using a sequence similar to one used for the conversion of Intermediate 2F to Example 2.

Example 3. 6-(4-Bromophenyl)-2-oxo-4-*p*-tolyl-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile

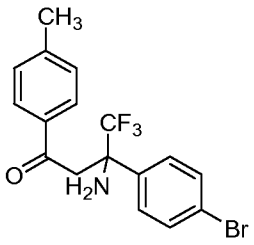


Intermediate 3A. (*Z*)-3-(4-Bromophenyl)-4,4,4-trifluoro-1-*p*-tolylbut-2-en-1-one



[00284] Intermediate 2D (1.84 g, 4.74 mmol) and 1-(4-bromophenyl)-2,2,2-trifluoroethanone (1.2 g, 4.74 mmol) were dissolved in THF (8 mL) and heated to 150 °C for 1000 s under microwave conditions. The reaction was cooled to rt and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (24 g silica gel, elute with EtOAc in hexanes) to yield Intermediate 3A (1.51 g, 86%) as a light brown solid. LCMS Anal. Calc'd for $C_{17}H_{12}BrF_3O$ 369.18, found [M+H] 371.0.

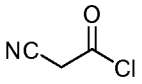
Intermediate 3B. 3-Amino-3-(4-bromophenyl)-4,4,4-trifluoro-1-*p*-tolylbutan-1-one



[00285] To a solution of Intermediate 3A (1.53 g, 4.14 mmol) in DMSO (23 mL) was added 15 N aq NH_4OH (10 mL). The reaction vessel was sealed and the reaction was stirred at rt for 16 h. Additional DMSO (3 mL) and 15 N aq NH_4OH (1 mL) were added

and the reaction was stirred at rt for 16 h. Addition of DMSO (4 mL) was repeated and the reaction was stirred for another 16 h. The solution was concentrated *in vacuo* followed by lyophilization to provide Intermediate 3B (1.8 g, 100%) as a brown oil. LCMS Anal. Calc'd for $C_{17}H_{15}BrF_3NO$ 386.21, found [M+H] 388.1.

Intermediate 3C. 2-Cyanoacetyl chloride

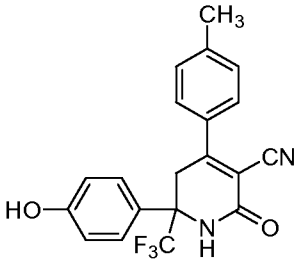


[00286] To a mixture of 2-cyanoacetic acid (893 mg, 10.5 mmol) and DMF (16 μL) in anhydrous CH_2Cl_2 (20 mL) at 0 C was added dropwise a 2 M solution of oxalyl chloride (6 mL, 12 mmol) in CH_2Cl_2. The reaction was stirred at 0 °C for 20 min, and then warmed to rt and stirred for 2 h. The solvent was removed *in vacuo* to provide Intermediate 3C, which was used in the next reaction without purification.

Example 3

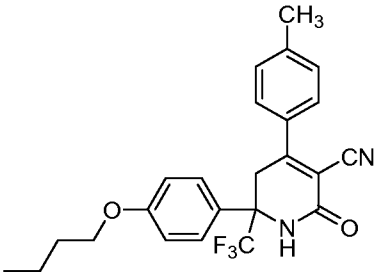
[00287] To a solution of Intermediate 3B (1.6 g, 4.1 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0 °C was added a solution of Intermediate 3C (1.1 g, 10.5 mmol), pyridine (0.85 mL), and DMAP (20 mg) in anhydrous CH_2Cl_2 (5 mL),. The reaction was stirred at 0 °C for 20 min, then at rt for 2.5 h. The solvent was removed *in vacuo*. The crude product was dissolved in EtOAc (30 mL), washed with sat'd aq Na_2CO_3 and sat'd aq NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated to yield a brown solid. The solid was triturated with CH_2Cl_2/diethyl ether to provide Example 3 (1.27 g) as an off white solid. The supernatant was evaporated and the residue was purified by silica gel chromatography (eluted with EtOAc in hexanes) to provide a second batch of Example 3 (0.22 g). The combined yield was 1.49 g (80%). LCMS Anal. Calc'd for $C_{20}H_{14}BrF_3N_2O$ 435.24, found [M+H] 437.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42 (s, 3 H), 3.45 - 3.67 (m, 2 H), 7.30 (d, J = 7.70 Hz, 2 H), 7.39 (d, J = 8.25 Hz, 2 H), 7.45 (d, J = 7.70 Hz, 2 H), 7.60 (d, J = 8.80 Hz, 2 H).

Example 4. 6-(4-Hydroxyphenyl)-2-oxo-4-*p*-tolyl-6-(trifluoromethyl)-1,2,5,6-tetrahydro-pyridine-3-carbonitrile



[00288] Example 3 (1.49 g, 3.42 mmol), Pd_2dba_3 (78 mg, 0.086 mmol), KOH (403 mg, 7.2 mmol) and bis(1,1-dimethylethyl)[2′,4′,6′-tris(1-methylethyl)[1,1′-biphenyl]-2-yl]- phosphine (73 mg, 0.17 mmol) were placed in a microwave vial. The vial was evacuated and back filled with Ar. 1,4-Dioxane (23 mL) and water (13 mL) were added to the vial and the reaction mixture was heated to 140 °C for 15 min under microwave conditions. The reaction was cooled to rt, neutralized with 1 N HCl, diluted with water, and extracted with EtOAc. The combined organic extracts were washed with water and sat'd aq NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography to provide Example 4 (1.14 g, 85%) as a light brown solid. LCMS Anal. Calc'd for $C_{20}H_{15}F_3N_2O_2$ 372.34, found [M+H] 373.2. ^1H NMR (500 MHz, DMSO-d_6) δ 2.30 (s, 3 H), 3.65 (q, J = 18.15 Hz, 2 H), 6.73 (d, J = 8.25 Hz, 2 H), 7.28 (d, J = 8.25 Hz, 2 H), 7.38 (d, J = 8.80 Hz, 2 H), 7.47 (d, J = 8.25 Hz, 2 H), 9.63 (s, 1 H), 9.70 (s, 1 H).

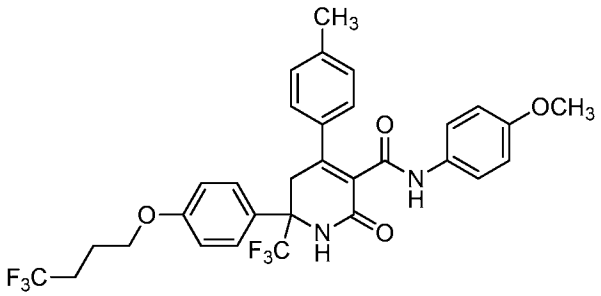
Example 5. 6-(4-Butoxyphenyl)-2-oxo-4-*p*-tolyl-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile



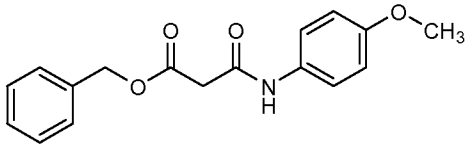
[00289] To a solution of Example 4 (20 mg, 0.054 mmol) and *n*-butanol (6 mg, 0.081 mmol) in anhydrous CH_2Cl_2 (0.3 mL) under Ar was added sequentially triphenylphosphine (21 mg, 0.081 mmol) in CH_2Cl_2 (0.3 mL) and DEAD (14 mg, 0.081 mmol) in CH_2Cl_2 (0.3 mL). The reaction mixture was stirred at 0 °C under argon for 20 min, then at rt for 2 h. The solvent was evaporated *in vacuo* and the product was purified

by preparative HPLC (CH_3CN/H_2O/TFA) to provide Example 5 (5.6 mg, 24%). LCMS Anal. Calc'd for $C_{24}H_{23}F_3N_2O_2$ 428.45, found [M+H] 429.3. ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (t, J = 7.42 Hz, 3 H), 1.41 - 1.56 (m, 2 H), 1.73 - 1.84 (m, 2 H), 2.41 (s, 3 H), 3.56 (q, J = 18.15 Hz, 2 H), 3.92-4.03 (m, 2 H), 6.94 (d, J = 8.25 Hz, 3 H), 7.29 (d, J = 8.25 Hz, 2 H), 7.37 (d, J = 8.80 Hz, 2 H), 7.45 (d, J = 7.70 Hz, 2 H).

Example 6. *N*-(4-Methoxyphenyl)-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoro-methyl)-1,2,5,6-tetrahydropyridine-3-carboxamide



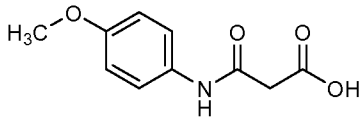
Intermediate 6A. Benzyl 3-(4-(methylamino)phenylamino)-3-oxopropanoate



[00290] To a solution of monobenzyl malonate (12.2 g, 63.1 mmol) and DMF (90 μL) in anhydrous CH_2Cl_2 (100 mL) at 0 °C was added 2 M oxalyl chloride (35 mL, 70 mmol) in CH_2Cl_2. The reaction was stirred at 0 °C for 30 min, then at rt for 2.5 h. The solvent was removed *in vacuo* to provide freshly prepared acid chloride. This was dissolved in anhydrous CH_2Cl_2 (50 mL) and added dropwise to a solution of 4-methoxyaniline (7.76 g, 63 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0 °C followed by the addition of pyridine (5.35 mL, 66.2 mmol). The reaction was stirred at 0 °C for 0.5 h, then at rt overnight. The reaction was washed with water and sat'd aq NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was triturated with EtOAc/ CH_2Cl_2 to yield the first batch of Intermediate 6A as a light brown solid (6.95 g). The supernatant was evaporated and the residue was purified by silica gel chromatography (eluted with EtOAc in hexanes) to provide a second batch of Intermediate 6A as a light brown solid (7.4 g).

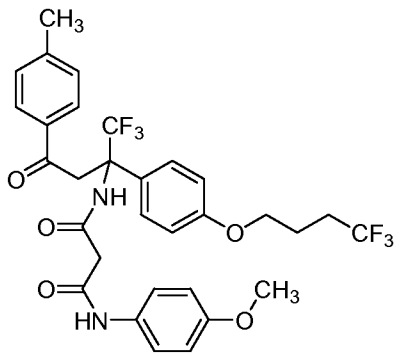
The combined yield was 14.4 g (76%). LCMS Anal. Calc'd for $C_{17}H_{18}N_2O_3$ 298.34, found [M+H] 300.2.

Intermediate 6B. 3-(4-Methoxyphenylamino)-3-oxopropanoic acid



[00291] To a solution of Intermediate 6A (14.4 g, 4.8 mmol) in 10:1 EtOAc/MeOH (220 mL) was added 10% Pd/C (250 mg). The reaction mixture was stirred vigorously under an atmosphere of hydrogen (40 psi) for 2 h. More 10% Pd/C (250 mg) was added and the reaction was stirred under 50 psi hydrogen for another 1 h. Additional 10% Pd/C (500 mg) was added and the reaction was stirred under 50 psi hydrogen for an additional 1 h. The reaction was filtered through a pad of Celite® and the filtrate was concentrated *in vacuo* to yield Intermediate 6B (11.1 g, 96%) as an off-white solid. LCMS Anal. Calc'd for $C_{10}H_{11}NO_4$ 209.20, found [M+H] 210.1.

Intermediate 6C. N^1-(4-Methoxyphenyl)-N^3-(1,1,1-trifluoro-4-oxo-4-*p*-tolyl-2-(4-(4,4,4-trifluoro-butoxy)phenyl)-butan-2-yl)malonamide



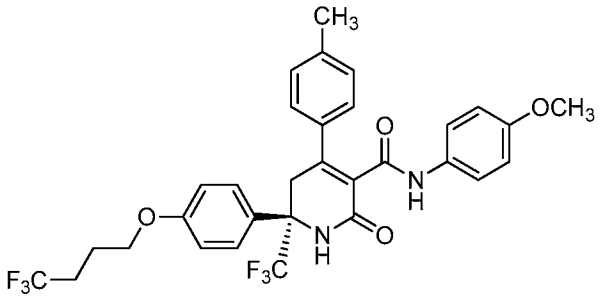
[00292] To triphenylphosphine (8.42 g, 32.1 mmol) in anhydrous CH_2Cl_2 (70 mL) was added Intermediate 6B (2.24 g, 10.7 mmol) in anhydrous CH_2Cl_2 (30 mL) followed by trichloroacetonitrile (1.86 g, 12.8 mmol). The mixture was stirred at rt for 3 h. The freshly prepared acid chloride was added to a solution of Intermediate 2F (1.13 g, 2.61 mmol) in anhydrous CH_2Cl_2 (20 mL), followed by the addition of pyridine (1.04 mL, 1.02 g, 12.85 mmol). The reaction was stirred at rt under argon overnight. The reaction was cooled to 0 °C and MeOH (40 mL) was added. The reaction was stirred at 0 °C for

10 min, then at rt for 30 min. The solvent was removed *in vacuo* and the crude product was purified by silica gel chromatography (120 g silica gel, eluted with EtOAc in hexanes). Product and triphenylphosphine oxide co-eluted. Fractions containing both were combined and evaporated to dryness. The solids were triturated with hexanes/EtOAc to remove most of the triphenylphosphine oxide. The product was again purified by silica gel chromatography (40 g silica gel, eluted with EtOAc in hexanes) to provide Intermediate 6C (1.03 g, 63%) as a brown oil. LCMS Anal. Calc'd for $C_{31}H_{30}F_6N_2O_5$ 624.57, found [M+H] 625.3.

Example 6

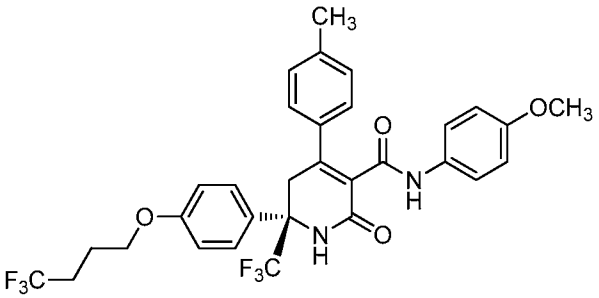
[00293] To a solution of Intermediate 6C (1.03 g, 1.65 mmol) in MeOH (10 mL) was added piperidine (100 μL, 1.01 mmol). The reaction was stirred at 75 °C for 1 h. The solvent was removed *in vacuo* and the crude product was purified by silica gel chromatography (120 g silica gel, eluted with EtOAc in hexanes). Mixed fractions from the first column were purified again by silica gel chromatography (40 g silica gel, eluted with EtOAc in hexanes) to provide Example 6 (546 mg, 55%) as a off-white solid. LCMS Anal. Calc'd for $C_{31}H_{28}F_6N_2O_4$ 606.56, found [M+H] 607.3. ^{1}H NMR (500 MHz, CD_3OD) δ 1.97-2.08 (m, 2 H), 2.30 (s, 3 H), 2.32-2.44 (m, 2 H), 3.45-3.67 (m, 2 H), 3.72 (s, 3 H), 4.06 (t, J = 6.05 Hz, 2 H), 6.77 (d, J = 9.35 Hz, 2 H), 6.97 (d, J = 8.80 Hz, 2 H), 7.13-7.24 (m, 4 H), 7.28 (d, J = 8.25 Hz, 2 H), 7.52 (d, J = 8.80 Hz, 2 H).

Example 6-1. (*R*)-*N*-(4-Methoxyphenyl)-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoro-methyl)-1,2,5,6-tetrahydropyridine-3-carboxamide



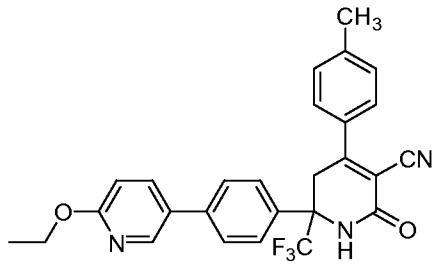
[00294] Example 6-1 was prepared using a procedure analogous to Example 6 by replacing Intermediate 2F with Intermediate 2F, isomer 1.

Example 6-2. (*S*)-*N*-(4-Methoxyphenyl)-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoro-methyl)-1,2,5,6-tetrahydropyridine-3-carboxamide



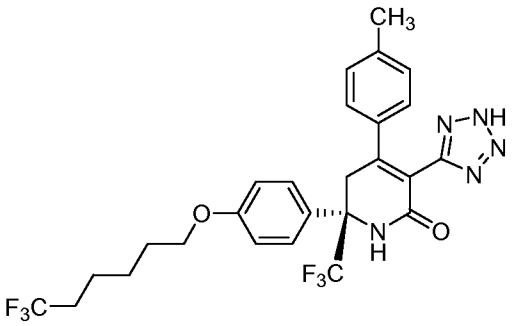
[00295] Example 6-2 was prepared using a procedure analogous to Example 6 by replacing Intermediate 2F with Intermediate 2F, isomer 2.

Example 7. 6-(4-(6-Ethoxypyridin-3-yl)phenyl)-2-oxo-4-*p*-tolyl-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile

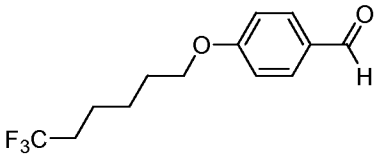


[00296] To a solution of Example 3 (20 mg, 0.046 mmol), 6-ethoxypyridin-3-yl boronic acid (11 mg, 0.07 mmol) and tetrakis(triphenylphosphine) palladium(0) (5 mg, 10 mol%) in DMF (0.6 mL) sparged with Ar was added 2 N aq K_2CO_3 (46 µL, 0.096 mmol). The vessel was sealed and the reaction heated to 80 °C for 22 h. The reaction was cooled to rt and the product was purified twice by preparative HPLC (CH_3CN/H_2O/TFA and CH_3OH/H_2O/TFA sequentially) to provide Example 7 (10 mg, 45%) as a light brown solid. LCMS Anal. Calc'd for $C_{27}H_{22}F_3N_3O_2$ 477.48, found [M+H] 478.3. ^{1}H NMR (500 MHz, CD_3OD) δ 1.40 (t, *J* = 6.87 Hz, 3 H), 2.40 (s, 3 H), 3.71 - 3.88 (m, 2 H), 4.37 (q, *J* = 7.15 Hz, 2 H), 6.94 (d, *J* = 8.25 Hz, 1 H), 7.33 (d, *J* = 7.70 Hz, 2 H), 7.54 (d, *J* = 8.25 Hz, 2 H), 7.66 - 7.78 (m, 4 H), 8.05 (dd, *J* = 8.80, 2.20 Hz, 1 H), 8.42 (d, *J* = 2.20 Hz, 1 H).

Example 8. (*S*)-3-(2*H*-Tetrazol-5-yl)-4-*p*-tolyl-6-(4-(6,6,6-trifluorohexyloxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one

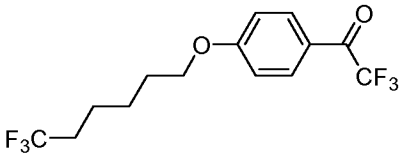


Intermediate 8A. 4-(6,6,6-Trifluorohexyloxy)benzaldehyde



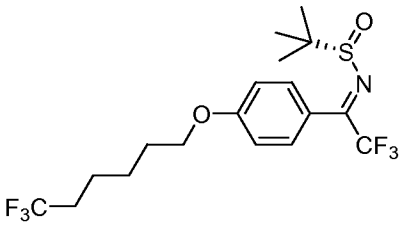
[00297] To a suspension of 4-hydroxybenzaldehyde (488 mg, 4 mmol) and 6-bromo-1,1,1-trifluorohexane (657 mg, 3 mmol) in MeCN (10 mL) was added K_2CO_3 (829 mg, 6.00 mmol). The resulting mixture was reflux overnight. Insoluble material was filtered off and rinsed with MeCN. The combined filtrate was concentrated to afford a white solid. This white solid was partitioned between EtOAc and 1 N NaOH solution. The organic layer was separated, washed with sat'd NH_4Cl, dried over $MgSO_4$, filtered and concentrated to afford Intermediate 8A as a clear liquid. LCMS Anal. Calc'd for $C_{13}H_{15}F_3O_2$ 260.10, found [M+H] 261.0.

Intermediate 8B. 2,2,2-Trifluoro-1-(4-(6,6,6-trifluorohexyloxy)phenyl)ethanone



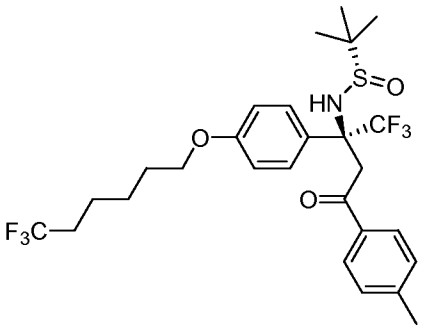
[00298] Intermediate 8B was prepared using a procedure analogous to Intermediate 2C except that Intermediate 2A was replaced with Intermediate 8A. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 - 8.02 (m, 2 H), 6.99 - 6.97 (m, 1 H), 4.08 (t, J = 6.2 Hz, 2 H), 2.19 - 2.06 (m, 2 H), 1.92 - 1.82 (m, 2 H), 1.71 - 1.55 (m, 4 H).

Intermediate 8C. (*S*,*E*)-2-Methyl-*N*-(2,2,2-trifluoro-1-(4-(6,6,6-trifluorohexyloxy)phenyl)ethylidene)propane-2-sulfinamide



[00299] To a solution of Intermediate 8B (717 mg, 2.184 mmol) and (*S*)-2-methylpropane-2-sulfinamide (529 mg, 4.37 mmol) in THF (10 mL) was added tetraethoxytitanium (1993 mg, 8.74 mmol) in THF (20 mL). The resulting mixture was reflux for 5 h. TLC (20% EtOAc in hexane) indicated the starting ketone was completely consumed. The solvent was evaporated to afford a yellow oil. This yellow oil was dissolved in EtOAc and then washed with saturated $NaHCO_3$ (25 mL) and a large amount of white precipitation formed which was removed by filtering through a bed of Celite®. The white precipitation was rinsed with EtOAc. The combined EtOAc solution was washed again with saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated. The crude product was purified by silica gel chromatography (40 g silica gel, eluted with EtOAc in hexanes) to afford Intermediate 8C (620 mg, 66%).

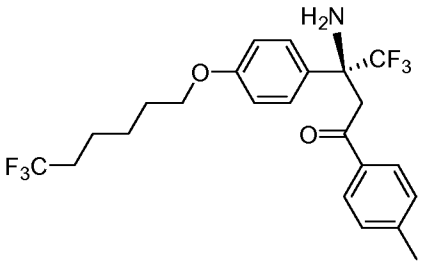
Intermediate 8D. (*S*)-2-Methyl-*N*-((*S*)-1,1,1-trifluoro-4-oxo-4-*p*-tolyl-2-(4-(6,6,6-trifluorohexyloxy)phenyl)butan-2-yl)propane-2-sulfinamide



[00300] To a solution of 1-(*p*-tolyl)ethanone (609 mg, 4.31 mmol) in THF (10 mL) was cooled to -78 °C and to this solution was added lithium bis(trimethylsilyl)amide (4.31 mL, 4.31 mmol). The resulting mixture was stirred at -78 °C for 20 min and then Intermediate 8C (620 mg, 1.437 mmol) in THF (3 mL) was added dropwise. The resulting mixture was stirred at -78 °C for 1.5 h and then at 0 °C for 1.5 h. The reaction was quenched with NH_4Cl and concentrated. The crude product was purified by silica gel chromatography (80 g silica gel, eluted with EtOAc in hexanes) to afford Intermediate 8D

(482 mg, 59%) as the slower eluting diastereomer on silica gel column. LCMS Anal. Calc'd for $C_{27}H_{33}F_6NO_3S$ 565.21, found [M+H] 566.0.

Intermediate 8E. (*S*)-3-Amino-4,4,4-trifluoro-1-*p*-tolyl-3-(4-(6,6,6-trifluorohexyloxy)phenyl)butan-1-one

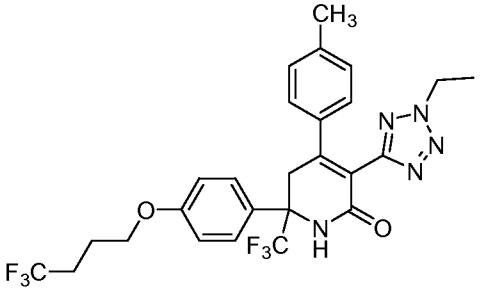


[00301] To a solution of Intermediate 8D (482 mg, 0.852 mmol) in MeOH (4 mL) was added 4 M HCl (1 mL, 4.00 mmol) in dioxane. The resulting mixture was stirred at rt for 2 h and then concentrated. The residue was taken up in EtOAc, washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated to afford Intermediate (386 mg, 58%) as a colorless oil, which was used for the subsequent reaction without further purification. LCMS Anal. Calc'd for $C_{23}H_{25}F_6NO_2$ 461.18, found [M+H] 461.9.

Example 8

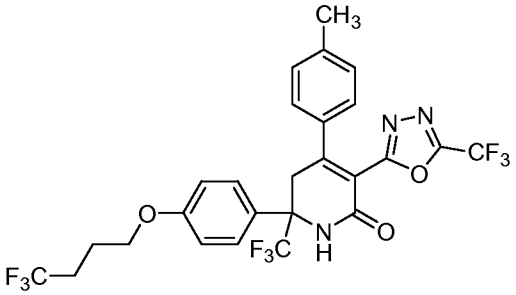
[00302] To a solution of Intermediate 8E (140 mg, 0.303 mmol) and 2-(2*H*-tetrazol-5-yl)acetic acid (117 mg, 0.910 mmol) in THF (3 mL) at 0 °C was added DCC (188 mg, 0.910 mmol). The resulting mixture was stirred overnight. The solvent was evaporated and the crude mixture was taken up in EtOAc. The organic solution was washed with saturated $NaHCO_3$, 1 N HCl and brine, dried ($MgSO_4$), filtered and concentrated to afford a brown oil. This oil was dissolved in EtOH (3 mL) and added piperidine (300 µL, 3.03 mmol). The resulting mixture was stirred at 80 °C overnight. The reaction mixture was diluted with MeOH and purified by preparative HPLC (MeCN/H_2O/TFA) to yield Example 8 (86 mg, 51%) as a solid. LCMS Anal. Calc'd for $C_{26}H_{25}F_6N_5O_2$ 553.19, found [M+H] 554.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.8 Hz, 2 H), 7.19 (d, *J* = 8.0 Hz, 3 H), 7.02 - 6.93 (m, 4 H), 3.99 (t, *J* = 6.3 Hz, 2 H), 3.68 - 3.56 (m, 2 H), 2.39 (s, 3 H), 2.19 - 2.07 (m, 2 H), 1.89 - 1.79 (m, 2 H), 1.71 - 1.63 (m, 2 H), 1.62 - 1.53 (m, 2 H).

Example 9. 3-(2-Ethyl-2*H*-tetrazol-5-yl)-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one



[00303] To Example 2 (30 mg, 0.057 mmol) in anhydrous CH_2Cl_2 (0.6 mL) was added iodoethane (9 mg, 0.057 mmol) and triethylamine (24 μL, 0.17 mmol). The reaction was heated to 120 °C for 10 min under microwave conditions. The solvent was evaporated *in vacuo* and the residue was purified by preparative HPLC (CH_3CN/H_2O/TFA) to provide Example 9 (2.3 mg, 7%) as a light brown solid. LCMS Anal. Calc'd for $C_{26}H_{25}F_6N_5O_2$ 553.50, found [M+H] 554.3. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (t, *J* = 7.42 Hz, 2 H), 1.98 - 2.13 (m, 2 H), 2.21 - 2.39 (m, 5 H), 3.51 (d, *J* = 17.60 Hz, 1 H), 3.72 (d, *J* = 17.60 Hz, 1 H), 4.04 (t, *J* = 6.05 Hz, 2 H), 4.56 (q, *J* = 7.52 Hz, 2 H) 6.87 (d, *J* = 8.25 Hz, 2 H), 6.95 (d, *J* = 8.80 Hz, 2 H), 7.02 (d, *J* = 8.25 Hz, 2 H), 7.46 (d, *J* = 8.80 Hz, 2 H), 7.93 (s, 1 H).

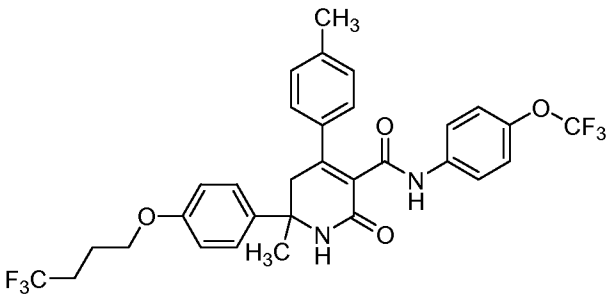
Example 10. 4-*p*-Tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)-5,6-dihydropyridin-2(1*H*)-one



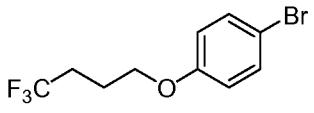
[00304] To Example 2 (29 mg, 0.055 mmol) in anhydrous CH_2Cl_2 (0.3 mL) was added a solution of trifluoroacetic anhydride (23.2 mg, 0.11 mmol) in anhydrous CH_2Cl_2 (0.2 mL) dropwise. The mixture was stirred at rt for 4 h and then concentrated. The residue was purified by preparative HPLC to provide Example 10 (19 mg, 58%) as a white solid. LCMS Anal. Calc'd for $C_{26}H_{20}F_9N_3O_3$ 593.44, found [M+H] 594.2. ^{1}H NMR (500 MHz,

CD_3OD) δ 1.97 - 2.11 (m, 2 H), 2.31 (s, 3 H), 2.34 - 2.44 (m, 2 H), 3.64 - 3.88 (m, 2 H), 4.08 (t, *J* = 6.05 Hz, 2 H), 6.98 (d, *J* = 8.25 Hz, 2 H), 7.03 (d, *J* = 8.80 Hz, 2 H), 7.16 (d, *J* = 8.25 Hz, 2 H), 7.57 (d, *J* = 8.80 Hz, 2 H).

Example 11. 6-Methyl-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-*N*-(4-(trifluoromethoxy)-phenyl)-1,2,5,6-tetrahydropyridine-3-carboxamide

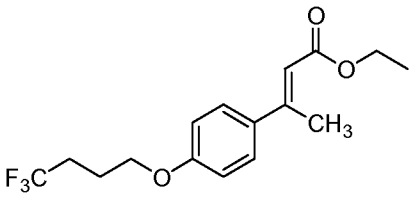


Intermediate 11A. 1-Bromo-4-(4,4,4-trifluorobutoxy)benzene



[00305] To a solution of 4-bromophenol (2.2 g, 12.7 mmol) and 4-bromo-1,1,1-trifluorobutane (2.4 g, 12.7 mmol) in anhydrous DMF (15 mL) was added K_2CO_3 (3.5 g, 25.4 mmol). The mixture was stirred at rt overnight. The mixture was diluted with EtOAc (120 mL) and the solids were removed by filtration. The filtrate was washed with water and sat'd aq NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography (40 g silica gel, eluted with EtOAc in hexanes) to provide Intermediate 11A (3.05 g, 85%) as a colorless oil.

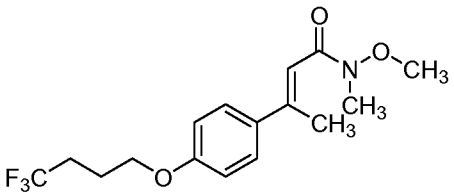
Intermediate 11B. (*E*)-Ethyl 3-(4-(4,4,4-trifluorobutoxy)phenyl)but-2-enoate



[00306] Intermediate 11A (2.81 g, 9.93 mmol), (*E*)-ethyl but-2-enoate (1.25 g, 10.9 mmol), palladium(II) acetate (0.11 g, 0.5 mmol), tetraethylammonium chloride (1.65 g,

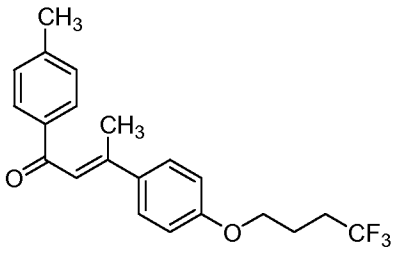
9.9 mmol), *N*-cyclohexyl-*N*-methylcyclohexanamine (2.91 g, 14.9 mmol) and dimethylacetamide (30 ml) were placed in a oven-dried vial and sparged with argon for 5 min. The vial was sealed and the reaction heated to 110 °C for 6 h. The reaction was cooled to rt, diluted with EtOAc (75 mL), washed with water and sat'd aq NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc in hexanes to provide Intermediate 11B (1.81 g, 49%) as a colorless oil. LCMS Anal. Calc'd for $C_{16}H_{19}F_3O_3$ 316.32, found [M+H] 317.2.

Intermediate 11C. (*E*)-*N*-Methoxy-*N*-methyl-3-(4-(4,4,4-trifluorobutoxy)phenyl)but-2-enamide



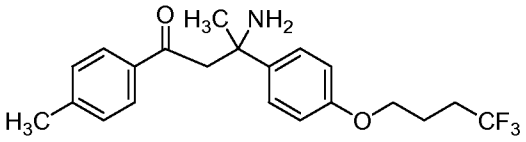
[00307] A solution of Intermediate 11B (2.67 g, 8.44 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (1.65 g, 16.9 mmol) in anhydrous THF (35 mL) was cooled to -61°C ($CHCl_3$/dry ice) under an atmosphere of Ar. To this solution was added 0.5 M isopropylmagnesium chloride (16.9 mL, 33.8 mmol) in THF slowly via a syringe. The reaction was stirred at -61 °C for 1.5 h, warmed to -20 °C (sat'd aq NaCl/ice) and stirred for 40 min, then warmed to 0 °C and stirred for 20 min. The reaction was poured into 10 mL of sat'd aq NH_4Cl and 12 mL of water, and then extracted with EtOAc. The organic layer was washed with sat'd aq NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc in hexanes to provide Intermediate 11C (1.62 g, 58%) as a light brown oil. LCMS Anal. Calc'd for $C_{16}H_{20}F_3NO_3$ 331.33, found [M+H] 332.2.

Intermediate 11D. (*E*)-1-*p*-Tolyl-3-(4-(4,4,4-trifluorobutoxy)phenyl)but-2-en-1-one



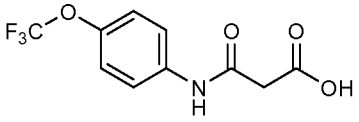
[00308] To a solution of Intermediate11C (1.62 g, 4.89 mmol) in anhydrous THF (25 mL) at -78 °C was added dropwise 0.5 M *p*-tolylmagnesium bromide in ether (25 mL, 12.5 mmol). The reaction was stirred at -78 °C for 40 min, then gradually warmed to rt. The reaction was poured into 1:1 sat'd aq NH_4Cl and water (60 mL). The mixture was extracted with EtOAc. The organic layer was washed with sat'd aq NaCl, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography (eluted with EtOAc in hexanes) to provide Intermediate 11D (1.34 g, 76%) as a light brown solid. LCMS Anal. Calc'd for $C_{21}H_{21}F_3O_2$ 362.39, found [M+H] 363.2. ^1H NMR (500 MHz, $CDCl_3$) δ 2.01 - 2.11 (m, 2 H), 2.29 - 2.37 (m, 2 H), 2.42 (s, 3 H), 2.58 (s, 3 H), 4.07 (t, J = 6.05 Hz, 2 H), 6.92 (d, J = 8.80 Hz, 2 H), 7.14 (s, 1 H), 7.23 - 7.34 (m, J = 8.25 Hz, 2 H), 7.55 (d, J = 8.80 Hz, 2 H), 7.90 (d, J = 8.25 Hz, 2 H).

Intermediate 11E. 3-Amino-1-*p*-tolyl-3-(4-(4,4,4-trifluorobutoxy)phenyl)butan-1-one



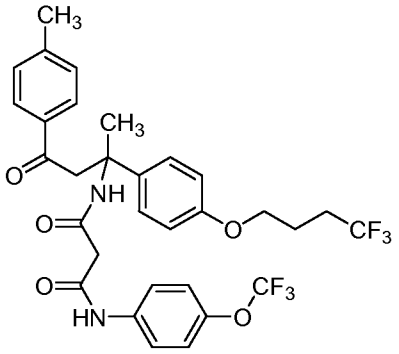
[00309] Ammonia was bubble into a solution of Intermediate 11D (1.34 mg, 0.64 mmol) in EtOH (20 mL) and DMSO (12 mL) for 10 min at 0 °C. The reaction was stirred at rt overnight in a sealed pressure vessel. Analytical HPLC showed reaction to have progressed only ca. 10%. The mixture was cooled to -15 °C, then ammonia was bubbled through for 7 min. The vessel was sealed and the reaction was stirred at rt overnight. Analytical HPLC showed the reaction to be ca. 25-30% complete. The mixture was diluted with EtOAc (75 mL), washed with water and sat'd aq NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography to provide Intermediate11E (281 mg, 20%) as a light brown oil. LCMS Anal. Calc'd for $C_{21}H_{24}F_3NO_2$ 379.42, found [M+H] 380.3.

Intermediate 11F. 3-Oxo-3-(4-(trifluoromethoxy)phenylamino)propanoic acid



[00310] By sequential application of the procedures for Intermediates 6A and 6B, 4-trifluoromethoxyaniline (2.3 g, 13 mmol) was converted to Intermediate 11F (2.8 g, 11 mmol), which was isolated as a white solid. LCMS Anal. Calc'd for $C_{10}H_8F_3NO_4$ 263.17, found [M+H] 264.1.

Intermediate 11G. N^1-(4-Oxo-4-*p*-tolyl-2-(4-(4,4,4-trifluorobutoxy)phenyl)butan-2-yl)-N^3-(4-(trifluoromethoxy)-phenyl)malonamide



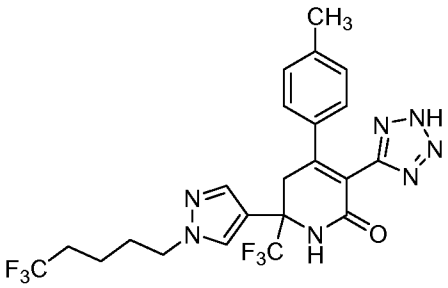
[00311] To a solution of Intermediate 11F (41.6 mg, 0.158 mmol) in anhydrous CH_2Cl_2 (0.6 mL) was added PPh_3 (124 mg, 0.474 mmol) followed by dropwise addition of trichloroacetonitrile (27.4 mg, 0.19 mmol). The reaction was stirred at rt for 3 h. To the freshly prepared acid chloride was added a solution of Intermediate 11E (20 mg, 0.053 mmol) in anhydrous CH_2Cl_2 (0.3 mL) followed by pyridine (19 μL, 0.237 mmol). The mixture was stirred at rt overnight. The solvent was removed *in vacuo*. The product was purified by preparative HPLC (MeOH/H_2O/TFA) to yield Intermediate 11G (11 mg, 33%) as a brown solid. LCMS Anal. Calc'd for $C_{31}H_{30}F_6N_2O_5$ 624.57, found [M+H] 625.4.

Example 11

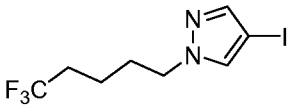
[00312] To a solution of Intermediate 11G (11 mg, 0.018 mmol) in MeOH (0.8 ml) was added piperidine (15 μL). The reaction was stirred at 75 °C for 1.5 h. The product was isolated by preparative HPLC (CH_3CN/H_2O/TFA) to provide Example 11 (5.2 mg, 44%) as a brown solid. LCMS Anal. Calc'd for $C_{31}H_{28}F_6N_2O_4$ 606.56, found [M+H] 607.4. ^{1}H NMR (500 MHz, CD_3OD) δ 1.68 (s, 3 H), 1.95 - 2.07 (m, 2 H), 2.27 (s, 3 H), 2.30 - 2.41 (m, 2 H), 3.11 - 3.26 (m, 2 H), 4.03 (t, J = 6.05 Hz, 2 H), 6.91 (d, J = 8.80 Hz,

2 H), 7.08 - 7.18 (m, 4 H), 7.22 (d, J = 8.25 Hz, 2 H), 7.38 (d, J = 8.80 Hz, 2 H), 7.45 (d, J = 8.80 Hz, 2 H).

Example 12. 3-(2*H*-Tetrazol-5-yl)-4-*p*-tolyl-6-(trifluoromethyl)-6-(1-(5,5,5-trifluoropentyl)-1*H*-pyrazol-4-yl)-5,6-dihydropyridin-2(1*H*)-one

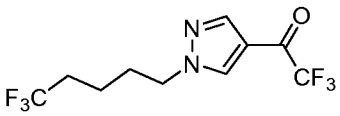


Intermediate 12A. 4-Iodo-1-(5,5,5-trifluoropentyl)-1*H*-pyrazole



[00313] To a stirred solution of 4-iodo-1*H*-pyrazole (337 mg, 1.737 mmol) in DMF (10 mL) was added sodium hydride (104 mg, 2.61 mmol). After 30 min, 5-bromo-1,1,1-trifluoropentane (427 mg, 2.085 mmol) was added. The reaction was stirred at rt for 2 h. 3:1 hexane:ether and water were added. The organic layer was washed with H_2O, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by silica gel chromatography (24 g silica gel, eluted with 0-60% EtOAc in hexanes) to give the desired product (460 mg, 83%) as clear oil. LCMS Anal. Calc'd for $C_8H_{10}F_3IN_2$ 318.0, found [M+H] 319.0. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1 H), 7.40 (s, 1 H), 4.12 (t, J = 6.9 Hz, 2 H), 2.00 - 2.15 (m, 2 H), 1.85 - 1.96 (m, 2 H), 1.47 - 1.61 (m, 2 H).

Intermediate 12B. 2,2,2-Trifluoro-1-(1-(5,5,5-trifluoropentyl)-1*H*-pyrazol-4-yl)ethanone



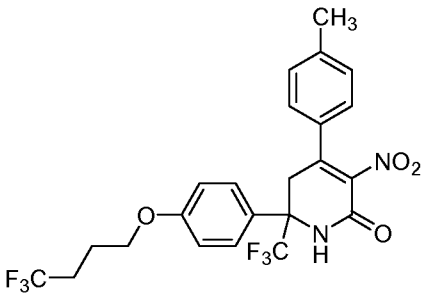
[00314] To a stirred solution of Intermediate 12A (460 mg, 1.446 mmol) in tetrahydrofuran (5 mL) at 0 °C was added isopropylmagnesium chloride (0.795 mL, 1.591 mmol) quickly. After 30 min, additional 0.25 eq of *i*PrMgCl was added and after

30min, the mixure was cooled to -78 °C. 2,2,2-Trifluoro-1-(piperidin-1-yl)ethanone (288 mg, 1.591 mmol) was added quickly and the reaction was warmed to rt and stirred for 3 h. The reaction was quenched with sat'd aq NH_4Cl and diluted with EtOAc. The organic layer was washed with sat'd aq NH_4Cl, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by silica gel chromatography (40 g silica gel, eluted with 0-100% EtOAc in hexanes) to give the desired product (265 mg, 64%) as clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 2 H), 4.22 (t, *J* = 7.0 Hz, 2 H), 2.07 - 2.20 (m, 2 H), 1.98 - 2.05 (m, 2 H), 1.55 - 1.65 (m, 2 H).

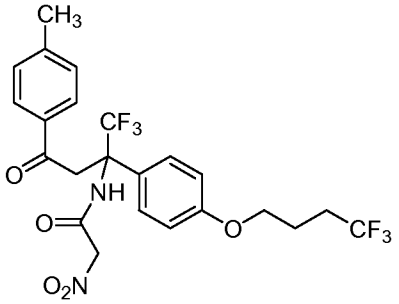
Example 12

[00315] Example 12 was prepared using a procedure analogous to Example 2 by replacing Intermediate 2C with Intermediate 12B. LCMS Anal. Calc'd for $C_{22}H_{21}F_6N_7O$ 513.2, found [M+H] 514.3. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 1 H), 7.63 (s, 1 H), 7.54 - 7.59 (m, 1 H), 7.06 (d, *J* = 8.0 Hz, 2 H), 6.88 (d, *J* = 8.0 Hz, 2 H), 4.16 (t, *J* = 7.0 Hz, 2 H), 3.58 (d, *J* = 18.2 Hz, 1 H), 3.39 (d, *J* = 17.9 Hz, 1 H), 2.28 (s, 3 H), 2.02 - 2.17 (m, 2 H), 1.93 (quin, *J* = 7.4 Hz, 2 H), 1.46 - 1.55 (m, 2 H).

Example 13. 3-Nitro-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one



Intermediate 13A. 2-Nitro-*N*-(1,1,1-trifluoro-4-oxo-4-*p*-tolyl-2-(4-(4,4,4-trifluorobutoxy)phenyl)butan-2-yl)-acetamide

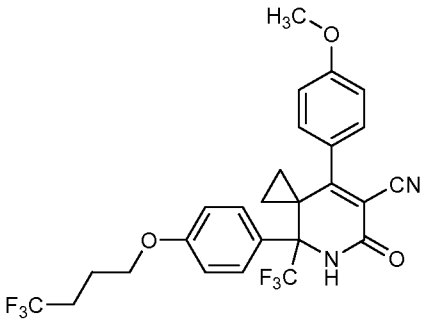


[00316] To a solution of Intermediate 2F (130 mg, 0.3 mmol) in anhydrous THF (1 mL) at 0 °C was added DCC (204 mg, 0.99 mmol) followed by a solution of 2-nitroacetic acid (104 mg, 0.99 mmol) in anhydrous THF (0.5 mL) dropwise. The reaction was stirred at 0 °C for 1 h then at rt overnight. The reaction was heated to 70 °C for 4 h. The reaction was cooled to rt and diluted with EtOAc (3 mL). The solids were filtered off and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (eluted with EtOAc in hexanes) to provide Intermediate 13A (129 mg, 83%) as a brown oil. LCMS Anal. Calc'd for $C_{23}H_{22}F_6N_2O_5$ 520.42, found [M+H] 521.1.

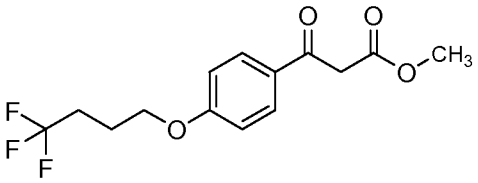
Example 13

[00317] To a solution of Intermediate 13A (126 mg, 0.24 mmol) in MeOH (2 mL) was added piperidine (35 µL). The reaction mixture was heated at 75 °C for 1.5 h. The product was isolated by preparative HPLC (MeOH/H_2O/TFA) to provide Example 13 (21 mg, 17%) as a off-white solid. LCMS Anal. Calc'd for $C_{23}H_{20}F_3N_2O_4$ 502.41, found [M+H] 503.1. ^{1}H NMR (500 MHz, CD_3OD) δ 1.98 - 2.08 (m, 2 H), 2.28 - 2.45 (m, 5 H), 3.58 (d, *J* = 17.60 Hz, 1 H), 3.76 (d, *J* = 17.60 Hz, 1 H), 4.08 (t, *J* = 6.05 Hz, 2 H), 7.02 (d, *J* = 8.80 Hz, 2 H), 7.12 - 7.19 (m, 2 H), 7.22 - 7.30 (m, 2 H), 7.53 (d, *J* = 8.80 Hz, 2 H).

Example 14. 8-(4-Methoxyphenyl)-6-oxo-4-(4-(4,4,4-trifluorobutoxy)phenyl)-4-(trifluoro-methyl)-5-azaspiro[2.5]oct-7-ene-7-carbonitrile

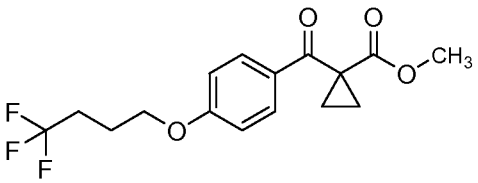


Intermediate 14A. Methyl 3-oxo-3-(4-(4,4,4-trifluorobutoxy)phenyl)propanoate



[00318] To a solution of methyl 3-(4-hydroxyphenyl)-3-oxopropanoate (7.8 g, 40.2 mmol) and 4,4,4-trifluorobutan-1-ol (5.15 g, 40.2 mmol) in CH_2Cl_2 (201 mL) at 0 °C was added triphenylphosphine (12.6 g, 48.2 mmol). The mixture was stirred for a few min, and then DIAD (9.37 mL, 48.2 mmol) was added. The reaction was stirred at 0 °C for 30 min, then warmed to rt and stirred for 3 days. The reaction was loaded directly onto a 300 g silica gel column and eluted with EtOAc in hexanes. Fractions containing the product were combined and concentrated to provide Intermediate 14A (9.9 g, 80%) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.03 - 2.13 (m, 2 H), 2.26 - 2.39 (m, 2 H), 3.75 (s, 3 H), 3.96 (s, 2 H), 4.09 (t, J = 6.05 Hz, 2 H), 6.92 - 6.96 (m, 2 H), 7.86 - 7.97 (m, 2 H).

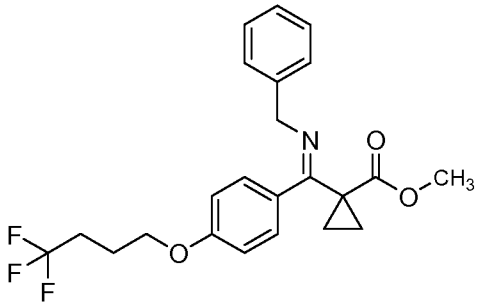
Intermediate 14B. Methyl 1-(4-(4,4,4-trifluorobutoxy)benzoyl)cyclopropanecarboxylate



[00319] To a solution of Intermediate 14A (6.0 g, 19.7 mmol) in DMF (197 mL) was added K_2CO_3 (8.18 g, 59.2 mmol) followed by 1,2-dibromoethane (2.6 mL, 30 mmol). The reaction mixture was stirred at rt for 2 days. The reaction was reduced in volume *in vacuo*, then diluted with EtOAc, washed with a 1:1 solution of sat'd aq NaCl and water,

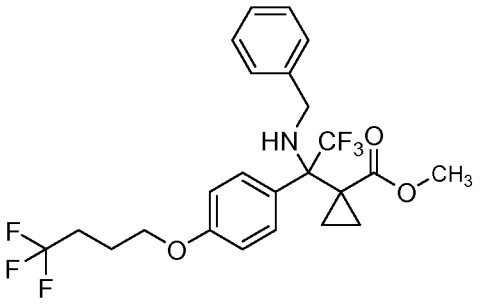
dried over anhydrous $MgSO_4$, filtered and concentrated. The product was isolated by silica gel chromatography (220 g silica gel, eluted with EtOAc in hexanes) to provide Intermediate 14B (4.2 g, 61%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 - 1.49 (m, 2 H), 1.56 - 1.61 (m, 2 H), 2.03 - 2.14 (m, 2 H), 2.26 - 2.39 (m, 2 H), 3.60 (s, 3 H), 4.09 (t, J = 6.05 Hz, 2 H), 6.90 - 6.94 (m, 2 H), 7.86 - 7.93 (m, 2 H).

Intermediate 14C. Methyl 1-((benzylimino)(4-(4,4,4-trifluorobutoxy)phenyl)methyl)cyclopropane carboxylate



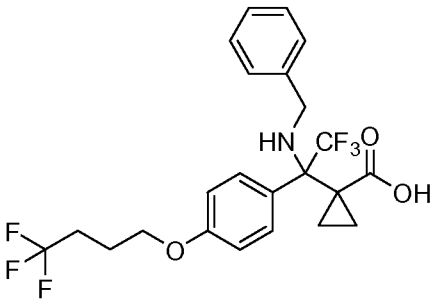
[00320] To a solution of Intermediate 14B (4.2 g, 13 mmol) and benzylamine (5.5 mL, 50 mmol) in diethyl ether (63 mL) at 0 °C was added 1.0 M $TiCl_4$ in CH_2Cl_2 (7.6 mL, 7.5 mmol). The reaction was stirred at 0 °C for a few minutes, then warmed to rt and stirred for 16 h. Celite® was added to the reaction and the solids were removed by filtering through a bed of Celite®. The filtrate was concentrated and purified by silica gel chromatography (120 g silica gel, eluted with EtOAc in hexanes) to provide Intermediate 14C (4.6 g, 83%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 8.8 Hz, 2H), 7.42 - 7.38 (m, 2H), 7.34 (t, J = 7.7 Hz, 2H), 7.27 - 7.24 (m, 1H), 6.87 (d, J = 8.8 Hz, 2H), 4.90 (s, 2H), 4.04 (t, J = 6.0 Hz, 2H), 3.69 (s, 3H), 2.39 - 2.26 (m, 2H), 2.11 - 2.02 (m, 2H), 1.78 - 1.72 (m, 2H), 1.11 (d, J = 3.3 Hz, 2H).

Intermediate 14D. Methyl 1-(1-(benzylamino)-2,2,2-trifluoro-1-(4-(4,4,4-trifluorobutoxy)phenyl)ethyl)-cyclopropane carboxylate



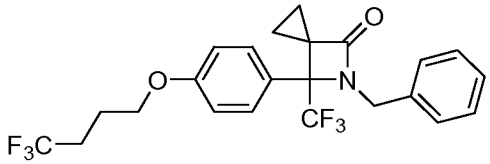
[00321] To a solution of Intermediate 14C (4.6 g, 11 mmol) in acetonitrile (22 mL) and DMF (2.6 mL, 33 mmol) at 0 °C was added neat TFA (1.1 mL, 13.7 mmol) followed by potassium hydrogen fluoride (0.64 g, 8.2 mmol). The reaction was stirred for ca. 5 min, then trimethyl(trifluoromethyl)silane (2.4 mL, 16.4 mmol) was added and the reaction was warmed to rt and stirred for 16 h. Sat'd aqueous $NaHCO_3$ was added to the reaction and the mixture was extracted with EtOAc. The combined organic extracts were washed with sat'd aq NaCl, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (220 g silica gel, eluted with EtOAc in hexanes) to provide Intermediate 14D (1.8 g, 31%) as an oil. LCMS Anal. Calc'd for $C_{24}H_{25}F_6NO_3$ 489.45, found [M+H] 490.1.

Intermediate 14E. 1-(1-(Benzylamino)-2,2,2-trifluoro-1-(4-(4,4,4-trifluorobutoxy)phenyl)ethyl)-cyclopropane carboxylic acid



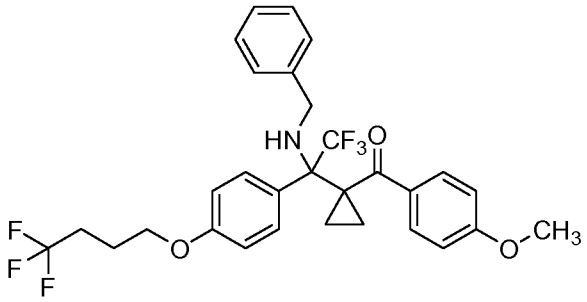
[00322] To a solution Intermediate 14D (558 mg, 1.140 mmol) in pyridine (5.7 mL) was added lithium iodide (1.53 g, 11.4 mmol). The reaction was heated to reflux overnight. The reaction was cooled to rt and diluted with water and EtOAc. The aqueous layer was made acidic with 1 N HCl and the layers were separated. The organic layer was washed with sat'd aq NaCl, dried over $MgSO_4$, filtered and concentrated to provide Intermediate 14E (506 mg, 84%) which was used in the next step without further purification. LCMS Anal. Calc'd for $C_{23}H_{23}F_6NO_3$ 475.42, found [M+H] 476.2.

Intermediate 14F. 5-Benzyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5-azaspiro[2.3]-hexan-4-one



[00323] To a solution of Intermediate 14E (506 mg, 1.1 mmol) in CH_2Cl_2 (11 mL) was added oxalyl chloride (0.12 mL, 2.2 mmol) followed by several drops of DMF. The reaction was stirred at rt for 16 h. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (24 g silica gel, eluted with EtOAc in hexanes) to provide Intermediate 14F (389 mg, 72%) as a yellow oil. LCMS Anal. Calc'd for $C_{23}H_{21}F_6NO_2$ 457.41, found [M+H] 458.2.

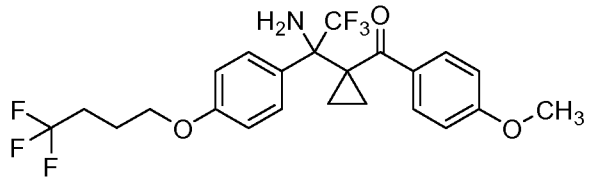
Intermediate 14G. (1-(1-(Benzylamino)-2,2,2-trifluoro-1-(4-(4,4,4-trifluorobutoxy)phenyl)ethyl)-cyclopropyl)-(4-methoxyphenyl)methanone



[00324] Magnesium turnings (130 mg, 5.4 mmol) were suspended in anhydrous THF (13 mL). 4-Bromoanisole (1 g, 670 µL, 5.4 mmol) was added followed by a few drops of 1,2-dibromoethane. The reaction mixture was stirred at rt for 1.5 h after which most of the magnesium had dissolved. The reaction was warmed to 50 °C for 30 min, then cooled to rt. Final concentration of the Grignard reagent was 0.4 M assuming complete conversion. To a cold solution (-40 °C) of Intermediate 14F (200 mg, 0.44 mmol) in THF (4.4 mL) was added the freshly prepared Grignard reagent. The reaction was warmed from -40 °C to rt, then heated to reflux overnight. The reaction was cooled to room temperature and quenched with sat'd aq NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with sat'd aq NaCl, dried over $MgSO_4$, filtered and concentrated. The product was

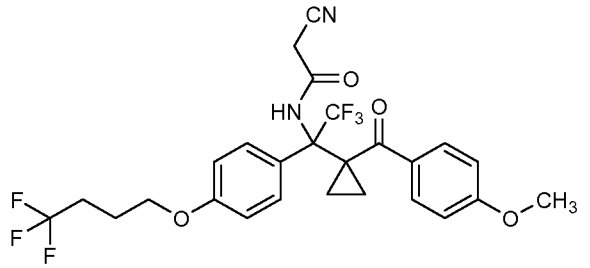
isolated using preparative HPLC (MeOH/H_2O/TFA). Fractions containing the product were combined and reduced in volume *in vacuo*. The resulting aqueous solution was made basic with sat'd aq $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were washed with sat'd aq NaCl, dried over Na_2SO_4, filtered and concentrated to provide Intermediate 14G (6.1 mg, 2.5%). LCMS Anal. Calc'd for $C_{30}H_{29}F_6NO_3$ 565.55, found [M+H] 566.3.

Intermediate 14H. (1-(1-Amino-2,2,2-trifluoro-1-(4-(4,4,4-trifluorobutoxy)phenyl)ethyl)cyclopropyl)(4-methoxy-phenyl)methanone



[00325] To a solution of Intermediate 14G (6 mg, 10.6 μmol) in MeOH (1 mL) containing 4.4% formic acid was added 10% palladium on carbon (2 mg, 2 μmol). The reaction was stirred at rt overnight. The reaction was filtered through Celite®. The filtrate was made basic with sat'd aq $NaHCO_3$, and then evaporated to remove MeOH. The aqueous residue was diluted with sat'd aq NaCl and extracted with EtOAc. The combined organic extracts were washed with sat'd aq NaCl, dried over Na_2SO_4, filtered and concentrated to provide Intermediate 14H (4 mg, 71%) as a tan glass. LCMS Anal. Calc'd for $C_{23}H_{23}F_6NO_3$ 475.42, found [M+H] 476.2.

Intermediate 14I. 2-Cyano-*N*-(2,2,2-trifluoro-1-(1-(4-methoxybenzoyl)cyclopropyl)-1-(4-(4,4,4-trifluorobutoxy)-phenyl)ethyl)acetamide



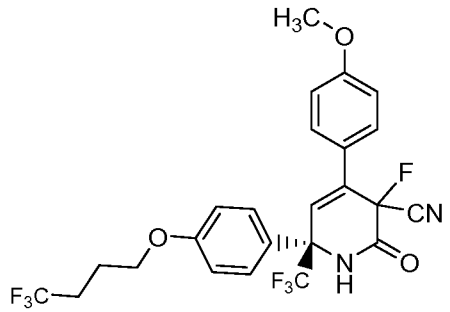
[00326] To a solution of 2-cyanoacetic acid (320 mg, 3.8 mmol) in CH_2Cl_2 (9.1 mL) was added oxalyl chloride (523 mg, 360 μL, 4.1 mmol) followed by a few drops of DMF. The reaction was stirred at rt for 1 h. Final concentration of 2-cyanoacetyl chloride was

0.4 M assuming complete conversion. To a solution of Intermediate 14H (4 mg, 8.4 μmol) and pyridine (2.0 μL, 0.025 mmol) in CH_2Cl_2 (100 μL) at 0 °C was added the freshly prepared 0.4 M 2-cyanoacetyl chloride in CH_2Cl_2 (0.032 mL, 0.013 mmol). The reaction was warmed to rt and stirred for 16 h. The reaction was quenched with one drop of MeOH, diluted with EtOAc and washed with 1:1 sat'd aq NaCl and water, dried over $MgSO_4$, filtered and concentrated to provide Intermediate 14I (7 mg, 153%), which was used in the next step without further purification. LCMS Anal. Calc'd for $C_{26}H_{24}F_6N_2O_4$ 542.47, found [M+H] 543.3.

Example 14

[00327] To a solution of Intermediate 14I (7 mg, 0.013 mmol) in EtOH (2 mL) was added 25% w/w sodium methoxide (0.015 mL, 0.065 mmol). The reaction was stirred at rt for 1.5 h. The reaction was made acidic with a few drops of 1 N aqueous HCl and then concentrated. The product was isolated by preparative HPLC (MeOH/H_2OTFA). The fraction containing the product was reduced in volume *in vacuo*, made basic with sat'd aq $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were washed with sat'd aq NaCl, dried over $MgSO_4$, filtered and concentrated to provide Example 14 (2.9 mg, 42%). LCMS Anal. Calc'd for $C_{26}H_{22}F_6N_2O_3$ 524.46, found [M+H] 525.2. ^{1}H NMR (500 MHz, CD_3OD) δ 0.65 (t, J = 8.80 Hz, 2 H), 1.18 - 1.25 (m, 2 H), 1.99 - 2.08 (m, 2 H), 2.31 - 2.43 (m, 2 H), 3.85 (s, 3 H), 4.09 (t, J = 6.05 Hz, 2 H), 7.03 (d, J = 8.80 Hz, 2 H), 7.06 (br. s., 2 H), 7.23 (br. s., 2 H), 7.58 (d, J = 9.35 Hz, 2 H).

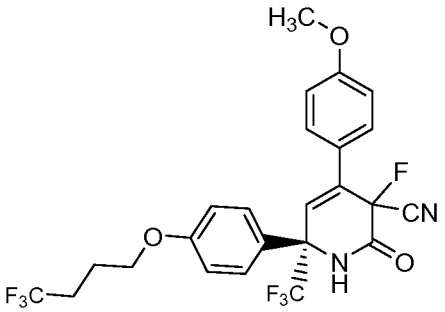
Examples 15-1 and Example 15-2. 3-Fluoro-4-(4-methoxyphenyl)-2-oxo-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,3,6-tetrahydropyridine-3-carbonitrile



[00328] To a solution of the Example 77 (70 mg, 0.140 mmol) in DMF (1.4 mL) was added Na_2CO_3 (30 mg, 0.28 mmol) followed by 1-fluoro-4-hydroxy-1,4-

diazoniabicyclo[2,2,2]octane-bis-(tetrafluoroborate) (196 mg, 0.28 mmol). The reaction was heated to 80 °C overnight. The reaction was cooled to rt and diluted with EtOAc and water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with sat'd aq NaCl, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC (MeOH/H_2OTFA) to yield the product (44 mg, 61%) as a mixture of two diastereoisomers. The two diastereoisomers were separated by preparative chiral SFC method B to provide Example 15-1 (14.6 mg, 20%) and Example 15-2 (17.2 mg, 23%). Data for Example 15-1: LCMS Anal. Calc'd for $C_{24}H_{19}F_7N_2O_3$ 516.41, found [M+H] 517.2. ^{1}H NMR (500 MHz, CD_3OD) δ 2.00 - 2.08 (m, 2 H), 2.32 - 2.44 (m, 2 H), 3.85 (s, 3 H), 4.10 (t, *J* = 6.05 Hz, 2 H), 6.92 (d, *J* = 1.10 Hz, 1 H), 7.02 (d, *J* = 8.80 Hz, 2 H), 7.07 (d, *J* = 9.35 Hz, 2 H), 7.50 (d, *J* = 8.25 Hz, 2 H), 7.57 (d, *J* = 8.80 Hz, 2 H). Analytical chiral HPLC method B: RT = 3.23 min, 99% ee. Data for Example 15-2: LCMS Anal. Calc'd for $C_{24}H_{19}F_7N_2O_3$ 516.41, found [M+H] 517.2. ^{1}H NMR (500 MHz, CD_3OD) δ 2.00 - 2.08 (m, 2 H), 2.32 - 2.44 (m, 2 H), 3.85 (s, 3 H), 4.10 (t, *J* = 6.05 Hz, 2 H), 6.92 (d, *J* = 1.10 Hz, 1 H), 7.02 (d, *J* = 8.80 Hz, 2 H), 7.07 (d, *J* = 9.35 Hz, 2 H), 7.50 (d, *J* = 8.25 Hz, 2 H), 7.57 (d, *J* = 8.80 Hz, 2 H). Analytical chiral HPLC method B: RT = 4.84 min, 99% ee.

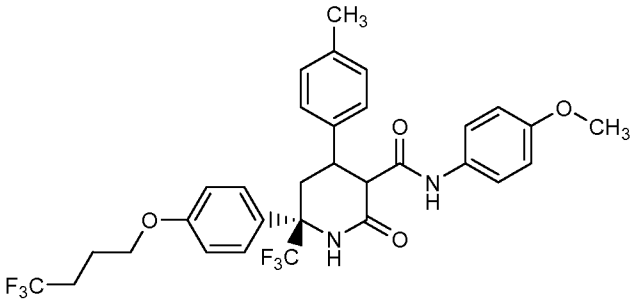
Examples 15-3 and Example 15-4. 3-Fluoro-4-(4-methoxyphenyl)-2-oxo-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,3,6-tetrahydropyridine-3-carbonitrile



[00329] Application of the method described for Example 15-1 and Example 15-2 provided Example 15-3 (4.6 mg, 43%) and Example 15-4 (4.6 mg, 43%) from the *R*-isomer of Example 65 (10 mg, 0.02 mmol). Data for Example 15-3: LCMS Anal. Calc'd for $C_{24}H_{19}F_7N_2O_3$ 516.41, found [M+H] 517.1. ^{1}H NMR (500 MHz, CD_3OD) δ 2.00 - 2.08 (m, 2 H) 2.31 - 2.44 (m, 2 H) 3.85 (s, 3 H) 4.10 (t, *J* = 6.05 Hz, 2 H) 6.92 (d, *J* = 1.65 Hz, 1 H) 7.02 (d, *J* = 8.80 Hz, 2 H) 7.07 (d, *J* = 8.80 Hz, 2 H) 7.50 (d, *J* = 8.25 Hz,

2 H) 7.57 (d, *J* = 8.80 Hz, 2 H). Analytical chiral HPLC method B: RT = 5.13 min, 99% ee. Data for Example 15-4: LCMS Anal. Calc'd for $C_{24}H_{19}F_7N_2O_3$ 516.41, found [M+H] 517.1. ^{1}H NMR (500 MHz, CD_3OD) δ 1.99 - 2.07 (m, 2 H) 2.30 - 2.43 (m, 2 H) 3.84 (s, 3 H) 4.09 (t, *J* = 6.05 Hz, 2 H) 6.78 (s, 1 H) 7.02 (d, *J* = 8.80 Hz, 2 H) 7.05 (d, *J* = 9.35 Hz, 2 H) 7.54 (dd, *J* = 8.25, 4.95 Hz, 4 H). Analytical chiral HPLC method B: RT = 5.13 min, 99% ee.

Example 16-1 and Example 16-2. *N*-(4-Methoxyphenyl)-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)piperidine-3-carboxamide

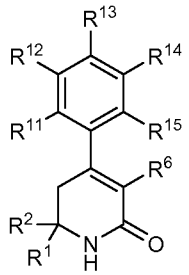


[00330] To a solution of Example 6-2 (90 mg, 0.15 mol) in MeOH (2 mL) was added 10% palladium on carbon (5 mg). The mixture was stirred under hydrogen (50 psi) overnight. Additional palladium on carbon (5 mg) was added and the reaction was stirred under hydrogen (50 psi) for an additional 1 h. The catalyst was removed by filtration through a pad of Celite® and the solution was concentrated *in vacuo*. The products were partly separated by preparative HPLC (CH_3CN/H_2O/TFA). Fractions containing the two products were combined and separated by chiral HPLC method D to provide Example 16-1 and Example 16-2. Data for Example 16-1: LCMS Anal. Calc'd for $C_{31}H_{30}F_6N_2O_4$ 608.57, found [M+H] 609.2. ^{1}H NMR (400 MHz, CD_3OD) δ 1.97 - 2.14 (m, 2 H), 2.25 (s, 3 H), 2.32 - 2.46 (m, 2 H), 2.54 - 2.69 (m, 2 H), 3.17 (td, *J* = 11.82, 3.85 Hz, 1 H), 3.60 (d, *J* = 11.54 Hz, 1 H), 3.71 (s, 3 H), 4.10 (t, *J* = 6.05 Hz, 2 H), 6.76 (d, *J* = 8.79 Hz, 2 H), 6.99 - 7.12 (m, 6 H), 7.13 - 7.23 (m, 2 H), 7.55 (d, *J* = 8.79 Hz, 2 H). Analytical chiral HPLC method D RT = 6.75 min, 99% ee. Data for Example 16-2: LCMS Anal. Calc'd for $C_{31}H_{30}F_6N_2O_4$ 608.57, found [M+H] 609.2. ^{1}H NMR (400 MHz, CD_3OD) δ 7.52 (d, *J* = 8.8 Hz, 2H), 7.25 - 7.20 (m, 2H), 7.19 - 7.15 (m, 2H), 7.14 - 7.10 (m, 2H), 7.02 - 6.97 (m, 2H), 6.81 - 6.75 (m, 2H), 4.07 (t, *J* = 6.0 Hz, 2H), 3.94 - 3.84 (m, 1H), 3.73 (s, 3H), 3.60 (d, *J* = 12.1 Hz, 1H), 2.90 (dd, *J* = 14.8, 3.3 Hz, 1H), 2.45 - 2.32 (m,

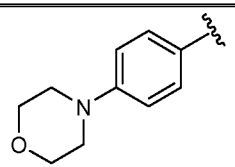
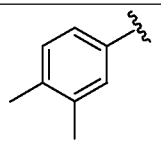
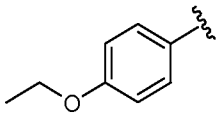
2H), 2.31 (dd, 1H, overlaps with peak at δ 2.27), 2.27 (s, 3H), 2.08 - 1.98 (m, 2H). Preparative chiral HPLC method D: RT = 10.9 min, 99% ee.

[00331] Examples 17-101 expressed by Formula (IIa), unless noted in the table, may be made by one skilled in the art by appropriate application of the procedures described for Examples 1-16. R^{11} to R^{15} are hydrogen, unless noted in the table.

Table 2

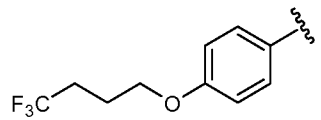
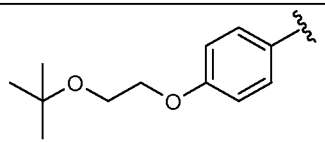
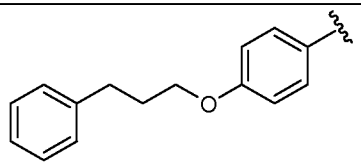


(IIa)

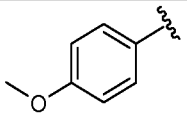
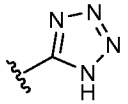
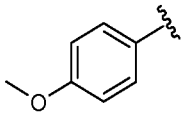
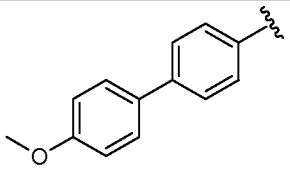
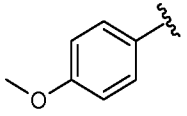
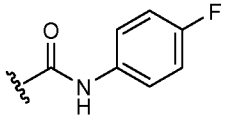
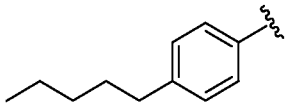
Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
17 Rac		CH_3	CN	R^{13} = morpholine	459.2*	
18 Rac		CH_3	CN	$R^{12} = CH_3$ $R^{13} = CH_3$	345.1*	
19 Rac		CH_3	CN	$R^{13} = OCH_2CH_3$	377.2*	

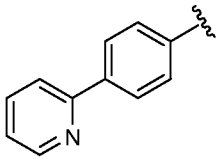
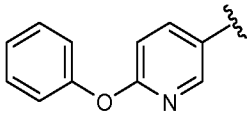
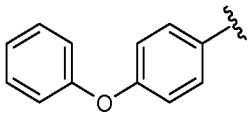
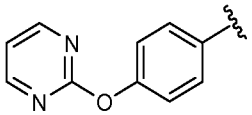
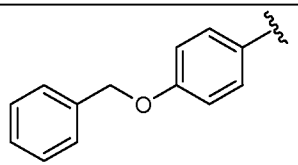
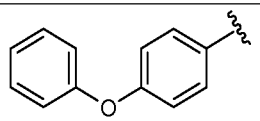
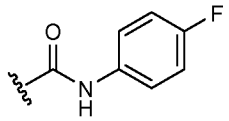
Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
20 Rac		CH_3	CN	R^{13} = *t*-Bu	401.2*	
21 Rac		CH_3		$R^{13} = CH_3$	360.2	
22 Rac		CF_3	CN	$R^{13} = CH_3$	371.2	
23 Rac		CH_3	CN	$R^{13} = CH_3$	331.3	
24 Rac		CF_3	CN	$R^{13} = CH_3$	391.1	
25 Rac		CF_3	CN	$R^{13} = CH_3$	375.2	
26 Rac		CF_3	CN	$R^{13} = CH_3$	393.2	

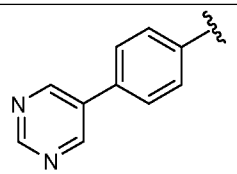
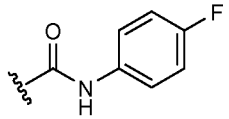
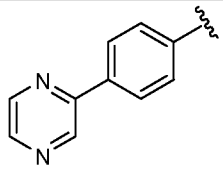
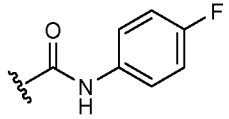
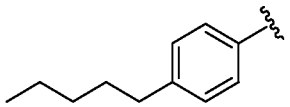
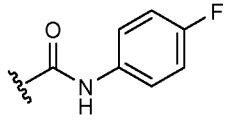
Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
27 Rac		CF_3	CN	$R^{13} = CH_3$	375.2	
28 Rac		CF_3	CN	$R^{13} = CH_3$	413.3	
29 Rac		CF_3	CN	$R^{12} = CH_3$	387.2	
30 Rac		CF_3	CN	$R^{13} = CH_3$	387.2	
31 Rac		CF_3	CN	$R^{13} = CH_3$	400.2	
32 Rac		CF_3	CN	$R^{13} = CH_3$	435.2	

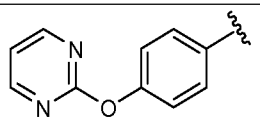
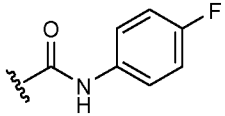
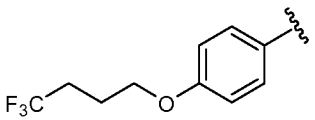
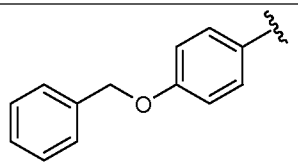
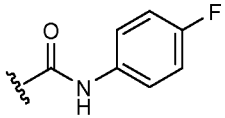
Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
33 Rac		CF_3	CN	$R^{13} = CH_3$	483.3	2.03 - 2.12 (m, 2 H) 2.25 - 2.36 (m, 2 H) 2.42 (s, 3 H) 3.51 - 3.68 (m, 2 H) 4.04 (t, *J* = 5.50 Hz, 2 H) 6.94 (d, *J* = 8.80 Hz, 2 H) 7.31 (d, *J* = 7.70 Hz, 2 H) 7.40 (d, *J* = 8.80 Hz, 2 H) 7.47 (d, *J* = 7.70 Hz, 2 H) 7.64 (br. s., 1 H).
34 Rac		CF_3	CN	$R^{13} = CH_3$	471.4 [M-H]-	
35 Rac		CF_3	CN	$R^{13} = CH_3$	491.3	2.06 - 2.18 (m, 2 H) 2.41 (s, 3 H) 2.81 (t, *J* = 7.70 Hz, 2 H) 3.45 - 3.68 (m, 2 H) 3.97 (t, *J* = 6.32 Hz, 2 H) 6.55 (s, 1 H) 6.93 (d, *J* = 8.80 Hz, 2 H) 7.21 (d, *J* = 7.15 Hz, 3 H)

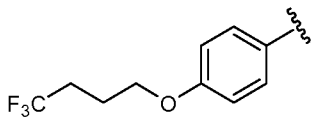
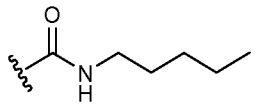
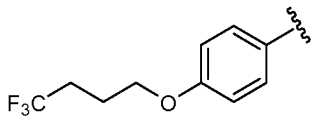
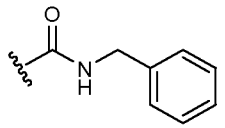
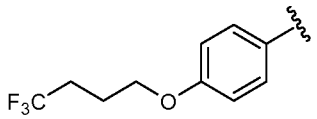
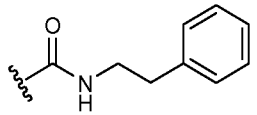
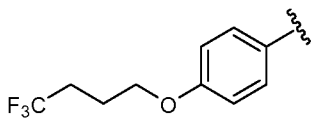
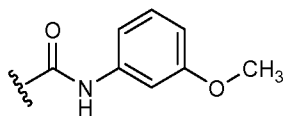
Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						7.25 - 7.31 (m, 4 H) 7.37 (d, *J* = 8.25 Hz, 2 H) 7.45 (d, *J* = 8.25 Hz, 2 H).
36 Rac		CF_3	CN	$R^{13} = CH_3$	469.3	1.16 (dd, *J* = 12.10, 8.25 Hz, 2 H) 1.54 (dd, *J* = 7.42, 4.67 Hz, 2 H) 1.60 - 1.70 (m, 2 H) 1.81 (q, *J* = 6.60 Hz, 4 H) 1.96 (m, *J* = 7.70 Hz, 1 H) 2.41 (s, 3 H) 3.45 - 3.64 (m, 2 H) 3.98 (t, *J* = 6.60 Hz, 2 H) 6.50 (s, 1 H) 6.94 (d, *J* = 9.35 Hz, 2 H) 7.23 - 7.32 (m, 2 H) 7.37 (d, *J* = 8.80 Hz, 2 H) 7.44 (d, *J* = 8.25 Hz, 2 H).
37 Rac		CF_3	CN	$R^{13} = CH_3$	443.3	

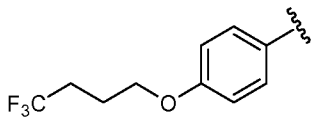
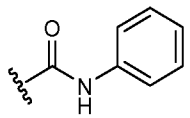
Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
38 Rac		CF_3		$R^{13} = CH_3$	430.1	
39 S-isomer		CF_3	CN	$R^{13} = CH_3$	387.2	
40 Rac		CF_3	CN	$R^{13} = CH_3$	463.2	
41 Rac		CF_3		$R^{13} = CH_3$	499.2	
42 Rac		CF_3	CN	$R^{13} = CH_3$	427.4	0.85 - 0.96 (m, 3 H) 1.33 (d, *J* = 2.75 Hz, 4 H) 1.47 - 1.69 (m, 4 H) 2.41 (s, 3 H) 2.56 - 2.67 (m, 2 H) 3.45 - 3.66 (m, 2 H) 6.46 (br. s., 1 H) 7.20 - 7.31 (m, 4 H) 7.37 (d, *J* = 7.15 Hz, 2 H) 7.45 (d, *J* =

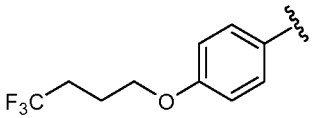
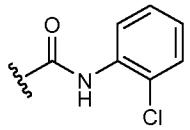
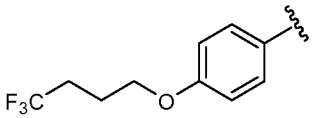
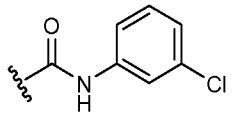
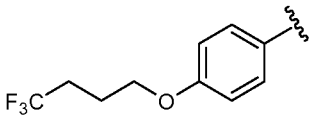
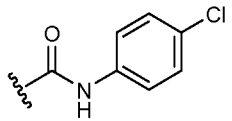
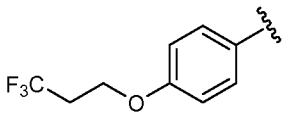
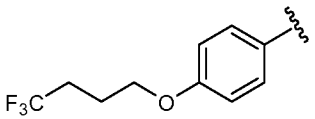
Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						6.60 Hz, 2 H).
43 Rac		CF_3	CN	$R^{13} = CH_3$	434.3	
44 Rac		CF_3	CN	$R^{13} = CH_3$	450.3	
45 Rac		CF_3	CN	$R^{13} = CH_3$	449.3	
46 Rac		CF_3	CN	$R^{13} = CH_3$	451.3	
47 Rac		CF_3	CN	$R^{13} = CH_3$	463.3	
48 Rac		CF_3		$R^{13} = CH_3$	561.4	2.36 (s, 3 H) 3.40 - 3.59 (m, 2 H) 6.82 (s, 1 H) 6.93 (t, *J* = 8.79 Hz, 2 H) 7.01 - 7.13 (m,

Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						5 H) 7.15 - 7.20 (m, 3 H) 7.34 - 7.45 (m, 4 H) 7.48 (d, *J* = 8.79 Hz, 2 H) 9.86 (s, 1 H).
49 Rac		CF_3		$R^{13} = CH_3$	547.4	2.30 (s, 3 H) 3.57 - 3.81 (m, 2 H) 6.96 (t, *J* = 8.79 Hz, 2 H) 7.17 (d, *J* = 7.70 Hz, 2 H) 7.27 - 7.38 (m, 4 H) 7.83 (m, 4 H) 9.11 (s, 2 H) 9.16 (s, 1 H).
50 Rac		CF_3		$R^{13} = CH_3$	547.4	
51 Rac		CF_3		$R^{13} = CH_3$	539.5	0.90 (t, *J* = 6.87 Hz, 3 H) 1.28 - 1.40 (m, 4 H) 1.58 - 1.71 (m, 2 H) 2.35 (s, 3 H) 2.55 - 2.71 (m, 2 H) 3.30 - 3.60 (m, 2 H) 6.63 (s, 1 H) 6.92 (t, *J* = 8.52 Hz, 2 H)

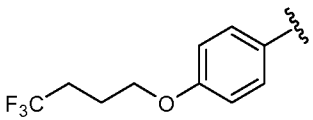
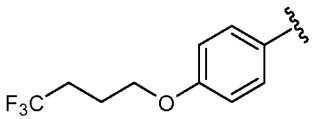
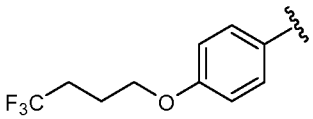
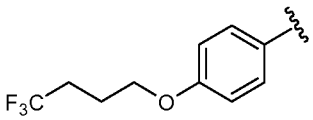
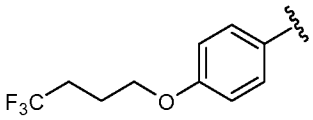
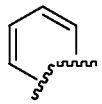
Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						7.05 - 7.12 (m, 2 H) 7.14 - 7.20 (m, 2 H) 7.22 - 7.31 (m, 2 H) 7.37 - 7.49 (m, 4 H) 9.94 (s, 1 H).
52 Rac		CF_3		$R^{13} = CH_3$	563.4	
53 S-isomer		CF_3	CN	$R^{13} = CH_3$	483.2	1.93 - 2.09 (m, 2 H) 2.27 - 2.38 (m, 2 H) 2.40 (s, 3 H) 3.62 - 3.78 (m, 2 H) 4.06 (t, *J* = 6.05 Hz, 2 H) 7.00 (d, *J* = 8.80 Hz, 2 H) 7.33 (d, *J* = 7.70 Hz, 2 H) 7.44 - 7.58 (m, 4 H).
54 Rac		CF_3		$R^{13} = CH_3$	575.3	

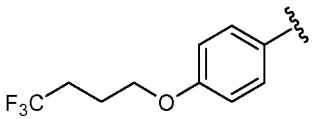
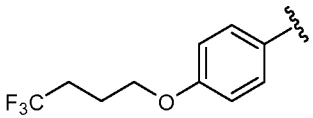
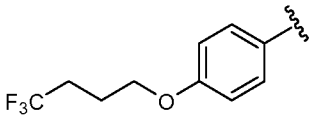
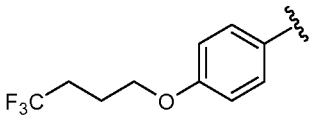
Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
55 Rac		CF_3		$R^{13} = CH_3$	571.4	
56 Rac		CF_3		$R^{13} = CH_3$	591.3	
57 Rac		CF_3		$R^{13} = CH_3$	605.4	2.02 (dd, *J* = 9.90, 6.05 Hz, 2 H) 2.28 - 2.40 (m, 5 H) 2.45 - 2.58 (m, 2 H) 3.12 - 3.35 (m, 2 H) 3.37 - 3.60 (m, 2 H) 4.05 (t, *J* = 6.05 Hz, 2 H) 6.91 - 7.01 (m, 4 H) 7.09 - 7.20 (m, 5 H) 7.21 - 7.26 (m, 2 H) 7.50 (d, *J* = 8.80 Hz, 2 H).
58 Rac		CF_3		$R^{13} = CH_3$	607.3	1.96 - 2.07 (m, 2 H) 2.26 - 2.32 (m, 3 H) 2.32 - 2.42 (m, 2 H) 3.45 - 3.67 (m, 2 H) 4.06 (t, *J* = 6.05 Hz, 2 H)

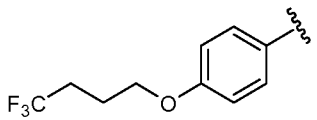
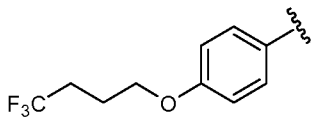
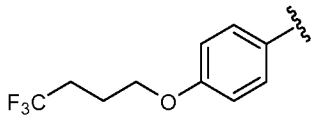
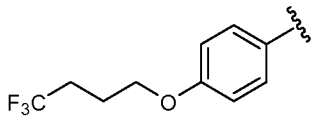
Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						6.61 (dd, *J* = 8.25, 2.20 Hz, 1 H) 6.83 (d, *J* = 8.25 Hz, 1 H) 6.98 (d, *J* = 8.80 Hz, 2 H) 7.03 (s, 1 H) 7.09 (t, *J* = 8.25 Hz, 1 H) 7.16 (d, *J* = 8.25 Hz, 2 H) 7.28 (d, *J* = 8.25 Hz, 2 H) 7.52 (d, *J* = 8.80 Hz, 2 H).
59 Rac		CF_3		$R^{13} = CH_3$	577.3	1.95 - 2.08 (m, 2 H) 2.28 (s, 3 H) 2.32 - 2.42 (m, 2 H) 3.42 - 3.70 (m, 2 H) 4.05 (t, *J* = 6.05 Hz, 2 H) 6.97 (d, *J* = 8.80 Hz, 2 H) 7.00 - 7.06 (m, 1 H) 7.15 (d, *J* = 8.25 Hz, 2 H) 7.20 (t, *J* = 7.97 Hz, 2 H) 7.30 (dd, *J* = 16.77, 7.97 Hz, 4 H) 7.52 (d, *J* = 8.80 Hz, 2 H).

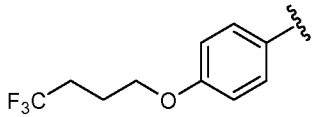
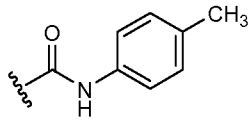
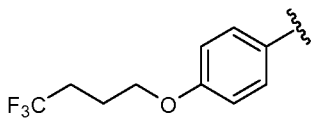
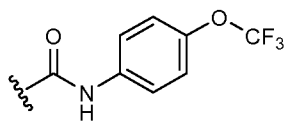
Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
60 Rac		CF_3		$R^{13} = CH_3$	611.3	
61 Rac		CF_3		$R^{13} = CH_3$	611.3	
62 Rac		CF_3		$R^{13} = CH_3$	611.3	
63 Rac		CF_3	CN	$R^{13} = CH_3$	469.1	2.40 (s, 3 H) 2.63 - 2.75 (m, 2 H) 3.65 - 3.77 (m, 2 H) 4.24 (t, *J* = 6.05 Hz, 2 H) 7.01 (d, *J* = 9.35 Hz, 2 H) 7.33 (d, *J* = 7.70 Hz, 2 H) 7.50 (d, *J* = 8.25 Hz, 2 H) 7.54 (d, *J* = 8.80 Hz, 2 H).
64 Rac		CF_3	CN	$R^{12} = OCH_3$	499.2	

Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
65 Rac		CF_3	CN	$R^{13} = OCH_3$	499.2	1.95 - 2.07 (m, 2 H) 2.29 - 2.43 (m, 2 H) 3.88 (s, 3 H) 3.92 (d, J = 16.51 Hz, 1 H) 4.06 (t, J = 6.05 Hz, 2 H) 4.55 (d, J = 16.23 Hz, 1 H) 6.96 (d, J = 9.08 Hz, 2 H) 7.01 (d, J = 8.80 Hz, 2 H) 7.52 (d, J = 9.08 Hz, 2 H) 7.97 (d, J = 9.08 Hz, 2 H)
66 Rac		CF_3	CN	R^{13} = CN	494.2	
67 Rac		CF_3	CN	R^{11} = F	487.2	
68 Rac		CF_3	CN	R^{12} = Cl	503.2	

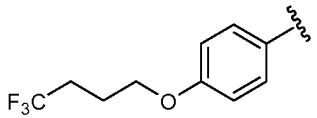
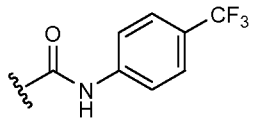
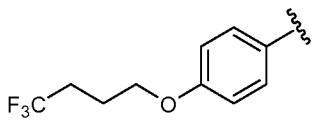
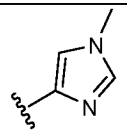
Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
69 Rac		CF_3	CN	R^{12} = CN	494.2	
70 Rac		CF_3	H	R^{13} = CH_3	458.2	
71 Rac		CF_3	CN	all H	469.2	
72 Rac		CF_3	CN	R^{13} = Cl	503.1	
73 Rac		CF_3	CN	R^{12} and R^{13} 	519.2	8.15 (d, *J* = 1.7 Hz, 1H), 8.01 - 7.95 (m, 2H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.65 - 7.55 (m, 5H), 7.05 - 7.00 (m, 2H), 4.07 (t, *J* = 6.1 Hz, 2H), 3.85 (ABq, *J* = 18.1 Hz, 2H), 2.42 - 2.29 (m, 2H), 2.06 - 1.98

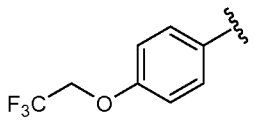
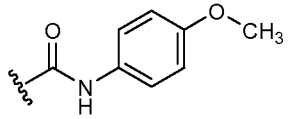
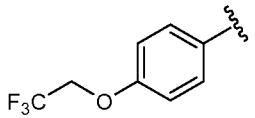
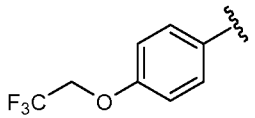
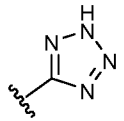
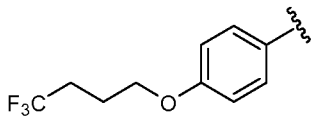
Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						(m, 2H)
74 Rac		CF_3	CN	R^{13} = F	487.2	
75 Rac		CF_3	CN	R^{13} = CF_3	537.2	
76 Rac		CF_3	CN	R^{12} = CH_3	483.2	
77 S-isomer		CF_3	CN	R^{13} = OCH_3	499.2	1.97 - 2.06 (m, 2 H) 2.27 - 2.42 (m, 2 H) 3.66 (d, *J* = 17.90 Hz, 1 H) 3.75 (d, *J* = 17.90 Hz, 1 H) 3.87 (s, 3 H) 4.06 (t, *J* = 6.05 Hz, 2 H) 6.96 - 7.02 (m, 2 H) 7.03 - 7.08 (m, 2 H) 7.52 (d, *J* = 8.80 Hz, 2 H) 7.61 - 7.68 (m, 2 H)

Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
78 Rac		CF_3	CN	$R^{13} = OCHF_2$	535.1	7.69 - 7.63 (m, 2H), 7.54 (d, *J* = 9.1 Hz, 2H), 7.31 - 7.25 (m, 2H), 7.01 (m, 2H), 6.96 (t, *J* = 73.5 Hz, 1 H), 4.07 (t, *J* = 6.1 Hz, 2H), 3.78 - 3.67 (m, 2H), 2.44 - 2.30 (m, 2H), 2.07 - 1.97 (m, 2H)
79 Rac		CF_3	CN	$R^{13} = OCF_3$	553.1	
80 Rac		CF_3	CN	$R^{13} = OCH_2CH_3$	513.2	
81 Rac		CF_3	CN	$R_{11} = F$ $R^{13} = OCH_3$	517.2	7.51 (d, *J* = 9.1 Hz, 2H), 7.36 (t, *J* = 8.8 Hz, 1H), 7.04 - 6.97 (m, 2H), 6.91 - 6.83 (m, 2H), 4.08 (t, *J* = 6.1 Hz, 2H), 3.87 (s, 3H), 3.65 (s, 2H), 2.46 - 2.29 (m, 2H), 2.08 -

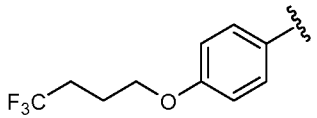
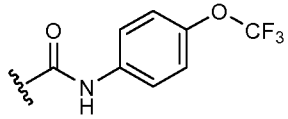
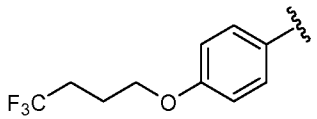
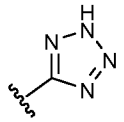
Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						1.98 (m, 2H)
82 Rac		CF_3		$R^{13} = CH_3$	591.2	7.52 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 7.7 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.98 (d, *J* = 7.7 Hz, 2H), 4.06 (t, *J* = 6.0 Hz, 2H), 3.64 (d, *J* = 17.0 Hz, 1H), 3.48 (d, *J* = 17.0 Hz, 1H), 2.39 - 2.32 (m, 2H), 2.29 (s, 3H), 2.24 (s, 3H), 2.06 - 1.98 (m, 2H).
83 Rac		CF_3		$R^{13} = CH_3$	661.2	7.53 (d, *J* = 8.8 Hz, 2H), 7.46 - 7.41 (m, 2H), 7.31 - 7.24 (m, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.17 (d, *J* = 7.7 Hz, 2H), 7.01 - 6.96 (m, 2H), 4.07 (t, *J* = 6.0 Hz, 2H),

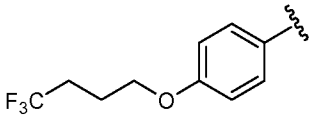
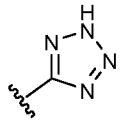
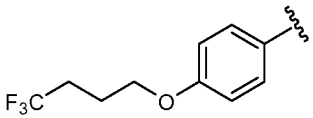
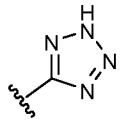
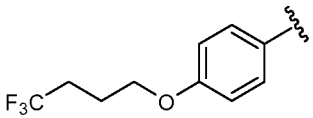
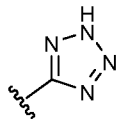
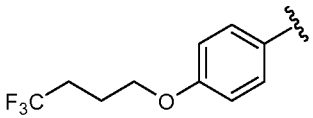
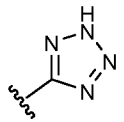
Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						3.65 (d, J = 17.0 Hz, 1H), 3.50 (d, J = 17.0 Hz, 1H), 2.43 - 2.33 (m, 2H), 2.30 (s, 3H), 2.07 - 1.99 (m, 2H).
84 Rac		CF_3		$R^{13} = CH_3$	625.2	7.52 (d, J = 8.8 Hz, 2H), 7.30 - 7.24 (m, 3H), 7.17 (d, J = 7.7 Hz, 2H), 7.01 - 6.90 (m, 4H), 4.06 (t, J = 6.0 Hz, 2H), 3.82 - 3.77 (s, 3H), 3.64 (d, J = 17.0 Hz, 1H), 3.49 (d, J = 17.0 Hz, 1H), 2.42 - 2.33 (m, 2H), 2.30 (s, 3H), 2.08 - 1.96 (m, 2H).
85 Rac		CF_3		$R^{13} = CH_3$	609.2	7.56 - 7.50 (ab quartet, J = 9.3 Hz, 2H), 7.30 - 7.20 (m, 3H), 7.16 (d, J = 8.2 Hz, 2H), 7.05 (t, J = 8.2 Hz, 1H), 7.01 - 6.95 (m, J = 8.8 Hz, 2H),

Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						6.91 (dd, *J* = 8.2, 1.6 Hz, 1H), 4.07 (t, *J* = 6.0 Hz, 2H), 3.64 (d, *J* = 17.6 Hz, 1H), 3.49 (d, *J* = 17.0 Hz, 1H), 2.43 - 2.32 (m, 2H), 2.30 (s, 3H), 2.16 (s, 3H), 2.08 - 1.97 (m, 2H).
86 Rac		CF_3		$R^{13} = CH_3$	645.2	7.58 - 7.48 (m, 6H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.00 - 6.95 (m, 2H), 4.06 (t, *J* = 6.0 Hz, 2H), 3.65 (d, *J* = 17.6 Hz, 1H), 3.50 (d, *J* = 17.0 Hz, 1H), 2.43 - 2.31 (m, 2H), 2.28 (s, 3H), 2.09 - 1.95 (m, 2H).
87 Rac S-isomer		CF_3		$R^{13} = CH_3$	538.2	

Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
88 Rac		CF_3		$R^{13} = CH_3$	579.2	2.31 (s, 3 H) 3.45 - 3.69 (m, 2 H) 3.70 - 3.76 (s, 3 H) 4.56 (q, J = 8.25 Hz, 2 H) 6.78 (d, J = 9.35 Hz, 2 H) 7.07 (d, J = 9.35 Hz, 2 H) 7.13 - 7.22 (m, 4 H) 7.29 (d, J = 8.25 Hz, 2 H) 7.59 (d, J = 8.80 Hz, 2 H).
89 Rac		CF_3	CN	$R^{13} = CH_3$	455.1	
90 Rac		CF_3		$R^{13} = CH_3$	498.1	2.28 (s, 3 H) 3.63 - 3.82 (m, 2 H) 4.58 (q, J = 8.61 Hz, 2 H) 6.88 (d, J = 8.25 Hz, 2 H) 7.10 (dd, J = 12.65, 8.80 Hz, 4 H) 7.65 (d, J = 8.80 Hz, 2 H).
91 S-isomer		CF_3	CN	$R_{11} = F$ $R^{13} = OCH_3$	517.2	7.51 (d, *J* = 9.1 Hz, 2H), 7.36 (t, *J* = 8.8 Hz, 1H), 7.03 - 6.99 (m, 2H), 6.90 - 6.84 (m,

Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						2H), 5.49 (s, 1H), 4.08 (t, *J* = 6.1 Hz, 2H), 3.87 (s, 3H), 3.65 (s, 2H), 2.46 - 2.28 (m, 2H), 2.10 - 1.97 (m, 2H)
92 Rac		CF_3		$R^{13} = OCH_2CH_3$	556.3	1.34 (t, J = 6.87 Hz, 3 H) 1.96 - 2.09 (m, 2 H) 2.26 - 2.43 (m, 2 H) 3.70 (s, 2 H) 3.98 (q, J = 6.78 Hz, 2 H) 4.06 (t, J = 6.05 Hz, 2 H) 6.78 (d, J = 8.80 Hz, 2 H) 6.92 (d, J = 8.80 Hz, 2 H) 7.01 (d, J = 8.80 Hz, 2 H) 7.58 (d, J = 8.80 Hz, 2 H).
93 Rac		CF_3		$R^{13} = OCHF_2$	578.3	1.96 - 2.12 (m, 2 H) 2.28 - 2.45 (m, 2 H) 3.63 - 3.85 (m, 2 H) 4.07 (t, J = 6.05 Hz, 2 H) 6.95 - 7.08 (m, 7 H) 7.59 (d, J = 8.80 Hz, 2 H).

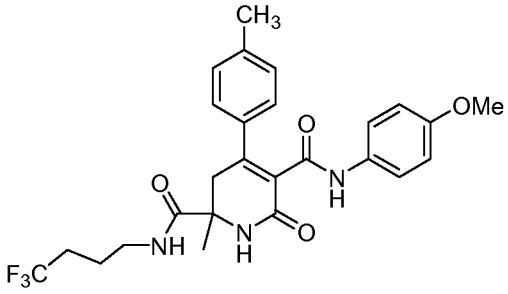
Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
94 S-isomer		CF_3		$R^{13} = CH_3$	661.3	1.97 - 2.08 (m, 2 H) 2.29 (s, 3 H) 2.32 - 2.40 (m, 2 H) 3.50 (d, J = 17.05 Hz, 1 H) 3.65 (d, J = 17.60 Hz, 1 H) 4.06 (t, J = 6.05 Hz, 2 H) 6.98 (d, J = 8.80 Hz, 2 H) 7.14 (dd, J = 16.77, 8.52 Hz, 4 H) 7.28 (d, J = 8.25 Hz, 2 H) 7.43 (d, J = 9.35 Hz, 2 H) 7.52 (d, J = 8.80 Hz, 2 H).
95 S-isomer		CF_3		$R^{11} = F$ $R^{13} = OCH_3$	560.3	1.95 - 2.08 (m, 2 H) 2.28 - 2.42 (m, 2 H) 3.58 - 3.71 (m, 2 H) 3.76 (s, 3 H) 4.06 (t, J = 6.05 Hz, 2 H) 6.59 (dd, J = 12.92, 2.47 Hz, 1 H) 6.69 (dd, J = 8.80, 2.75 Hz, 1 H) 6.91 - 6.96 (m, 1 H) 7.00 (d, J = 8.80 Hz, 2 H) 7.57 (d, J =

Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						8.80 Hz, 2 H).
96 Rac		CF_3		$R^{12} = CH_3$	526.3	
97 Rac		CF_3		All H	512.2	
98 Rac		CF_3		$R^{13} = CF_3$	580.3	7.60 (t, *J* = 8.2 Hz, 4H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 4.08 (t, *J* = 6.0 Hz, 2H), 3.80 (d, *J* = 18.1 Hz, 1H), 3.69 (d, *J* = 18.1 Hz, 1H), 2.45 - 2.31 (m, 2H), 2.11 - 1.93 (m, 2H).
99 Rac		CF_3		$R^{12} = Cl$	546.2	

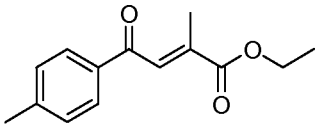
Example	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
100 Rac		CF_3		$R^{12} = OCH_3$	542.3	
101 Rac		CF_3		$R^{13} = Cl$	546.2	

*Data reported as molecular weight of compound based on electrospray mass spec results

Example 102. N^5-(4-Methoxyphenyl)-2-methyl-6-oxo-4-*p*-tolyl-N^2-(4,4,4-trifluorobutyl)-1,2,3,6-tetrahydropyridine-2,5-dicarboxamide

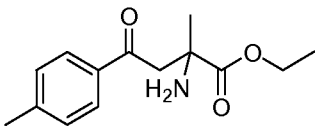


Intermediate 102A. (*E*)-Ethyl 2-methyl-4-oxo-4-*p*-tolylbut-2-enoate



[00332] A solution of Intermediate 2D (3.02 g, 7.65 mmol) and ethyl 2-oxopropanoate (0.74 g, 6.37 mmol) in THF (12 mL) in a 5 mL microwave vial equipped with a magnetic stirrer was heated at 150 °C under microwave conditions for 20 min. The solvent was removed under vacuum and the residue was purified by silica gel chromatography (80 g silica gel, eluted with EtOAc in hexanes) to provide the desired product (1.067 g, 72%) as a yellow oil. LCMS Anal. Calc'd for $C_{14}H_{16}O_3$ 232.11, found [M+H] 233.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.87 (d, *J* = 8.25 Hz, 2 H), 7.69 (q, *J* = 1.56 Hz, 1 H), 7.28 (d, *J* = 7.98 Hz, 2 H), 4.30 (q, *J* = 7.15 Hz, 2 H), 2.42 (s, 3 H), 2.16 (d, *J* = 1.38 Hz, 3 H), 1.36 (t, *J* = 7.02 Hz, 3 H).

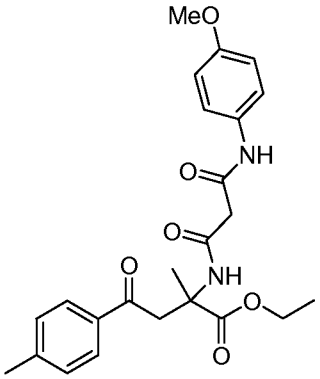
Intermediate 102B. Ethyl 2-amino-2-methyl-4-oxo-4-*p*-tolylbutanoate



[00333] To a solution of Intermediate 102A (1.067 g, 4.59 mmol) in DMSO (20 mL) under argon was added NH_4OH (18.04 mL, 271 mmol) and the reaction mixture was stirred at rt overnight. The reaction mixture was diluted with EtOAc (75 mL) and washed sequentially with water (40 mL) and brine (20 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. The oil was purified by silica gel

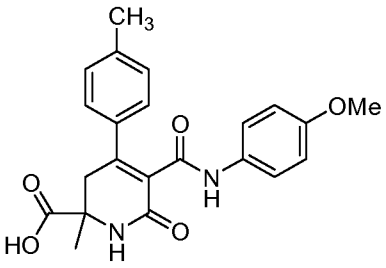
chromatography (120 g silica gel) to provide the desired product (0.632 g, 55%) as a clear oil. LCMS Anal. Calc'd for $C_{14}H_{19}NO_3$ 249.14, found [M+H] 250.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.25 Hz, 2 H), 7.24 (d, *J* = 7.98 Hz, 2 H), 4.14 (dd, *J* = 7.15, 2.75 Hz, 2 H), 3.65 (d, *J* = 17.61 Hz, 1 H), 3.20 (d, *J* = 17.61 Hz, 1 H), 2.40 (s, 3 H), 2.18 - 2.27 (m, 2 H), 1.39 (s, 3 H), 1.19 (t, *J* = 7.01 Hz, 3 H).

Intermediate 102C. Ethyl 2-(3-(4-methoxyphenylamino)-3-oxopropanamido)-2-methyl-4-oxo-4-*p*-tolylbutanoate



[00334] To a solution of Intermediate 6B (0.388 g, 1.855 mmol) in DCM (10 mL) under argon was added 1-chloro-*N*,*N*,2-trimethylprop-1-en-1-amine (0.293 g, 2.192 mmol) and the reaction mixtrue was stirred at rt for 20 min. A solution of Intermediate 102B (0.4204 g, 1.686 mmol) in DCM (1.000 mL) followed by pyridine (0.409 mL, 5.06 mmol) were added and the reaction mixture was stirred at rt for 2.5 h. The reaction mixture was concentrated to give a dark oil which was dissolved in EtOAc (15 mL) and washed with water (5 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (80 g silica gel) to provide the desired product (0.650 g, 88%) as an orange oil. LCMS Anal. Calc'd for $C_{24}H_{28}N_2O_6$ 440.19, found [M+H] 441.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.25 Hz, 2 H), 7.24 (d, *J* = 7.98 Hz, 2 H), 4.14 (dd, *J* = 7.15, 2.75 Hz, 2 H), 3.65 (d, *J* = 17.61 Hz, 1 H), 3.20 (d, *J* = 17.61 Hz, 1 H), 2.40 (s, 3 H), 2.18 - 2.27 (m, 2 H), 1.39 (s, 3 H), 1.19 (t, *J* = 7.01 Hz, 3 H).

Intermediate 102D. 5-(4-Methoxyphenylcarbamoyl)-2-methyl-6-oxo-4-*p*-tolyl-1,2,3,6-tetrahydropyridine-2-carboxylic acid

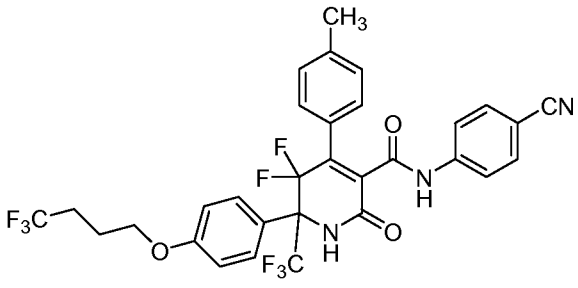


[00335] To a solution of Intermediate 102C (0.033 g, 0.075 mmol) in THF (8 mL) and water (1.600 mL) was added lithium hydroxide monohydrate (3.77 mg, 0.090 mmol) and the reaction mixture was stirred at rt for 1 h. The reaction mixture was acidified with AcOH (5 drops) and diluted with EtOAc (10 mL) and water (3 mL). The phases were separated and the aqueous phase was extracted with EtOAc (10 mL). The organic phases were combined and dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the desired product (0.0213 g, 72%) as a white solid. LCMS Anal. Calc'd for $C_{22}H_{22}N_2O_5$ 394.15, found [M+H] 395.0.

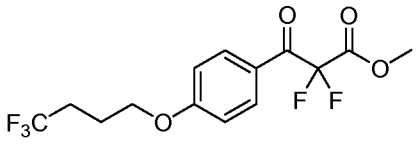
Example 102

[00336] To a solution of Intermediate 102D (0.0213 g, 0.054 mmol) in DCM (2 mL) under argon was added EDC (0.014 g, 0.076 mmol), HOBT (9.92 mg, 0.065 mmol), 4,4,4-trifluorobutan-1-amine (8.24 mg, 0.065 mmol), and DIEA (0.019 mL, 0.108 mmol). The reaction mixture was stirred at rt for 3 days. The reaction mixture was diluted with EtOAc (5 mL) and the solution was washed with water (2 mL) and brine (2 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give an orange solid which was purified by preparative HPLC (ACN/H_2O/TFA) to afford the desired product (4.6 mg, 15%) as a pale yellow solid. LCMS Anal. Calc'd for $C_{26}H_{28}F_3N_3O_4$ 503.2, found [M+H] 504.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (br. s., 1 H), 7.61 (br. s., 1 H), 7.24 - 7.32 (m, 4 H), 7.16 (d, *J* = 7.83 Hz, 2 H), 6.79 (d, *J* = 8.84 Hz, 2 H), 3.75 (s, 3 H), 3.56 (d, *J* = 17.18 Hz, 1 H), 3.22 - 3.37 (m, 2 H), 3.14 (br. s., 1 H), 2.73 (d, *J* = 17.18 Hz, 1 H), 2.34 (s, 3 H), 2.00 - 2.15 (m, 2 H), 1.70 - 1.80 (m, 2 H), 1.54 (s, 3 H).

Example 103. *N*-(4-Cyanophenyl)-5,5-difluoro-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxamide

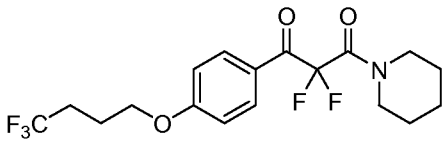


Intermediate 103A. Methyl 2,2-difluoro-3-oxo-3-(4-(4,4,4-trifluorobutoxy)phenyl)propanoate



[00337] To a solution of Intermediate 14A (3 g, 9.86 mmol) and selectFluor (10.48 g, 29.6 mmol) in acetonitrile (10 mL) was added 1 M methanolic tetrabutylammonium hydroxide (19.72 mL, 19.72 mmol). The reaction mixture was heated to 82 °C for 10 min under microwave conditions. The reaction was diluted with 1:1 ACN and MeOH and filtered rinsing with 1:1 ACN in MeOH (50 mL). The filtrate was evaporated to dryness and the crude product was purified by silica gel chromatography (80 g silica gel, elute with EtOAc in hexanes) to yield the desired product (2.34 g, 69%) as a clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 9.08 Hz, 2 H), 6.98 (d, J = 9.08 Hz, 2 H), 4.13 (t, J = 6.05 Hz, 2 H), 3.93 (s, 3 H), 2.27 - 2.39 (m, 2 H), 2.07 - 2.15 (m, 2 H).

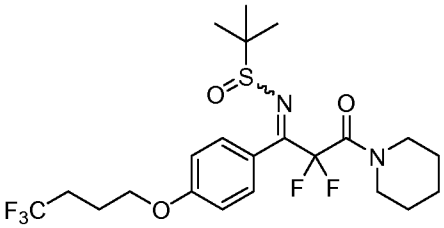
Intermediate 103B. 2,2-Difluoro-1-(piperidin-1-yl)-3-(4-(4,4,4-trifluorobutoxy)phenyl)propane-1,3-dione



[00338] Piperidine (175 µL, 1.763 mmol) was slowly added to Intermediate 103A (500 mg, 1.470 mmol) at rt. The reaction was stirred at rt for 3 h. The reaction was diluted with CH_2Cl_2, loaded onto a 12 g SiO_2 column and eluted with EtOAc in hexanes. Fractions containing the product were combined and evaporated to dryness to provide the

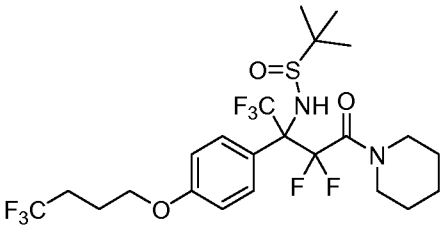
product (520 mg, 81%) as a clear oil. LCMS Anal. Calc'd for $C_{18}H_{20}F_5NO_3$ 393.14, found [M+H] 394.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9.1 Hz, 2 H), 6.98 - 6.91 (m, 2 H), 4.10 (t, *J* = 5.9 Hz, 2 H), 3.61 - 3.56 (m, 2 H), 3.54 - 3.50 (m, 2 H), 2.39 - 2.26 (m, 2 H), 2.14 - 2.05 (m, 2 H), 1.69 - 1.61 (m, 2 H), 1.60 - 1.51 (m, 4 H).

Intermediate 103C. *N*-(2,2-Difluoro-3-oxo-3-(piperidin-1-yl)-1-(4-(4,4,4-trifluorobutoxy)phenyl)propylidene)-2-methylpropane-2-sulfinamide



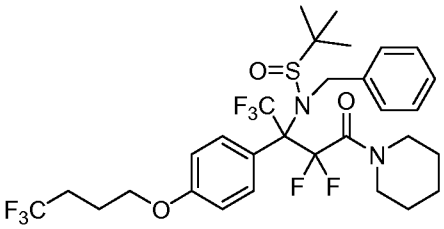
[00339] To a solution of Intermediate 103B (1.97 g, 5.01 mmol) and 2-methylpropane-2-sulfinamide (1.821 g, 15.02 mmol) in anhydrous THF (25.04 mL) was added $Ti(OEt)_4$ (5.19 mL, 25.04 mmol). The reaction was heated at refluxed temperature overnight. The reaction was cooled to rt, poured into brine, diluted with EtOAc, and stirred for 30 min. The titanium oxide was removed by filtering through a plug of Celite®. The filtrate layers were separated and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography (80 g silica gel, eluted with EtOAc in hexanes to yield the desired product (1.62 g, 59%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.80 Hz, 2 H), 6.95 (d, *J* = 9.08 Hz, 2 H), 4.07 (t, *J* = 6.05 Hz, 2 H), 3.62 - 3.69 (m, 1 H), 3.52 - 3.58 (m, 1 H), 3.39 (t, *J* = 5.09 Hz, 2 H), 2.26 - 2.37 (m, 2 H), 2.05 - 2.11 (m, 2 H), 1.53 - 1.70 (m, 7 H), 1.25 (s, 9 H).

Intermediate 103D. 2-Methyl-*N*-(1,1,1,3,3-pentafluoro-4-oxo-4-(piperidin-1-yl)-2-(4-(4,4,4-trifluorobutoxy)phenyl)butan-2-yl)propane-2-sulfinamide



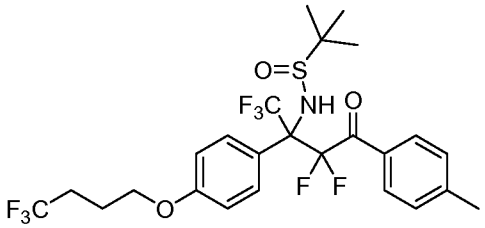
[00340] To a solution of TBAT (3.43 g, 6.36 mmol) in DMF (5.89 mL) was added a solution of Intermediate 103C (1.17 g, 2.356 mmol) in THF (5.89 mL). The solution was cooled to 0 °C, and then 2 M $TMSCF_3$ (3.53 mL, 7.07 mmol) in THF was added dropwise. The reaction was stirred at 0 °C for 1 h, and then quenched with brine (20 mL) at 0 °C. The mixture was warmed to rt and diluted with water and EtOAc. The layers were separated. The aqueous layer was washed with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (80 g silica gel, eluted with EtOAc in hexanes) to afford the desired product (773 mg, 58%) as a yellow gum. LCMS Anal. Calc'd for $C_{23}H_{30}F_8N_2O_3S$ 566.18, found [M+H] 567.1. ^1H NMR (500 MHz, CD_3OD) δ 7.69 (d, *J* = 8.53 Hz, 2 H), 6.91 (d, *J* = 9.08 Hz, 2 H), 4.03 (t, *J* = 5.91 Hz, 2 H), 3.50 - 3.62 (m, 2 H), 3.34 - 3.45 (m, 2 H), 2.23 - 2.35 (m, 2 H), 1.98 - 2.07 (m, 2 H), 1.48 - 1.69 (m, 6 H), 1.26 (s, 9 H).

Intermediate 103E. *N*-Benzyl-2-methyl-*N*-(1,1,1,3,3-pentafluoro-4-oxo-4-(piperidin-1-yl)-2-(4-(4,4,4-trifluorobutoxy)phenyl)butan-2-yl)propane-2-sulfinamide



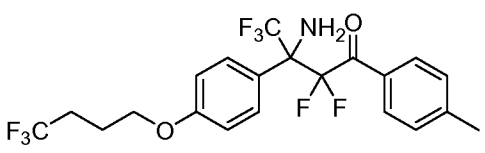
[00341] A solution of Intermediate 103D (461 mg, 0.814 mmol) in anhydrous DMF (0.5 mL) was added to a suspension of NaH (65 mg, 1.627 mmol) (60% in mineral oil) at 0 °C. After stirring for 5 min, BnBr (0.484 mL, 4.07 mmol) was added. The reaction mixture was warmed to rt and stirred for 1 h. The reaction was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (4 g silica gel, eluted with EtOAc in hexanes) to yield the desired product (260 mg, 44%) as a yellow gum. ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.5 Hz, 2 H), 7.33 - 7.27 (m, 3 H), 7.14 (dd, *J* = 7.3, 2.1 Hz, 2 H), 6.80 (d, *J* = 9.1 Hz, 2 H), 4.46 - 4.38 (m, 2 H), 4.00 - 3.95 (m, 2 H), 3.72 (br. s., 1 H), 3.51 (br. s., 1 H), 3.35 - 3.10 (m, 2 H), 2.37 - 2.25 (m, 2 H), 2.09 - 1.99 (m, 2 H), 1.70 - 1.39 (m, 6 H), 1.34 - 1.29 (m, 9 H).

Intermediate 103F. 2-Methyl-*N*-(1,1,1,3,3-pentafluoro-4-oxo-4-*p*-tolyl-2-(4-(4,4,4-trifluorobutoxy)phenyl)butan-2-yl)propane-2-sulfinamide



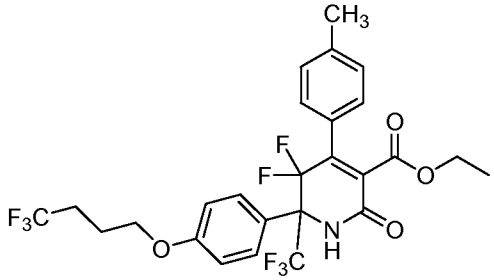
[00342] Mg turnings were suspended in 0.1 N aq HCl for a few minutes, rinsed with water, MeOH and dried under vacuum. A flame dried flask equipped with a stir bar was charged with Mg turnings (0.243 g, 10 mmol), anhydrous THF (4.4 mL) and 4-bromotoluene (1.71 g, 10 mmol) in anhydrous THF (4.4 mL) followed by several drops of 1,2-dibromoethane. The reaction initiated in a few minutes and the mixture became warm. The approximate concentration of the Grignard reagent is 1 M. The mixture was diluted with 10 mL anhydrous THF to produce a clear solution of *p*-tolylmagnesium bromide (~0.5 M). To a solution of Intermediate 103E (260 mg, 0.396 mmol) in THF (3959 µL) at 0 °C was added the freshly prepared *p*-tolylmagnesium bromide (3959 µL, 1.980 mmol). The reaction was warmed to rt, concentrated to half of the original volume, and stirred for 3 h. The reaction was cooled to 0 °C, quenched with sat'd aq NH_4Cl, and then diluted with EtOAc. The layers were separated and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography (24 g silica gel, eluted with EtOAc in hexanes) to afford the desired product (60 mg, 24%) as a yellow gum. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.19 (s, 1H), 4.01 (br. s., 2H), 2.40 (s, 3H), 2.31 (dd, *J* = 16.2, 10.2 Hz, 2H), 2.10 - 1.99 (m, 2H), 1.25 (s, 9H).

Intermediate 103G. 3-Amino-2,2,4,4,4-pentafluoro-1-*p*-tolyl-3-(4-(4,4,4-trifluorobutoxy)phenyl)butan-1-one, HCl



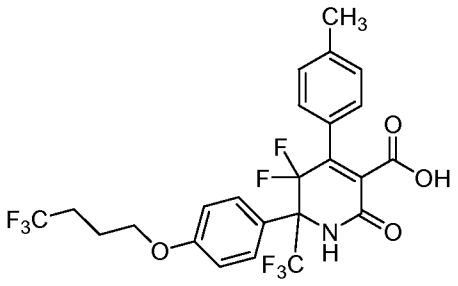
[00343] To a solution of Intermediate 103F (30 mg, 0.052 mmol) in MeOH (0.5 mL) was added 4.0 M HCl (0.026 mL, 0.105 mmol) in dioxane. The reaction was stirred at rt for 1 h. The reaction was concentrated and the crude product was used in the next step without further purification. LCMS Anal. Calc'd for $C_{21}H_{19}F_8NO_2$ 469.13, found [M+H] 470.1.

Intermediate 103H. Ethyl 5,5-difluoro-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxylate



[00344] Intermediate 103G (268 mg, 0.530 mmol) was dissolved in MeOH and then passed through $NaHCO_3$ resin (500 mg; 0.9 mmol). The solution was concentrated to yield the free base (230 mg). The free base was dissolved in 9:1 CH_2Cl_2/pyridine (3 mL) added ethyl 3-chloro-3-oxopropanoate (160 mg, 1.060 mmol). The resulting mixture was stirred at rt for 24 h and then concentrated. The residue was taken up with EtOH (1 mL) and treated with piperidine (20 uL). The resulting mixture was stirred at 65 °C for 24 h and then concentrated. The residue was purified by preparative HPLC (MeOH/H_2O/TFA) to yield the desired product (100 mg, 33%) as a foam. LCMS Anal. Calc'd for $C_{26}H_{23}F_8NO_4$ 565.15, found [M+H] 566.1.

Intermediate 103I. 5,5-Difluoro-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid

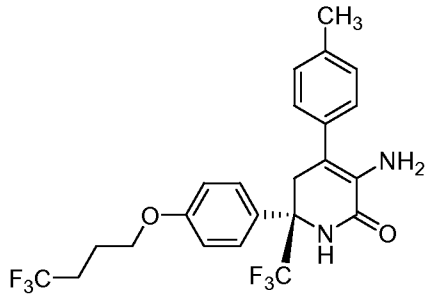


[00345] To a solution of Intermediate 103H (100 mg, 0.177 mmol) in MeOH (2 mL) was added 2 M LiOH (0.4 mL, 0.800 mmol). The resulting mixture was stirred at 100 °C for 15 min. LC-MS indicated the product to be the major component along with a trace amount of SM and 14% of the corresponding methyl ester. 2 M LiOH (100 uL) was then added and the reaction was stirred at 100 °C for an additional 15 min. The reaction was concentrated, acidified with 1 N HCl, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to yield the desired product (75 mg, 78%) as a solid. LCMS Anal. Calc'd for $C_{24}H_{19}F_8NO_4$ 537.12, found [M+H] 537.9.

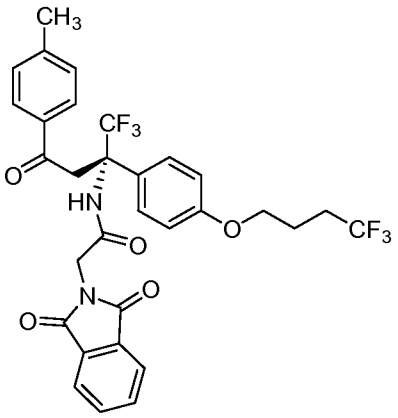
Example 103

[00346] To a solution of Intermediate 103I (20 mg, 0.037 mmol) in MeCN (1 mL) was added 3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-ol (7.60 mg, 0.056 mmol), 4-aminobenzonitrile (6.59 mg, 0.056 mmol), and EDC (10.70 mg, 0.056 mmol). The resulting mixture was stirred at rt overnight. The reaction mixture was diluted with MeCN and purified by preparative HPLC (MeCN/H_2O/TFA) to yield the desired product (11 mg, 46%) as a solid. LCMS Anal. Calc'd for $C_{31}H_{23}F_8N_3O_3$ 637.16, found [M+H] 637.9. ^{1}H NMR (500 MHz, CD_3OD) δ 7.67 (d, *J* = 9.08 Hz, 2 H), 7.56 - 7.63 (m, 4 H), 7.22 - 7.26 (m, 2 H), 7.15 - 7.20 (m, 2 H), 7.04 - 7.09 (m, 2 H), 4.12 (t, *J* = 6.05 Hz, 2 H), 2.33 - 2.44 (m, 2 H), 2.30 (s, 3 H), 2.02 - 2.09 (m, 2 H).

Example 104. (*S*)-3-Amino-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one

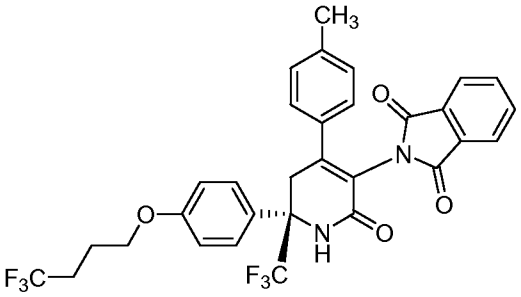


Intermediate 104A. (*S*)-2-(1,3-Dioxoisoindolin-2-yl)-*N*-(1,1,1-trifluoro-4-oxo-4-*p*-tolyl-2-(4-(4,4,4-trifluorobutoxy)phenyl)butan-2-yl)acetamide



[00347] To a solution of 2-(1,3-dioxoisoindolin-2-yl)acetic acid (592 mg, 2.88 mmol) in dry DCM (10 mL) was added PPh_3 (2269 mg, 8.65 mmol) fairy rapidly, and then CCl_3CN (500 mg, 3.46 mmol) was added dropwise. The mixture was stirred at rt for 3 h and a solution of Intermediate 2F, isomer 2 (500 mg, 1.15 mmol) in dry DCM (3 mL), followed by pyridine (0.3 mL) were added. The mixture was stirred at rt overnight. The mixture was diluted with DCM (10 mL) and washed with sat'd $NaHCO_3$ (2 × 8 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography to yield the desired product (620 mg, 87%). LCMS Anal. Calc'd for $C_{31}H_{26}F_6N_2O_5$ 620.17, found [M+H] 621.3.

Intermediate 104B. (*S*)-2-(2-Oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridin-3-yl)isoindoline-1,3-dione



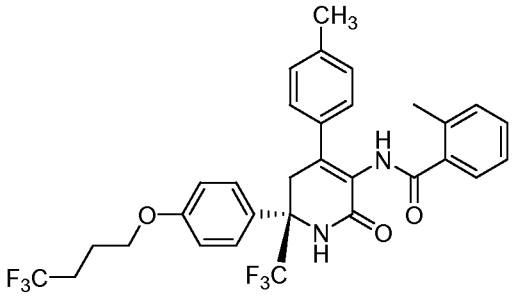
[00348] Intermediate 104A (145 mg, 0.234 mmol) was dissolved in MeOH (2.2 mL) and then 1 N NaOH (0.2 mL) was added. The mixture was stirred at 69 °C for 45 min and added another 0.2 mL of 1 N NaOH. The reaction was heated at 130 °C under microwave conditions for 10 min. The mixture was neutralized with 1 N HCl and then concentrated. The residue was purified by silica gel chromatography (12 g silica gel,

eluted with EtOAc in hexanes) to yield the desired product (80 mg, 57%). LCMS Anal. Calc'd for $C_{31}H_{24}F_6N_2O_4$ 602.16, found [M+H] 603.3.

Example 104

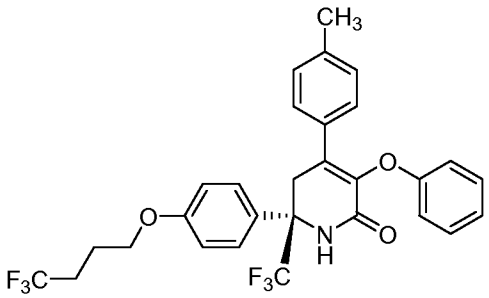
[00349] To a solution of Intermediate 104B (80 mg, 0.133 mmol) in 1 mL of EtOH was added 1 mL of 2 N $MeNH_2$ in MeOH. The mixture was stirred at 67 °C for 24 h. The solvent was removed *in vacuo* and the crude product was purified by silica gel chromatography (4 g silics gel, eluted with EtOAc in hexanes) to yield the desired product (32.3 mg, 52%) as a light brown solid. LCMS Anal. Calc'd for $C_{23}H_{22}F_6N_2O_2$ 472.16, found [M+H] 473.2. ^{1}H NMR (500 MHz, CD_3OD) δ 7.49 (d, J = 8.8 Hz, 2 H), 7.31 - 7.17 (m, 4 H), 7.04 - 6.92 (m, 2 H), 4.08 (s, 2 H), 3.46 (d, J = 16.2 Hz, 1 H), 3.21 (d, J = 16.2 Hz, 1 H), 2.44 - 2.30 (m, 5 H), 2.09 - 1.99 (m, 2 H).

Example 105. (*S*)-2-Methyl-*N*-(2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridin-3-yl)benzamide

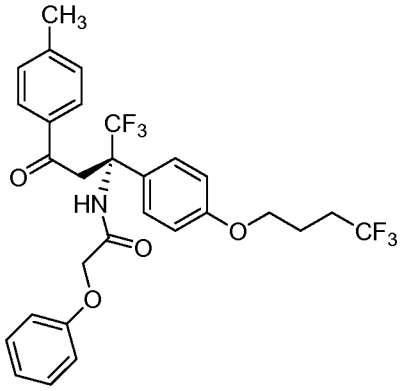


[00350] To a solution of 104 (15 mg, 0.032 mmol) in dry DCM (0.5 mL) was added 2-methylbenzoyl chloride (5.4 mg, 0.035 mmol) and pyridine (2.8 μL, 0.035 mmol). The mixture was stirred at rt for 2 h and then concentrated. The residue was purified by preparative HPLC (MeCN/H_2O/TFA) to yield the desired product. LCMS Anal. Calc'd for $C_{31}H_{28}F_6N_2O_3$ 590.20, found [M+H] 591.3. ^{1}H NMR (500 MHz, CD_3OD) δ 7.56 (d, J = 8.80 Hz, 2 H), 7.11 - 7.29 (m, 8 H), 6.98 (d, J = 9.08 Hz, 2 H), 4.06 (t, J = 6.05 Hz, 2 H), 3.73 (d, J = 17.06 Hz, 1 H), 3.46 (d, J = 16.78 Hz, 1 H), 2.33 (s, 3 H), 2.30 - 2.42 (m, 2 H), 2.22 (s, 3 H), 1.98 - 2.06 (m, 2 H).

Example 106. (*S*)-3-Phenoxy-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one



Intermediate 106A. (*S*)-2-Phenoxy-*N*-(1,1,1-trifluoro-4-oxo-4-*p*-tolyl-2-(4-(4,4,4-trifluorobutoxy)phenyl)butan-2-yl)acetamide



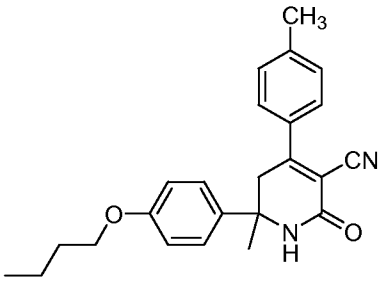
[00351] To a mixture of triphenylphosphine (138 mg, 0.318 mmol) in dry DCM (0.8 mL) was added 2-phenoxyacetic acid (26 mg, 0.173 mmol), followed by trichloroacetonitrile (30 mg, 0.208 mmol). The mixture was stirred at rt for 2.5 h. To the mixture was added a solution of Intermediate 2F, isomer 2 (30 mg, 0.069 mmol) in dry DCM (0.5 mL) followed by pyridine (17 µL, 0.208 mmol). The reaction was stirred at rt overnight. The mixture was concentrated and purified by preparative HPLC ($MeOH/H_2O/TFA$) to yield the desired product (27 mg, 69%) as a brown oil. LCMS Anal. Calc'd for $C_{29}H_{27}F_6NO_4$ 567.18, found [M+H] 568.3.

Example 106

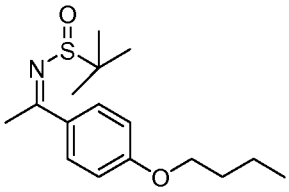
[00352] To a solution of Intermediate 106A (26 mg, 0.046 mmol) in MeOH (0.5 mL) was added 1 N NaOH (60 µL). The mixture was heated at 130 °C under microwave conditions for 10 min. The mixture was neutralized with 1 N HCl and concentrated. The residue was purified by preparative HPLC ($MeCN/H_2O/TFA$) to yield the desired product (1.5 mg, 6%) as a light brown oil. LCMS Anal. Calc'd for $C_{29}H_{25}F_6NO_3$ 549.17, found

[M+H] 550.3. ^{1}H NMR (500 MHz, CD_3OD) δ 7.59 (d, *J* = 8.80 Hz, 2 H), 7.33 (d, *J* = 8.25 Hz, 2 H), 7.13 (d, *J* = 8.25 Hz, 2 H), 7.01 - 7.08 (m, 4 H), 6.85 - 6.90 (m, 1 H), 6.38 (dd, *J* = 8.67, 0.96 Hz, 2 H), 4.10 - 4.15 (m, 2 H), 3.71 - 3.76 (m, 1 H), 3.61 - 3.67 (m, 1 H), 2.34 - 2.45 (m, 2 H), 2.30 (s, 3 H), 2.02 - 2.11 (m, 2 H).

Example 107. 6-(4-Butoxyphenyl)-6-methyl-2-oxo-4-*p*-tolyl-1,2,5,6-tetrahydropyridine-3-carbonitrile

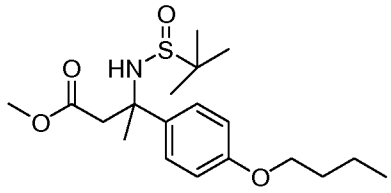


Intermediate 107A. (*Z*)-*N*-(1-(4-Butoxyphenyl)ethylidene)-2-methylpropane-2-sulfinamide



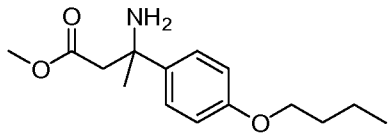
[00353] To a stirred solution of 1-(4-butoxyphenyl)ethanone (3 g, 15.60 mmol) and 2-methylpropane-2-sulfinamide (2.84 g, 23.41 mmol) in THF (50 mL) was added tetraethoxytitanium (8.90 g, 39.0 mmol). The reaction was heated to 70 °C for 3 d. Cold water was added and the reaction was stirred vigorously for 20 min. The mixture was filtered through Celite® and the filtrated was diluted with EtOAc. The organic solution was washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated. The crude product was by silica gel chromatography (220 g silica gel, eluted with EtOAc in hexanes) to yield the desired product (4 g, 87%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.80 Hz, 2 H), 6.91 (d, *J* = 8.80 Hz, 2 H), 4.02 (t, *J* = 6.46 Hz, 2 H), 2.73 (s, 3 H), 1.75 - 1.83 (m, 2 H), 1.46 - 1.56 (m, 2 H), 1.32 (s, 9 H), 0.99 (t, *J* = 7.43 Hz, 3 H).

Intermediate 107B. Methyl 3-(4-butoxyphenyl)-3-(1,1-dimethylethylsulfinamido)butanoate



[00354] To a stirred solution of diisopropylamine (3.86 mL, 27.1 mmol) in THF (40 mL) at -78 °C was added *n*-butyllithium (22.57 mL, 27.1 mmol) dropwise. The reaction was slowly warmed up to -20 °C and stirred for 45 min. The reaction was cooled to -78 °C and methyl acetate (2.006 g, 27.1 mmol) was added dropwise. After 30 min, chlorotitanium triisopropoxide (8.09 mL, 33.8 mmol) in THF (40 mL) was added dropwise. The reaction was stirred at -78 °C for 1 h. Intermediate 107A (4 g, 13.54 mmol) in THF (15 mL) was added dropwise and the reaction was stirred at -78 °C for 2 h. The reaction was quenched by addition of sat'd NH_4Cl solution and stirred vigorously while warmed to rt. The mixture was filtered through Celite® and washed with EtOAc. The filtrate was washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (220 g silica gel, eluted with EtOAc in hexanes) to yield the desired product (4.33 g, 87%) as a light yellow oil. LCMS Anal. Calc'd for $C_{19}H_{31}NO_4S$ 369.20, found [M+H] 370.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 8.80 Hz, 2 H), 6.85 (d, J = 8.80 Hz, 2 H), 3.95 (t, J = 6.46 Hz, 2 H), 3.62 (s, 3 H), 2.05 (s, 2 H), 1.74 - 1.80 (m, 2 H), 1.74 (s, 3 H), 1.44 - 1.54 (m, 2 H), 1.29 (s, 9 H), 0.98 (t, J = 7.43 Hz, 3 H).

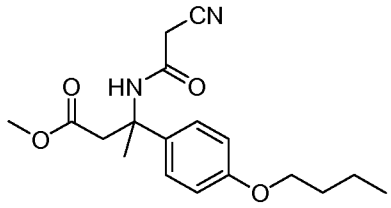
Intermediate 107C. Methyl 3-amino-3-(4-butoxyphenyl)butanoate



[00355] To a stirred solution of Intermediate 107B (1 g, 2.71 mmol) in MeOH (6 mL) was added 4 N HCl (3.38 mL, 13.53 mmol). The reaction was stirred at rt for 4 h. The reaction mixture was concentrated *in vacuo* and diluted with EtOAc. The organic layer was washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated to yield the desired product (700 mg, 97%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ

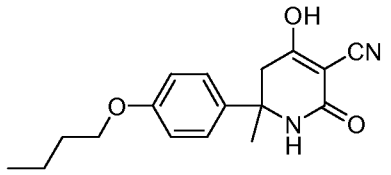
7.38 (d, *J* = 8.80 Hz, 2 H), 6.86 (d, *J* = 8.80 Hz, 2 H), 3.95 (t, *J* = 6.46 Hz, 2 H), 3.59 (s, 3 H), 1.73 - 1.80 (m, 2 H), 1.53 (s, 2 H), 1.45 - 1.52 (m, 2 H), 1.19 (s, 3 H), 0.98 (t, *J* = 7.29 Hz, 3 H).

Intermediate 107D. Methyl 3-(4-butoxyphenyl)-3-(2-cyanoacetamido)butanoate



[00356] To a stirred solution of 2-cyanoacetic acid (128 mg, 1.507 mmol) in CH_2Cl_2 (5 mL) was added oxalyl chloride (0.754 mL, 1.507 mmol) and 1 drop of DMF. The reaction was stirred at rt for 1 h and then concentrated. The resulting acid chloride was dissolved in CH_2Cl_2 (1 mL) and was then added to Intermediate 107C (200 mg, 0.754 mmol) and pyridine (0.183 mL, 2.261 mmol)in CH_2Cl_2 (5 mL). The reaction was stirred at rt for 5 h. The reaction mixture was concentrated and the residue was diluted with EtOAc. The organic layer was washed with saturated NH_4Cl, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (24 g silica gel, eluted with EtOAc in hexanes) to yield the desired product (218 mg, 87%) as a clear oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.80 Hz, 2 H), 6.85 (d, *J* = 8.80 Hz, 2 H), 3.94 (t, *J* = 6.46 Hz, 2 H), 3.65 (s, 3 H), 3.30 (s, 2 H), 3.03 (d, *J* = 15.13 Hz, 1 H), 2.85 (d, *J* = 15.13 Hz, 1 H), 1.80 (s, 3 H), 1.71 - 1.78 (m, 2 H), 1.44 - 1.53 (m, 2 H), 0.97 (t, *J* = 7.29 Hz, 3 H).

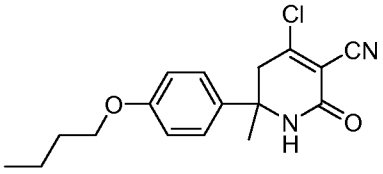
Intermediate 107E. 6-(4-Butoxyphenyl)-4-hydroxy-6-methyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carbonitrile



[00357] To a stirred solution of Intermediate 107D (218 mg, 0.656 mmol) in MeOH (5 mL) was added 4.37 M NaOMe (0.750 mL, 3.28 mmol) in methanol solution. The reaction was heated to 55 °C for 5 h. The reaction mixture was concentrated and the

residue was diluted with EtOAc. The organic layer was washed with 1 M HCl, dried over $MgSO_4$, filtered and concentrated to yield the desired product (200 mg, 102%) as a light yellow solid. LCMS Anal. Calc'd for $C_{17}H_{20}N_2O_3$ 300.15, found [M+H] 301.1.

Intermediate 107F. 6-(4-Butoxyphenyl)-4-chloro-6-methyl-2-oxo-1,2,5,6-tetrahydropyridine-3-carbonitrile



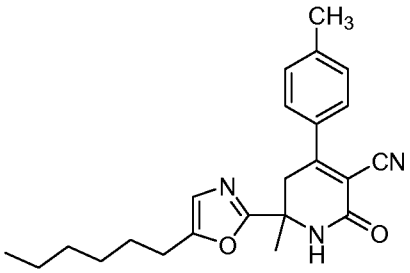
[00358] To a stirred solution of Intermediate 107E (130 mg, 0.433 mmol) in $ClCH_2CH_2Cl$ (3 mL) was added $POCl_3$ (0.056 mL, 0.606 mmol) and Hunig's base (0.113 mL, 0.649 mmol). The reaction was stirred at rt for 30 min and then heated to 85 °C for 3 h. The reaction mixture was concentrated and the residue was diluted with EtOAc. The organic layer was washed with saturated NH_4Cl, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (24 g silica gel, eluted with EtOAc in hexanes) to yiled the desired product (102 mg, 74%) as a white solid. LCMS Anal. Calc'd for $C_{17}H_{19}ClN_2O_2$ 318.11, found [M+H] 319.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.80 Hz, 2 H), 6.90 (d, *J* = 8.80 Hz, 2 H), 3.97 (t, *J* = 6.60 Hz, 2 H), 2.05 (s, 2 H), 1.74 - 1.82 (m, 2 H), 1.69 (s, 3 H), 1.46 - 1.55 (m, 2 H), 0.99 (t, *J* = 7.43 Hz, 3 H).

Example 107

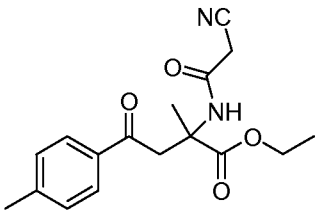
[00359] To a stirred solution of Intermediate 107F (11 mg, 0.035 mmol), *p*-tolylboronic acid (5.63 mg, 0.041 mmol), and 1,1'-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride (2.270 mg, 3.45 µmol) in dioxane (1 mL) was added CsF (10.48 mg, 0.069 mmol). The reaction was degassed for 10 min and heated to 80 °C for 2 h. The reaction mixture was concentrated. The residue was diluted with EtOAc, washed with H_2O, brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified by preparative HPLC (MeOH/H_2O/TFA) to yield the desired product (5.7 mg, 44%) as a brown solid. LCMS Anal. Calc'd for $C_{24}H_{26}N_2O_2$ 374.20, found [M+H] 375.2. ^{1}H NMR (400 MHz, CD_3OD) δ 7.41 (d, *J* = 8.14 Hz, 2 H), 7.32 (d, *J* = 8.80 Hz, 2 H),

7.28 (d, *J* = 8.14 Hz, 2 H), 6.89 (d, *J* = 8.80 Hz, 2 H), 3.96 (t, *J* = 6.38 Hz, 2 H), 3.46 (d, *J* = 18.05 Hz, 1 H), 3.24 (d, *J* = 17.83 Hz, 1 H), 2.38 (s, 3 H), 1.69 - 1.78 (m, 2 H), 1.65 (s, 3 H), 1.43 - 1.55 (m, 2 H), 0.97 (t, *J* = 7.48 Hz, 3 H).

Example 108. 6-(5-Hexyloxazol-2-yl)-6-methyl-2-oxo-4-*p*-tolyl-1,2,5,6-tetrahydropyridine-3-carbonitrile

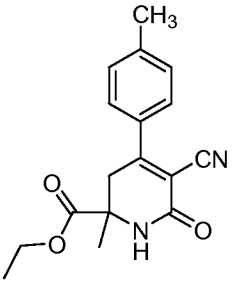


Intermediate 108A. Ethyl 2-(2-cyanoacetamido)-2-methyl-4-oxo-4-p-tolylbutanoate



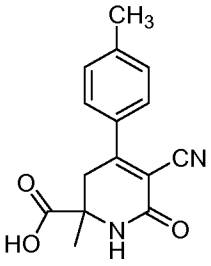
[00360] To a solution of Intermediate 3C (2.192 g, 21.18 mmol) in DCM (30 mL) under argon was added Intermediate 102C (1.2 g, 4.81 mmol), pyridine (0.779 mL, 9.63 mmol) and DMAP (0.059 g, 0.481 mmol). The reaction mixture was stirred at rt for 1 h. The reaction mixture was loaded onto silica gel (25 g) and washed with EtOAc (4 × 50 mL). The filtrate was concentrated in *vacuo* to a dark red oil. The oil was dissolved in EtOAc (100 mL) and washed with water (2 × 50 mL). The organic phase was dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by silica gel chromatography (80 g silica gel, eluted with EtOAc in hexanes) to afford the desired product (1.28 g, 84%) as yellow oil. LCMS Anal. Calc'd for $C_{17}H_{20}N_2O_4$ 316.1, found [M+H] 317.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 2 H), 7.39 (s, 1 H), 7.24 - 7.29 (m, 2 H), 4.45 (d, *J* = 18.2 Hz, 1 H), 4.22 - 4.31 (m, 2 H), 3.47 (d, *J* = 18.2 Hz, 1 H), 3.28 - 3.38 (m, 2 H), 2.42 (s, 3 H), 1.74 (s, 3 H), 1.24 (t, *J* = 7.0 Hz, 3 H).

Intermediate 108B. Ethyl 5-cyano-2-methyl-6-oxo-4-*p*-tolyl-1,2,3,6-tetrahydropyridine-2-carboxylate



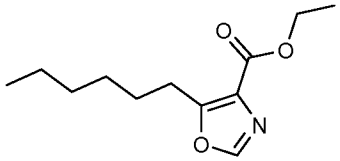
[00361] Intermediate 108A (1.2837 g, 4.06 mmol) was dissolved in a mixture of THF (15 mL) and water (3.00 mL) in a 25 mL 1 neck pear shaped flask that was equipped with a magnetic stirrer. Lithium hydroxide monohydrate (0.204 g, 4.87 mmol) was added and the reaxction mixture was stirred at rt for 1 h. The reaction mixture was acidified to pH 4 with AcOH, diluted with EtOAc (50 mL) and the solution was washed with water (20 mL). The organic phase was dried over $MgSO_4$ and concentrated in *vacuo* to give the desired product (1.40 g, 115%) as yellow oil. LCMS Anal. Calc'd for $C_{17}H_{18}N_2O_3$ 298.1, found [M+H] 299.1.

Intermediate 108C. 5-Cyano-2-methyl-6-oxo-4-*p*-tolyl-1,2,3,6-tetrahydropyridine-2-carboxylic acid



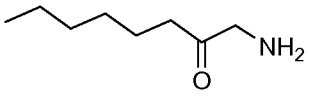
[00362] Intermediate 108B (1.211 g, 4.06 mmol) was dissolved in acetic acid (95 mL) in a 250 mL 1 neck pear shaped flask that was equipped with a magnetic stirrer. HCl (11.67 mL, 142 mmol) was added and the reaction mixture was stirred at 60 °C overnight. The reaction mixture was concentrated in vacuo to give the desired product as a pale yellow solid. LCMS Anal. Calc'd for $C_{15}H_{14}N_2O_3$ 270.1, found [M+H] 271.0. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.3 Hz, 2 H), 7.23 (d, *J* = 7.7 Hz, 2 H), 3.39 (d, *J* = 18.2 Hz, 1 H), 2.83 (d, *J* = 18.2 Hz, 1 H), 2.35 (s, 3 H), 1.54 (s, 3 H).

Intermediate 108D. Ethyl 5-hexyloxazole-4-carboxylate



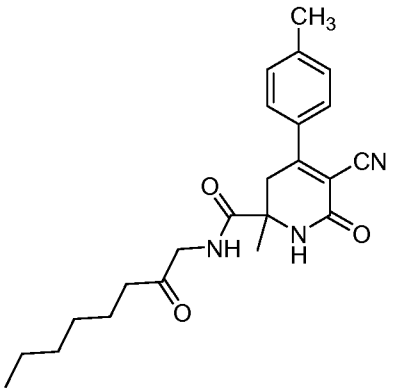
Ethyl 2-isocyanoacetate (1.0 g, 8.84 mmol) was dissolved in DMF (5 mL) in a 25 mL 1 neck pear shaped flask that was equipped with a magnetic stirrer and an Ar inlet. DBU (1.999 mL, 13.26 mmol) and heptanoyl chloride (1.770 mL, 11.49 mmol) were added and the reaction mixture was stirred at 80 °C for 6 h. The reaction mixture was poured into water(50 mL) and extracted with EtOAc (3 × 30 mL). The phases were seperated and the organic phase was dried over $MgSO_4$ and concentrated in *vacuo* to a a dark oil. The desired product was isolated by distillattion at 90-95°C at 0.3 mmHg as a clear oil (0.89 g, 45%). LCMS Anal. Calc'd for $C_{12}H_{19}NO_3$ 225.1, found [M+H] 226.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 3.03 (t, *J* = 7.6 Hz, 2H), 1.71 - 1.64 (m, 2H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.35 - 1.26 (m, 6H), 0.86 (t, *J* = 6.3 Hz, 3H).

Intermediate 108E. 1-Aminooctan-2-one, HCl salt



[00363] Intermediate 108D (0.8889 g, 3.95 mmol) was stirred in HCl (16.44 mL, 99 mmol) in a 100 mL 1 neck pear shaped flask that was equipped with a magnetic stirrer. The reaction mixture was heated to 100 °C and stirred for 6 h. The reaction mixture was concentrated in *vacuo* to a tan solid that was triturated in ether (15 mL). The slurry was filtered and was washed with ether (3 mL). The filter cake was dried under vacuum to give the desired product (0.57 g, 80%) as an off-white solid. ^{1}H NMR (500 MHz, MeOD) δ 3.97 (s, 2 H), 2.56 (t, *J* = 7.4 Hz, 2 H), 1.62 (quin, *J* = 7.4 Hz, 2 H), 1.26 - 1.40 (m, 6 H), 0.88 - 0.93 (m, 3 H).

Intermediate 108F. 5-Cyano-2-methyl-6-oxo-*N*-(2-oxooctyl)-4-*p*-tolyl-1,2,3,6-tetrahydropyridine-2-carboxamide

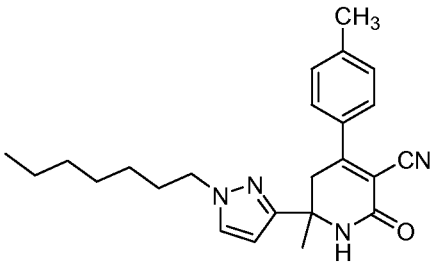


[00364] Intermediate 108C (0.1 g, 0.370 mmol) was dissolved in DCM (4 mL) in a 10 mL 1 neck pear shaped flask that was equipped with a magnetic stirrer and an Ar inlet. EDC (0.099 g, 0.518 mmol), HOBT (0.068 g, 0.444 mmol), Intermediate 108E (0.080 g, 0.444 mmol) and DIEA (0.194 mL, 1.110 mmol) were added and the reaction mixture was stirred at rt overnight. The reaction mixture was concentrated in *vacuo* to an orange oil that was purified by silica gel chromatography (40 g silica gel, eluted with 0-100% EtOAc in hexanes) to give the desired product (0.09 g, 61%) as yellow oil.

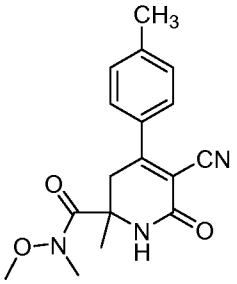
Example 108

[00365] Intermediate 108F (0.045 g, 0.114 mmol) was dissolved in 1,2-dichloroethane (2 mL) in a 10 mL 1 neck pear shaped flask that was equipped with a magnetic stirrer and an Ar inlet. $POCl_3$ (0.042 mL, 0.455 mmol) and DIEA (0.089 mL, 0.512 mmol) were added and the reaction mixture was stirred at 85 °C overnight. The reaction mixture was cooled in an ice/water bath and was quenched with water (3 mL). The mixture was extracted with EtOAc (2 × 5 mL) and the organic phases were combined, dried over $MgSO_4$ and concentrated in *vacuo* to a brown oil. The crude product was purified by preparative HPLC (MeOH/H_2O/TFA) to yield the desired product (3.5 mg, 8%) as a yellow solid. LCMS Anal. Calc'd for $C_{23}H_{27}N_3O_2$ 377.2, found [M+H] 378.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 6.81 (br. s., 1 H), 3.65 (d, *J* = 17.9 Hz, 1 H), 3.09 (d, *J* = 17.9 Hz, 1 H), 2.63 (t, *J* = 7.4 Hz, 2 H), 2.43 (s, 3 H), 1.76 (s, 3 H), 1.57 - 1.67 (m, 2 H), 1.23 - 1.42 (m, 6 H), 0.89 (t, *J* = 6.7 Hz, 3 H).

Example 109. 6-(1-Heptyl-1*H*-pyrazol-3-yl)-6-methyl-2-oxo-4-*p*-tolyl-1,2,5,6-tetrahydropyridine-3-carbonitrile

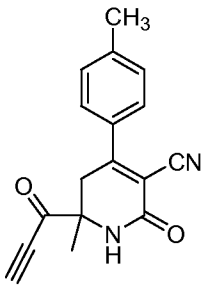


Intermediate 109A. 5-Cyano-*N*-methoxy-*N*,2-dimethyl-6-oxo-4-*p*-tolyl-1,2,3,6-tetrahydropyridine-2-carboxamide



[00366] Intermediate 108C (0.25 g, 0.925 mmol) was dissolved in DCM (15 mL) in a 25 mL 1 neck rb flask that was equipped with a magnetic stirrer and an Ar inlet. *N,O*-Dimethylhydroxylamine (0.062 g, 1.017 mmol), EDC (0.195 g, 1.017 mmol) and *N*-methylmorpholine (0.112 mL, 1.017 mmol) were added and the reaction mixture was stirred at rt overnight. The reaction solvent was removed under vacuum. The residue was dissolved in EtOAc (10 mL) and washed with water (5 mL). The organic phaase was dried over $MgSO_4$ and concentrated in *vacuo* to a dark solid. The crude product was purified by silica gel chromatography (40 g silica gel, eluted with 0-100% EtOAc in hexanes) to give the desired product (0089 g, 31%) as a white solid. LCMS Anal. Calc'd for $C_{17}H_{19}N_3O_3$ 313.3, found [M+H] 314.1. ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.3 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 3.81 (s, 3 H), 3.69 - 3.75 (m, 1 H), 3.22 (s, 3 H), 2.72 (d, *J* = 17.6 Hz, 1 H), 2.42 (s, 3 H), 1.63 (s, 3 H).

Intermediate 109B. 6-Methyl-2-oxo-6-propioloyl-4-*p*-tolyl-1,2,5,6-tetrahydropyridine-3-carbonitrile

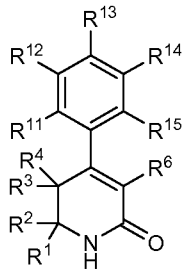


[00367] Intermediate 109A (0.0887 g, 0.283 mmol) was dissolved in tetrahydrofuran (1 mL) in a 25 mL 1 neck pear shaped flask that was equipped with a magnetic stirrer and an Ar inlet. Ethynylmagnesium bromide (5.66 mL, 2.83 mmol) was added dropwise and the reaction mixture was stirred at 35 °C for 4 h. The reaction mixture was cooled to rt, quenched with sat'd. aq NH_4Cl (5 mL) and extracted with EtOAc (2 × 10 mL). The organic phases were combined and concentrated in *vacuo*. The residue was purified by silica gel chromatography (24 g silica gel, eluted with 0-100% EtOAc in hexanes) to give the desired product (0.06 g, 78%) as an orange solid. LCMS Anal. Calc'd for $C_{17}H_{14}N_2O_2$ 278.1, found [M+H] 279.0.

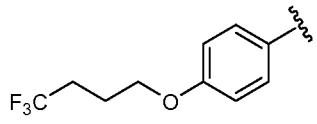
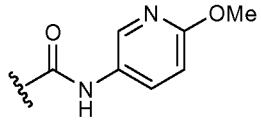
Example 109

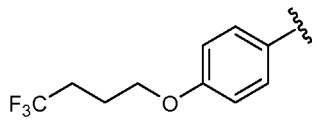
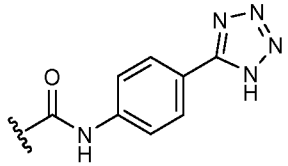
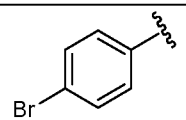
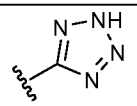
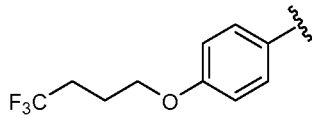
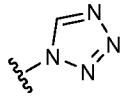
[00368] Intermediate 109B (0.0613 g, 0.220 mmol) was dissolved in ethanol (3 mL) in a 25 mL 1 neck pear shaped flask that was equipped with a magnetic stirrer. Heptylhydrazine, HCl (0.073 g, 0.441 mmol) and TEA (0.061 mL, 0.441 mmol) were added and the reaction mixture was stirred at rt overnight. The reaction mixture was concentrated and purified by preparative HPLC ($MeOH/H_2O$/TFA) to yield the desired product (3.2 mg, 4%) as a white solid. LCMS Anal. Calc'd for $C_{24}H_{30}N_4O$ 390.2, found [M+H] 391.2. ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 8.3 Hz, 2 H), 7.25 - 7.30 (m, 2 H), 6.35 (s, 1 H), 6.15 (d, J = 1.7 Hz, 1 H), 3.98 - 4.08 (m, 2 H), 3.57 (d, J = 17.9 Hz, 1 H), 3.01 (d, J = 17.9 Hz, 1 H), 2.41 (s, 3 H), 1.81 (quin, J = 7.3 Hz, 2 H), 1.70 - 1.77 (m, 2 H), 1.68 (s, 3 H), 1.16 - 1.34 (m, 6 H), 0.87 (t, J = 7.0 Hz, 3 H).

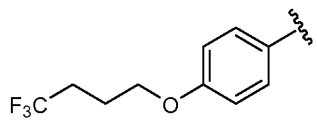
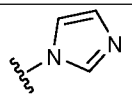
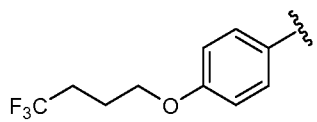
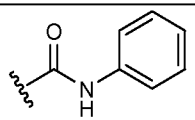
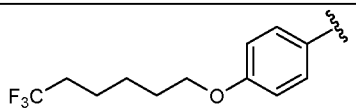
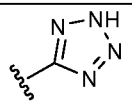
[00369] Examples 110-273 expressed by Formula (II), unless noted in the table, may be made by one skilled in the art by appropriate application of the procedures described for Examples 1-16 and Examples 102-. R^{11} to R^{15} are hydrogen, unless noted in the table.

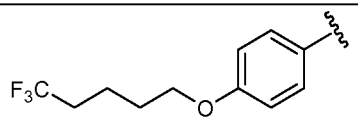
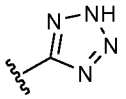
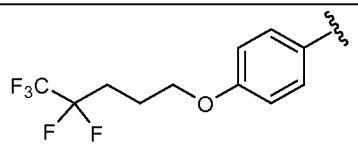
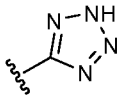
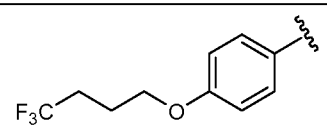
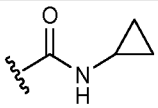


(II)

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
110 S-isomer		CF_3	H		$R^{13} = CH_3$	608.1	8.13 (d, *J* = 2.5 Hz, 1H), 7.93 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.46 (d, *J* = 9.1 Hz, 2H), 7.22 (s, 1H), 7.20 - 7.15 (m, 2H), 7.13 - 7.08 (m, 2H), 6.94 (d, *J* = 9.1 Hz, 2H), 6.67 (d, *J* = 9.1 Hz, 1H), 4.02 (t, *J* = 5.9 Hz, 2H), 3.90 (br. s., 3H), 3.56 - 3.38 (m, 2H), 2.39 - 2.25 (m, 5H), 2.10 - 2.01 (m, 2H).

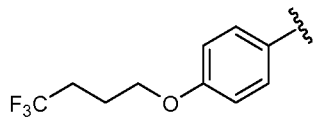
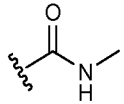
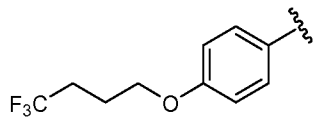
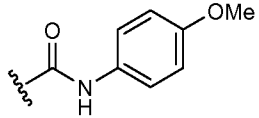
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
111 S-isomer		CF_3	H		$R^{13} = CH_3$	645.2	7.88 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 7.7 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 4.07 (t, J = 5.9 Hz, 2H), 3.75 - 3.46 (m, 2H), 2.43 - 2.32 (m, 2H), 2.29 (s, 3H), 2.11 - 1.97 (m, 2H).
112 Rac		CF_3	H		$R^{13} = CH_3$	480.0	
113 S-isomer		CF_3	H		$R^{13} = CH_3$	526.1	9.07 (d, *J* = 1.1 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.16 - 7.09 (m, *J* = 8.0 Hz, 2H), 7.09 - 7.03 (m, 2H), 6.93 - 6.86 (d, *J* = 7.7 Hz, 2H), 4.12 (t, *J* = 6.1 Hz, 2H), 4.00 (s, 1H), 3.92 (d, *J* =

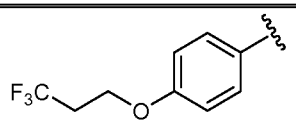
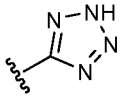
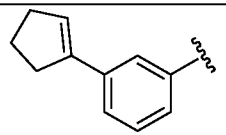
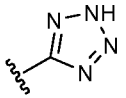
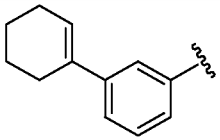
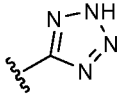
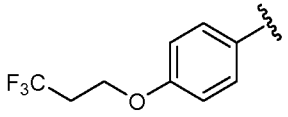
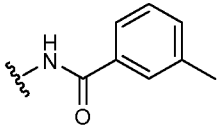
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							17.6 Hz, 1H), 3.77 (d, *J* = 17.6 Hz, 1H), 2.46 - 2.34 (m, 2H), 2.30 (s, 3H), 2.12 - 2.02 (m, 2H).
114 S-isomer		CF_3	H		$R^{13} = CH_3$	524.1	
115 S-isomer		CF_3	H		$R^{13} = CH_3$	577.2	
116 Rac		CF_3	H		$R^{13} = CH_3$	554.2	7.42 (d, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.10 (br. s., 1H), 6.95 (dd, *J* = 15.0, 8.4 Hz, 4H), 3.97 (t, *J* = 6.3 Hz, 2H), 3.59 (d, *J* = 5.5 Hz, 2H), 2.36 (s, 3H), 2.16 - 2.04 (m, 2H), 1.86 - 1.77 (m, 2H), 1.69 - 1.59 (m, 2H), 1.59 - 1.50 (m, 2H),

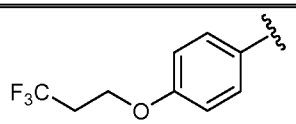
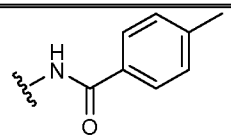
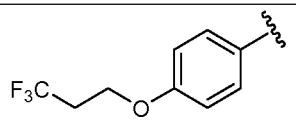
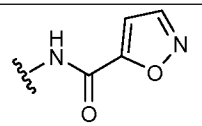
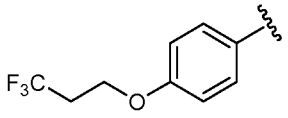
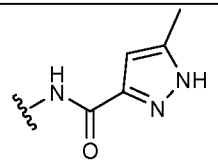
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							0.93 - 0.79 (m, 3H)
117 Rac		CF_3	H		$R^{13} = CH_3$	540.1	7.43 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 7.7 Hz, 2H), 7.03 - 6.91 (m, 5H), 3.99 (t, *J* = 5.9 Hz, 2H), 3.65 - 3.53 (m, 2H), 2.37 (s, 3H), 2.23 - 2.11 (m, 2H), 1.92 - 1.82 (m, 2H), 1.82 - 1.72 (m, 2H)
118 Rac		CF_3	H		$R^{13} = CH_3$	576.1	7.44 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.96 (dd, *J* = 11.4, 8.7 Hz, 4H), 6.80 (br. s., 1H), 4.07 - 4.01 (m, 2H), 3.59 (d, *J* = 7.4 Hz, 2H), 2.37 (s, 3H), 2.33 - 2.19 (m, 2H), 2.10 (dd, *J* = 9.5, 5.6 Hz, 2H)
119 S-isomer		CF_3	H		$R^{13} = CH_3$	541.2	7.44 (d, *J* = 8.3 Hz, 2H), 7.21 - 7.16 (m, 2H), 7.14 -

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							7.09 (m, 2H), 6.96 (d, J = 8.8 Hz, 2H), 4.06 (t, J = 5.9 Hz, 3H), 3.58 - 3.27 (m, 2H), 2.48 - 2.27 (m, 5H), 2.09 (dd, J = 9.5, 5.9 Hz, 2H), 0.97 - 0.80 (m, 2H), 0.75 - 0.61 (m, 2H), 0.38 (d, J = 3.6 Hz, 2H)
120 S-isomer		CF_3	H		$R^{13} = CH_3$	555.2	7.43 (d, J = 8.5 Hz, 2H), 7.20 - 7.03 (m, 5H), 6.97 - 6.88 (m, 2H), 4.36 - 4.22 (m, 1H), 4.08 - 3.98 (m, 2H), 3.53 - 3.27 (m, 2H), 2.44 - 2.16 (m, 8H), 2.12 - 2.02 (m, 2H), 1.78 - 1.51 (m, 4H)
121 S-isomer		CF_3	H		$R^{13} = CH_3$	583.3	7.49 - 7.37 (m, 2H), 7.22 - 7.07 (m, 4H), 6.97 - 6.84 (m, 3H), 6.74 (d, J = 8.0 Hz, 1H), 4.10 - 3.95 (m, 3H),

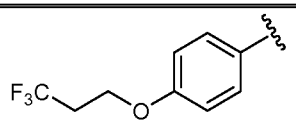
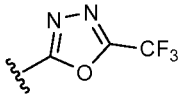
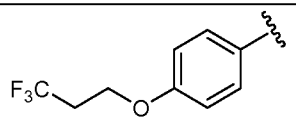
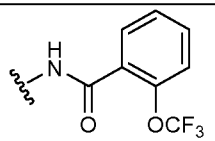
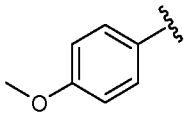
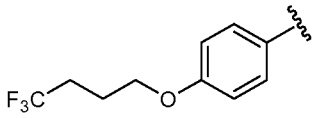
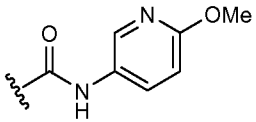
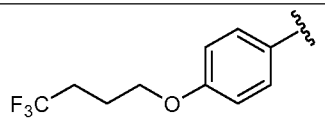
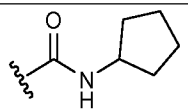
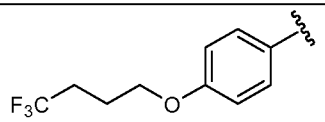
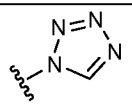
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							3.77 - 3.62 (m, 1H), 3.52 - 3.26 (m, 2H), 2.42 - 2.25 (m, 6H), 2.15 - 1.96 (m, 3H), 1.86 - 1.64 (m, 2H), 1.64 - 1.44 (m, 4H), 1.35 - 1.16 (m, 3H), 1.14 - 0.93 (m, 4H)
122 S-isomer		CF_3	H		$R^{13} = CH_3$	593.3	7.55 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.14 - 7.09 (d, J = 8.8 Hz, 2H), 7.02 - 6.97 (d, J = 8.8 Hz, 2H), 6.68 - 6.62 (m, 2H), 4.08 (t, J = 6.1 Hz, 2H), 3.67 (d, J = 17.1 Hz, 1H), 3.51 (d, J = 17.1 Hz, 1H), 2.45 - 2.35 (m, 2H), 2.34 (s, 3H), 2.09 - 2.00 (m, 2H).

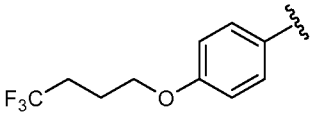
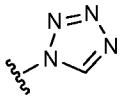
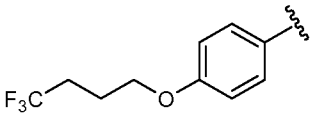
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
123 S-isomer		CF_3	H		$R^{13} = CH_3$	515.2	7.57 - 7.50 (m, *J* = 8.8 Hz, 2H), 7.27 - 7.23 (m, *J* = 8.3 Hz, 2H), 7.23 - 7.19 (m, *J* = 8.3 Hz, 2H), 7.02 - 6.97 (m, *J* = 9.1 Hz, 2H), 4.08 (t, *J* = 6.1 Hz, 2H), 3.60 (d, *J* = 17.1 Hz, 1H), 3.46 (d, *J* = 17.1 Hz, 1H), 2.57 (s, 3H), 2.45 - 2.37 (m, 2H), 2.36 (s, 3H), 2.11 - 1.99 (m, 2H).
124 Rac		CF_3	F		$R^{13} = CH_3$	643.3	7.90 (s, 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.25 - 7.17 (m, 6H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.95 (br. s., 1H), 6.78 (d, *J* = 9.1 Hz, 2H), 4.05 (t, *J* = 5.9 Hz, 2H), 3.81 - 3.71 (m, 3H), 2.44 - 2.27 (m, 5H), 2.13 - 2.03 (m, 2H)

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
125 Rac		CF_3	H		$R^{13} = CH_3$	512.1	7.45 (d, *J* = 8.5 Hz, 3H), 7.13 (d, *J* = 7.7 Hz, 2H), 6.93 (d, *J* = 7.7 Hz, 4H), 4.18 (t, *J* = 6.5 Hz, 2H), 3.68 - 3.52 (m, 2H), 2.67 - 2.56 (m, 2H)
126 Rac		CF_3	H		$R^{13} = CH_3$	466.2	
127 Rac		CF_3	H		$R^{13} = CH_3$	480.1	7.50 - 7.40 (m, 4H), 7.16 (d, *J* = 7.7 Hz, 2H), 7.09 (br. s., 1H), 6.98 (d, *J* = 7.7 Hz, 2H), 6.17 (br. s., 1H), 2.36 (s, 5H), 2.21 (d, *J* = 3.6 Hz, 2H), 1.82 - 1.74 (m, 2H), 1.70 - 1.62 (m, 2H)
128 S-isomer		CF_3	H		$R^{13} = CH_3$	591.3	

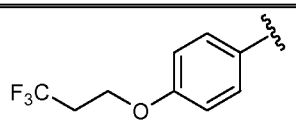
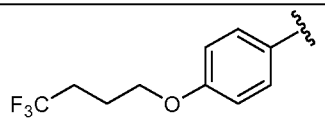
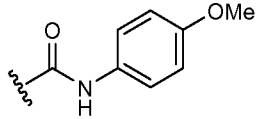
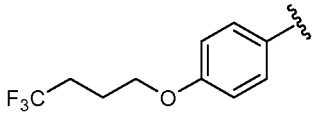
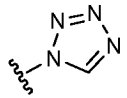
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
129 S-isomer		CF_3	H		$R^{13} = CH_3$	591.3	
130 S-isomer		CF_3	H		$R^{13} = CH_3$	568.2	8.47 (d, *J* = 1.9 Hz, 1H), 7.61 - 7.54 (ab quartet, *J* = 8.8 Hz, 2H), 7.24 - 7.20 (ab quartet, *J* = 8.3 Hz, 2H), 7.19 - 7.15 (ab quartet, *J* = 8.3 Hz, 2H), 7.04 - 6.98 (m, 2H), 6.93 - 6.87 (m, 1H), 4.09 (t, *J* = 6.1 Hz, 2H), 3.75 (d, *J* = 17.1 Hz, 1H), 3.51 (d, *J* = 16.8 Hz, 1H), 2.46 - 2.34 (m, 2H), 2.32 (s, 3H), 2.12 - 2.01 (m, 3H).
131 S-isomer		CF_3	H		$R^{13} = CH_3$	581.3	

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
132 S-isomer		CF_3	H		$R^{13} = CH_3$	570.2	
133 Rac		CF_3	F		$R^{13} = CH_3$	643.1	8.07 (br. s., 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.24 - 7.15 (m, 6H), 6.96 (d, J = 9.1 Hz, 2H), 6.76 (d, J = 8.8 Hz, 2H), 4.09 - 3.97 (m, 2H), 3.75 (s, 3H), 2.39 - 2.25 (m, 5H), 2.12 - 2.02 (m, 2H)
134 Rac		CF_3	F		$R^{13} = CH_3$	680.9	
135 Rac		CF_3	F		$R^{13} = CH_3$	626.9	

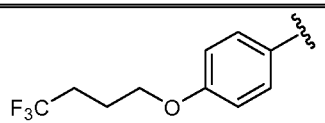
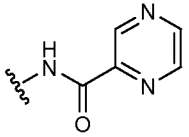
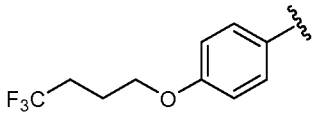
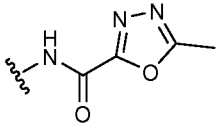
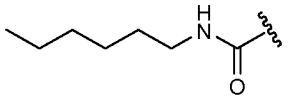
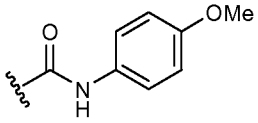
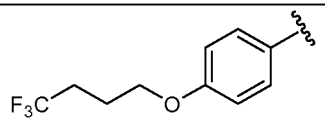
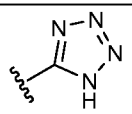
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
136 S-isomer		CF_3	H		$R^{13} = CH_3$	594.1	
137 S-isomer		CF_3	H		$R^{13} = CH_3$	661.1	
138 Rac		CF_3	F	CN	$R^{13} = CH_3$	422.8	
140 Rac		CF_3	F		$R^{13} = CH_3$	643.9	
141 Rac		CF_3	F		$R^{13} = CH_3$	604.9	
142 S-isomer		CF_3	H		$R^{11} = F$ $R^{13} = OCH_3$	560.1	9.17 (s, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.07 - 7.00 (m, 2H), 6.95 (t, J = 8.5 Hz, 1H), 6.69 (dd, J = 8.8, 2.5 Hz, 1H), 6.63 (dd, J = 12.7, 2.5 Hz,

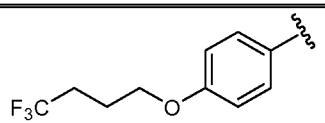
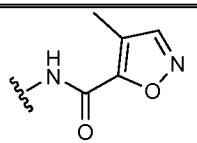
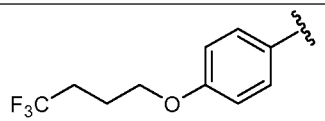
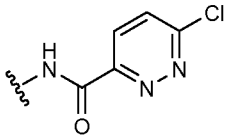
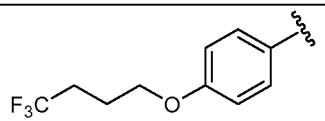
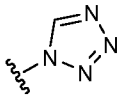
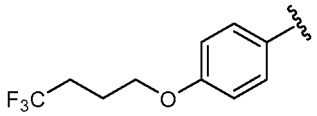
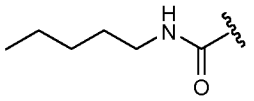
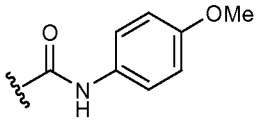
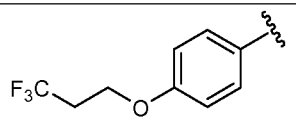
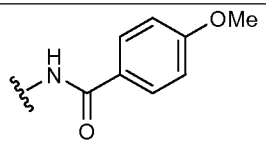
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							1H), 4.09 (t, J = 6.1 Hz, 2H), 3.90 - 3.81 (m, 1H), 3.76 (s, 3H), 3.74 - 3.66 (m, 1H), 2.47 - 2.30 (m, 2H), 2.12 - 1.94 (m, 2H).
143 S-isomer		CF_3	H		$R^{13} = OCH_3$	542.1	9.05 (s, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 9.1 Hz, 2H), 6.97 - 6.88 (m, 1H), 6.86 - 6.76 (m, 1H), 4.09 (t, J = 6.1 Hz, 2H), 3.92 - 3.70 (m, 2H), 3.75 (S, 3H), 2.45 - 2.29 (m, 2H), 2.10 - 1.94 (m, 2H).
144 S-isomer		CF_3	H	CN	$R^{13} = OCHF_2$	535.1	7.65 (br. s., 2H), 7.53 (d, J = 9.1 Hz, 2H), 7.32 - 7.24 (m, 2H), 7.05 - 6.98 (m, 2H), 6.96 (t, J = 75 Hz, 1H), 4.14 - 3.97 (m, 2H), 3.73 (d, J =

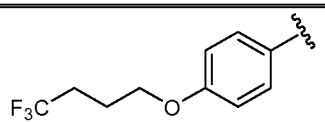
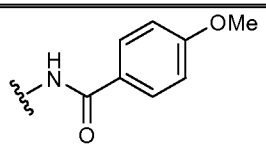
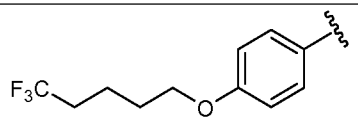
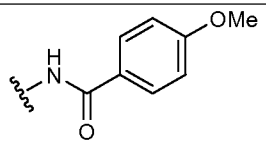
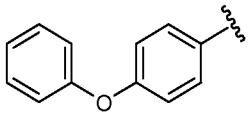
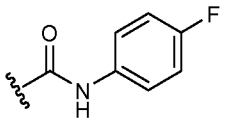
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							3.3 Hz, 2H), 2.42 - 2.27 (m, 2H), 2.09 - 1.96 (m, 2H).
145 S-isomer		CF_3	H	CN	R^{13} = OCH_2CH_3	513.1	7.64 (d, J = 9.1 Hz, 2H), 7.52 (d, J = 9.1 Hz, 2H), 7.03 (d, J = 9.1 Hz, 4H), 4.12 (d, J = 6.9 Hz, 2H), 4.08 - 4.03 (m, 2H), 3.82 - 3.58 (m, 2H), 2.45 - 2.26 (m, 2H), 2.08 - 1.95 (m, 2H), 1.41 (t, J = 6.9 Hz, 3H).
146 S-isomer		CF_3	H	CN	R^{12} and R^{13}	519.1	8.15 (d, J = 1.7 Hz, 1H), 8.01 - 7.96 (m, 2H), 7.93 (d, J = 8.0 Hz, 1H), 7.67 - 7.54 (m, 5H), 7.06 - 7.00 (m, 2H), 4.08 (s, 2H), 3.93 - 3.77 (m, 2H), 2.48 - 2.25 (m, 2H), 2.13 - 1.92 (m, 2H).

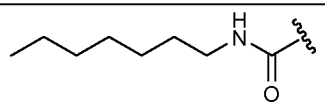
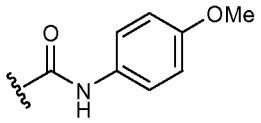
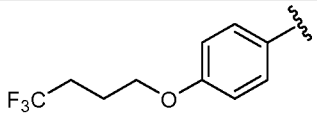
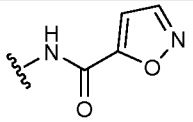
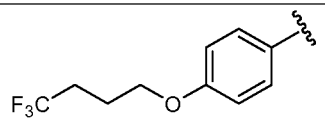
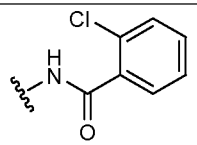
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
147 S-isomer		CF_3	H	CN	$R^{13} = CH_3$	469.1	7.55 (d, J = 8.8 Hz, 2H), 7.52 - 7.49 (m, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.04 - 6.99 (m, 2H), 4.24 (t, J = 6.1 Hz, 2H), 3.77 - 3.66 (m, 2H), 2.75 - 2.63 (m, 2H), 2.41 (s, 3H).
148 S-isomer		CF_3	H		$R^{11} = CH_3$ $R^{13} = CH_3$	621.2	7.49 - 7.41 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.03 - 6.65 (m, 7H), 4.07 - 3.99 (m, 2H), 3.71 (s, 3H), 3.51 - 3.42 (m, 1H), 3.28 – 3.14 (m, 1H), 2.38 - 2.21 (m, 8H), 2.11 - 1.99 (m, 2H).
149 S-isomer		CF_3	H		$R^{13} = OCHF_2$	578.1	9.09 (s, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.08 - 7.03 (m, 6H), 6.97 – 6.68 (m, 1H), 4.09 (t, *J* = 6.1 Hz, 2H), 3.92 (d, *J* = 17.9 Hz, 1H), 3.77 (d,

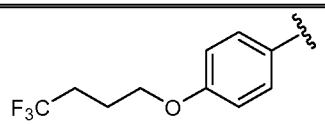
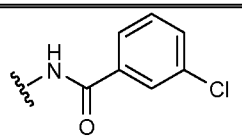
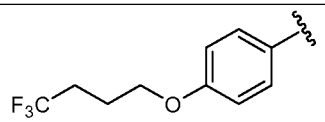
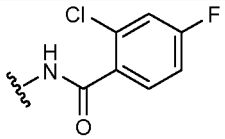
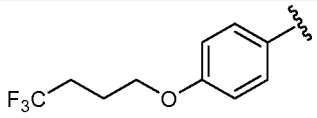
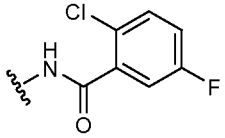
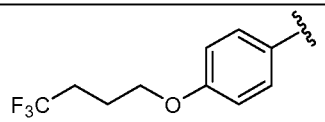
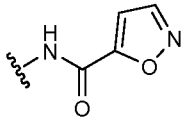
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							J = 17.9 Hz, 1H), 2.43 - 2.31 (m, 2H), 2.10 - 1.98 (m, 2H).
150 S-isomer		CF_3	F		$R^{13} = CH_3$	582.2	7.54 (d, J = 8.8 Hz, 2H), 7.23 - 7.11 (m, 4H), 7.03 - 6.94 (m, 2H), 6.71 (s, 1H), 4.06 (t, J = 6.1 Hz, 2H), 3.98 (s, 1H), 3.71 (d, J = 17.1 Hz, 1H), 3.47 (d, J = 16.8 Hz, 1H), 2.45 - 2.31 (m, 2H), 2.29 (d, J = 6.3 Hz, 6H), 2.12 - 1.96 (m, 2H).
151 S-isomer		CF_3	H		$R^{13} = CH_3$	568.2	
152 S-isomer		CF_3	H		$R^{13} = CH_3$	568.2	

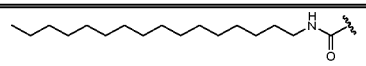
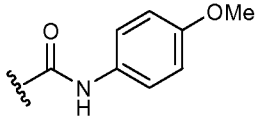
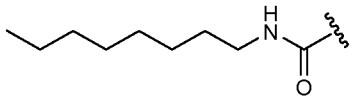
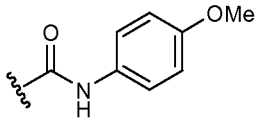
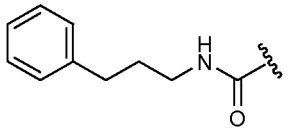
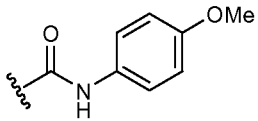
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
153 S-isomer		CF_3	H		$R^{13} = CH_3$	579.2	
154 S-isomer		CF_3	H		$R^{13} = CH_3$	583.1	7.58 - 7.49 (ab quartet, J = 8.8 Hz, 2H), 7.20 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 8.3 Hz, 2H), 7.03 - 6.92 (m, 2H), 4.06 (t, J = 6.1 Hz, 2H), 3.72 (d, J = 17.3 Hz, 1H), 3.49 (d, J = 17.1 Hz, 1H), 2.55 (s, 3H), 2.43 - 2.33 (m, 2H), 2.30 (s, 3H), 2.09 - 1.97 (m, 2H).
155 Rac		CH_3	H		$R^{13} = CH_3$	478.4	
156 S-isomer		CF_3	H		$R^{11} = CH_3$ $R^{13} = CH_3$	540.1	

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
157 S-isomer		CF_3	H		$R^{13} = CH_3$	582.2	
158 S-isomer		CF_3	H		$R^{13} = CH_3$	613.2	
159 Rac		CF_3	F		$R^{13} = CH_3$	562.2	
160 Rac		CF_3	F	CN	$R^{13} = CH_3$	519.2	
161 Rac		CH_3	H		$R^{13} = CH_3$	464.3	
162 Rac		CF_3	F		$R^{13} = CH_3$	628.9	

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
163 Rac		CF_3	F		$R^{13} = CH_3$	656.9	8.05 (s, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.25 - 7.16 (m, 6H), 7.02 - 6.94 (m, 2H), 6.82 - 6.73 (m, 2H), 6.60 (br. s., 1H), 4.01 (td, *J* = 6.1, 1.4 Hz, 2H), 3.75 (s, 3H), 2.35 (s, 3H), 2.24 - 2.10 (m, 2H), 1.93 - 1.85 (m, 2H), 1.83 - 1.74 (m, 2H), 1.67 (br. s., 3H)
164 Rac		CF_3	F		$R^{13} = CH_3$	671.0	
165 S-isomer		CF_3	H		$R^{13} = CH_3$	561.2	7.59 (d, *J* = 8.8 Hz, 2H), 7.42 - 7.36 (m, 2H), 7.35 - 7.28 (m, 4H), 7.20 - 7.16 (m, 3H), 7.06 - 6.99 (m, 4H), 6.98 - 6.93 (m, 2H), 3.66 (d,

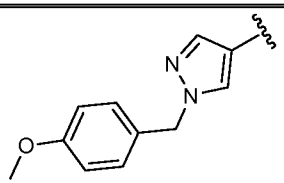
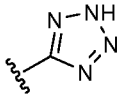
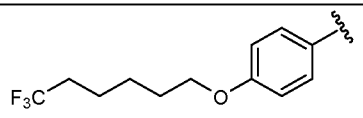
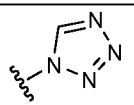
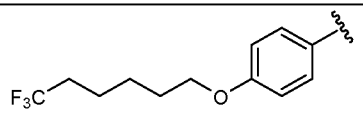
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							J = 17.3 Hz, 1H), 3.52 (d, J = 17.3 Hz, 1H), 2.30 (s, 3H).
166 Rac		CH_3	H		$R^{13} = CH_3$	492.2	
167 S-isomer		CF_3	H		$R^{13} = OHCF_2$	620.2	8.38 (d, J = 1.7 Hz, 1H), 7.61 (s, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.34 - 7.24 (m, 2H), 7.13 - 7.04 (ab quartet, J = 8.8 Hz, 2H), 6.99 - 6.92 (m, 2H), 6.86 (s, 1H), 4.26 (br. s., 1H), 4.05 (t, J = 5.9 Hz, 2H), 3.69 (d, J = 17.1 Hz, 1H), 3.42 (d, J = 17.1 Hz, 1H), 2.41 - 2.27 (m, 2H), 2.10 - 1.97 (m, 2H).
168 S-isomer		CF_3	H		$R^{13} = CH_3$	611.2	

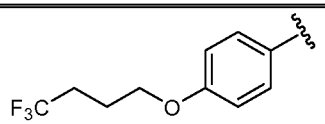
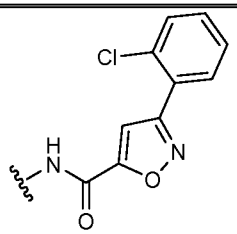
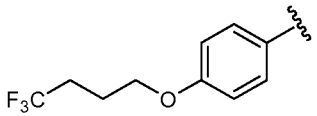
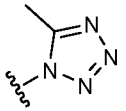
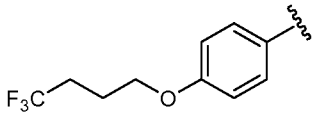
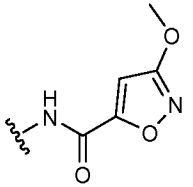
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
169 S-isomer		CF_3	H		$R^{13} = CH_3$	611.2	
170 S-isomer		CF_3	H		$R^{13} = CH_3$	629.2	
171 S-isomer		CF_3	H		$R^{13} = CH_3$	629.3	
172 S-isomer		CF_3	H		$R^{13} = OCH_3$	584.2	8.37 (d, *J* = 1.7 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.28 - 7.17 (m, 2H), 6.99 - 6.91 (m, 2H), 6.89 - 6.82 (m, 3H), 4.05 (t, *J* = 6.1 Hz, 2H), 3.78 (s, 3H), 3.68 (d, *J* = 16.8 Hz, 1H), 3.42 (d, *J* = 17.1 Hz, 1H), 2.45 - 2.23 (m, 2H), 2.10 - 1.98 (m, 2H).

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
173 Rac		CH_3	H		$R^{13} = CH_3$	618.4	7.34 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 9.1 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.79 (d, *J* = 9.1 Hz, 2H), 3.76 (s, 3H), 3.43 - 3.37 (d, *J* = 17.5 Hz, 1H), 3.22 (t, *J* = 7.1 Hz, 2H), 2.86 - 2.80 (d, *J* = 17.2 Hz, 1H), 2.32 (s, 3H), 1.53 (s, 3H), 1.31 - 1.21 (m, 28H), 0.88 (t, *J* = 7.1 Hz, 3H)
174 Rac		CH_3	H		$R^{13} = CH_3$	506.4	
175 Rac		CH_3	H		$R^{13} = CH_3$	512.4	

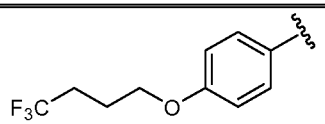
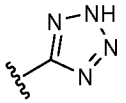
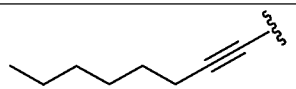
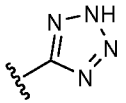
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
176 S-isomer		CF_3	H		$R^{13} = OCH_3$	598.2	7.54 (d, J = 8.8 Hz, 2H), 7.32 - 7.23 (m, 2H), 6.97 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.73 (s, 1H), 4.06 (t, J = 6.1 Hz, 2H), 3.76 (s, 3H), 3.71 (d, J = 17.1 Hz, 1H), 3.49 (d, J = 17.1 Hz, 1H), 2.45 - 2.32 (m, 2H), 2.31 - 2.26 (m, 3H), 2.08 - 1.97 (m, 2H).
177 Rac		CH_3	H	CN	$R^{13} = CH_3$	382.3	
178 Rac		CH_3	H		$R^{13} = CH_3$	526.4	

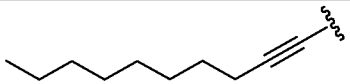
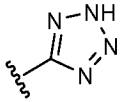
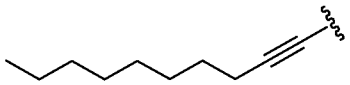
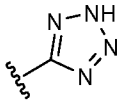
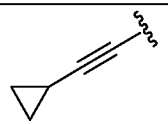
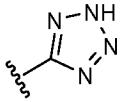
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
179 S-isomer		CF_3	H		$R^{13} = CH_3$	648.2	7.54 (d, J = 8.8 Hz, 2H), 7.23 - 7.11 (m, 4H), 7.03 - 6.93 (m, 3H), 4.06 (t, J = 6.1 Hz, 2H), 3.72 (d, J = 16.9 Hz, 1H), 3.48 (d, J = 17.2 Hz, 1H), 2.44 - 2.32 (m, 2H), 2.30 (s, 3H), 2.08 - 1.97 (m, 2H).
180 S-isomer		CF_3	H		$R^{13} = CH_3$	674.3	
181 Rac		CF_3	F		$R^{13} = CH_3$	547.0	

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
182 Rac		CF_3	H		$R^{13} = CH_3$	510.3	
183 Rac S-isomer		CF_3	H		$R^{13} = CH_3$	554.3	7.57 - 7.48 (m, 2H), 7.13 - 7.05 (m, 2H), 7.02 - 6.94 (m, 2H), 6.88 - 6.77 (m, 2H), 4.07 - 3.99 (m, 2H), 2.29 (s, 3H), 2.19 - 2.07 (m, 2H), 1.89 - 1.78 (m, 2H), 1.69 - 1.55 (m, 4H)
184 S-isomer		CF_3	H	CN	$R^{13} = CH_3$	511.1	7.46 (dd, *J* = 12.1, 8.5 Hz, 4H), 7.31 (d, *J* = 8.3 Hz, 2H), 6.95 (d, *J* = 9.1 Hz, 2H), 4.32 - 4.22 (m, 1H), 4.00 (s, 2H), 3.67 - 3.55 (m, 1H), 2.41 (s, 3H), 2.23 - 1.99 (m, 2H), 1.88 - 1.76 (m, 2H), 1.70 - 1.50 (m, 5H)

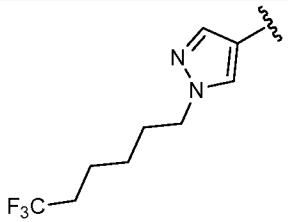
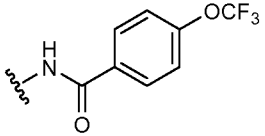
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
185 S-isomer		CF_3	H		$R^{13} = CH_3$	678.3	
186 S-isomer		CF_3	H		$R^{13} = CH_3$	540.3	
187 S-isomer		CF_3	H		$R^{13} = CH_3$	598.3	7.57 - 7.50 (m, *J* = 8.8 Hz, 2H), 7.21 - 7.12 (m, 4H), 7.01 - 6.94 (m, 2H), 6.48 (s, 1H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.95 (s, 3H), 3.71 (d, *J* = 17.1 Hz, 1H), 3.47 (d, *J* = 17.1 Hz, 1H), 2.44 - 2.32 (m, 2H), 2.30 (s, 3H), 2.07 - 1.98 (m, 2H).

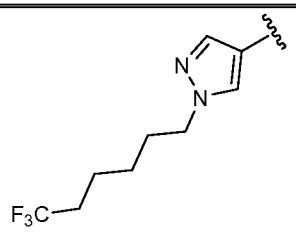
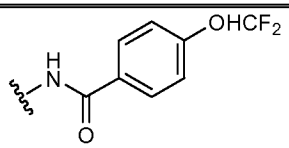
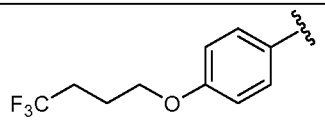
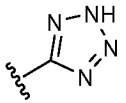
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
188 Rac		CH_3	H		$R^{13} = CH_3$	450.1	
189 Rac		CH_3	H		$R^{13} = CH_3$	484.1	
190 S-isomer		CF_3	H		$R^{13} = CH_3$	662.3	
191 Rac		CH_3	H		$R^{13} = CH_3$	520.2	
192 S-isomer		CF_3	H		$R^{13} = CH_3$	526.3	

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
193 S-isomer		CF_3	H		$R^{13} = OCH_3$	542.1	^{1}H NMR (500 MHz, $CDCl_3$: MeOD (1:1)) δ 7.65 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 4.07 (t, *J* = 6.0 Hz, 2H), 3.77 (s, 3H), 3.69 (d, *J* = 17.7 Hz, 1H), 3.60 (d, *J* = 17.7 Hz, 1H), 2.41 - 2.28 (m, 2H), 2.06 (dq, *J* = 12.1, 6.3 Hz, 2H).
194 Rac		CF_3	H		$R^{13} = CH_3$	432.3	7.21 (d, *J* = 7.9 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.25 (s, 1H), 3.39 (d, *J* = 18.5 Hz, 1H), 3.34 (d, *J* = 18.9 Hz, 1H), 2.39 (s, 3H), 2.23 (t, *J* = 7.2 Hz, 2H), 1.55 - 1.47 (m, 2H), 1.40 - 1.23

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							(m, 6H), 0.87 (t, *J* = 6.9 Hz, 3H).
195 Rac		CF_3	H		$R^{13} = CH_3$	460.4	7.21 (d, *J* = 7.9 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.32 (s, 1H), 3.37 (AB quartet, *J* = 18.7 Hz, 2H), 2.39 (s, 3H), 2.23 (t, *J* = 7.0 Hz, 2H), 1.51 (quin, *J* = 7.2 Hz, 2H), 1.39 - 1.20 (m, 10H), 0.91 - 0.84 (m, 3H).
196 R-isomer		CF_3	H		$R^{13} = CH_3$	460.4	7.17 (d, *J* = 7.9 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 6.74 (s, 1H), 3.43 - 3.32 (m, 2H), 2.37 (s, 3H), 2.23 (t, *J* = 7.0 Hz, 2H), 1.55 - 1.47 (m, 2H), 1.37 - 1.22 (m, 10H).
197 S-isomer		CF_3	H		$R^{13} = CH_3$	388.3	7.20 (d, *J* = 7.9 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 2H),

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							6.34 (s, 1H), 3.38, 3.32 (ABq, J = 18.9 Hz, 2H), 2.39 (s, 3H), 1.28 (tt, J = 8.3, 5.0 Hz, 1H), 0.89 - 0.83 (m, 2H), 0.76 - 0.71 (m, 2H).
198 S-isomer		CF_3	H		$R^{13} = CH_3$	452.3	7.30 - 7.23 (m, 2H), 7.22 - 7.13 (m, 5H), 6.99 (d, J = 8.1 Hz, 2H), 6.57 (s, 1H), 3.33 (d, J = 18.9 Hz, 1H), 3.26 (d, J = 18.9 Hz, 1H), 2.85 - 2.80 (m, 2H), 2.57 - 2.53 (m, 2H), 2.38 (s, 3H)
199 S-isomer		CF_3	H		$R^{13} = CH_3$	418.3	7.19 (d, J = 7.9 Hz, 2H), 7.06 (d, J = 8.1 Hz, 2H), 6.68 (s, 1H), 3.38, 3.35 (ABq, J = 18.9 Hz, 2H), 2.37 (s, 3H), 2.24 (t, J = 7.4 Hz, 2H), 1.63 (dquin, J = 13.4,

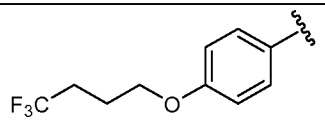
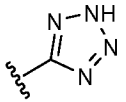
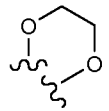
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							6.7 Hz, 1H), 1.41 (q, *J* = 7.3 Hz, 2H), 0.88 (d, *J* = 6.6 Hz, 6H)
200 Rac		CF_3	H		$R^{13} = CH_3$	663.2	9.63 (s, 1H), 7.62 (s, 1H), 7.54 (s, 1H), 7.50 (d, *J* = 8.9 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.87 (s, 1H), 4.13 (t, *J* = 7.2 Hz, 2H), 3.48 (d, *J* = 18.4 Hz, 1H), 3.25 (d, *J* = 18.4 Hz, 1H), 2.42 - 2.31 (m, 3H), 2.08 - 2.03 (m, 2H), 1.96 - 1.85 (m, 2H), 1.62 - 1.53 (m, 2H), 1.41 - 1.31 (m, 2H)

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
201 Rac		CF_3	H		$R^{13} = CH_3$	645.3	10.16 (s, 1H), 9.00 (s, 1H), 7.99 (s, 1H), 7.70 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 2H), 7.12 (t, *J* = 74.3 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 4.11 (t, *J* = 6.9 Hz, 2H), 3.41-3.37 (d, *J* = 17.4 Hz, 1H), 3.35 - 3.31 (d, *J* = 17.4 Hz, 1H), 2.28 (s, 3H), 2.23 - 2.17 (m, 2H), 1.85 - 1.75 (m, 2H), 1.52 - 1.44 (m, 2H), 1.31 - 1.22 (m, 2H).
202 S-isomer		CF_3	H		R^{13} = CH_2OCH_3	556.3	^{1}HNMR (500 MHz, DMSO-d_6) δ 9.57 (s, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.04 (d, *J* = 8.8

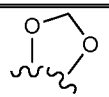
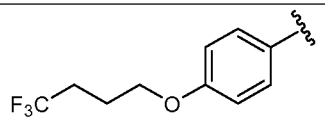
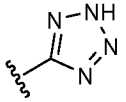
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							Hz, 2H), 6.99 (d, J = 7.9 Hz, 2H), 4.36 (s, 2H), 4.09 (t, J = 6.1 Hz, 2H), 3.75 (d, J = 17.5 Hz, 1H), 3.69 (d, J = 17.5 Hz, 1H), 3.27 (s, 3H), 2.48 - 2.37 (m, 2H), 2.01 - 1.89 (m, 2H)
203 S-isomer		CF_3	H		R^{12} = F R^{13} = OCH_2CH_3	574.3	
204 S-isomer		CF_3	H		R^{13} = CH_3	512.1	^{1}H NMR (500 MHz, MeOD:$CDCl_3$ (1:1)) δ 7.61 (s, 2H), 7.55 (d, J = 8.6 Hz, 2H), 6.97 (dd, J = 10.4, 8.3 Hz, 4H), 6.84 (d, J = 8.1 Hz, 2H), 4.24 (t, J = 6.4 Hz, 2H), 3.71 (d, J = 17.2 Hz, 1H), 3.50 (d, J = 17.2 Hz, 1H),

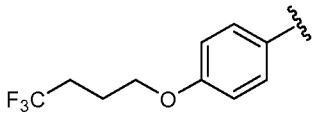
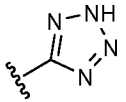
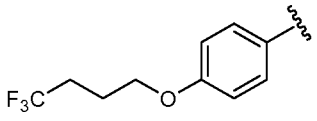
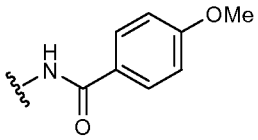
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							3.08 - 3.03 (m, 4H), 2.67 (qt, J = 10.8, 6.3 Hz, 2H), 1.78 (dq, J = 11.3, 5.5 Hz, 4H), 1.69 (q, J = 5.9 Hz, 2H).
205 S-isomer		CF_3	H		$R^{13} = OCHF_2$	578.1	^{1}H NMR (500 MHz, $CDCl_3$: MeOD (1:1)) δ 7.61 (s, 2H), 7.54 (d, J = 8.6 Hz, 2H), 7.05 - 6.96 (m, 5H), 6.66 (t, J = 73.4 Hz, 1H), 4.07 (t, J = 6.0 Hz, 2H), 3.70 (d, J = 17.9 Hz, 1H), 3.57 (d, J = 17.8 Hz, 1H), 2.41 - 2.28 (m, 2H), 2.11 - 2.02 (m, 2H).
206 S-isomer		CF_3	H		$R^{13} = CH_3$	498.1	^{1}H NMR (500 MHz, MeOD-$CDCl_3$ (1:1)) δ 7.60 - 7.57 (m, 2H), 7.07 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.0 Hz, 1H), 4.48 (q, J = 8.2 Hz,

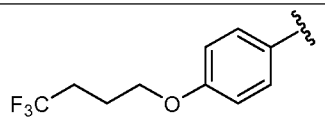
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							1H), 3.70 (d, J = 17.8 Hz, 1H), 3.58 (d, J = 17.8 Hz, 1H), 2.30 (s, 1H).
207 S-isomer		CF_3	H		R^{12} R^{13} =	562.1	^{1}H NMR (500 MHz, $CDCl_3$: MeOD (1:1)) δ 7.81 - 7.73 (m, 2H), 7.72 (d, J = 8.6 Hz, 1H), 7.61 (s, 1H), 7.60 - 7.55 (m, 3H), 7.53 - 7.46 (m, 2H), 7.01 (d, J = 8.8 Hz, 2H), 6.98 (dd, J = 8.5, 1.8 Hz, 1H), 4.08 (t, J = 6.0 Hz, 2H), 3.83 (d, J = 17.8 Hz, 1H), 3.70 (d, J = 17.8 Hz, 1H), 2.41 - 2.28 (m, 2H), 2.11 - 2.01 (m, 2H).
208 S-isomer		CF_3	H		R^{13} = OCH_2CH_3	556.1	^{1}H NMR (500 MHz, CDCl3: MeOD (1:1)) δ 7.62 (s, 1H), 7.54 (d, J = 8.5 Hz, 2H), 6.98 (d, J = 8.9 Hz, 2H), 6.91 (d, J

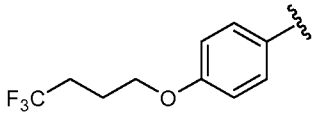
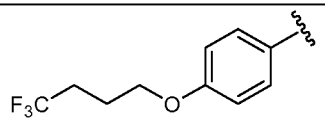
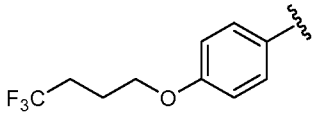
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							= 8.7 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 4.07 (t, *J* = 6.0 Hz, 2H), 4.00 (q, *J* = 7.0 Hz, 2H), 3.68 (d, *J* = 17.8 Hz, 1H), 3.59 (d, *J* = 17.7 Hz, 1H), 2.40 - 2.28 (m, 2H), 2.10 - 2.01 (m, 2H), 1.38 (t, *J* = 7.0 Hz, 3H).
209 S-isomer		CF_3	H		R^{12} R^{13} = 	570.2	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.57 (d, *J* = 2.2 Hz, 1H), 6.41 (dd, *J* = 8.5, 2.2 Hz, 1H), 4.25 - 4.14 (m, 4H), 4.06 (t, *J* = 6.2 Hz, 2H), 3.68 (d, *J* = 18.2 Hz, 1H), 3.63 (d, *J* = 18.5 Hz, 1H), 2.42 (ddd,

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							J = 16.4, 8.0, 5.1 Hz, 2H), 1.93 (dq, J = 12.3, 6.4 Hz, 2H).
210 S-isomer		CF_3	H		R^{12} R^{13} =	566.1	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.42 (s, 1H), 7.60 (d, J = 8.5 Hz, 2H), 7.01 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.0 Hz, 1H), 6.80 (s, 1H), 6.56 (d, J = 7.7 Hz, 1H), 4.06 (t, J = 6.1 Hz, 2H), 3.67 (d, J = 17.8 Hz, 1H), 3.60 (d, J = 17.9 Hz, 1H), 2.61 (s, 2H), 2.56 (s, 2H), 2.42 (ddd, J = 11.4, 8.3, 5.2 Hz, 2H), 1.98 - 1.88 (m, 2H), 1.65 (p, J = 2.8 Hz, 4H).
211 S-isomer		CF_3	H		R^{12} R^{13} =	556.2	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.37 (s, 1H), 7.60 (d, J

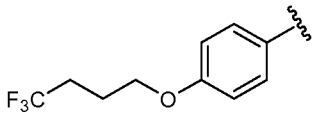
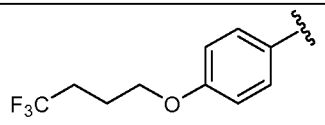
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							= 8.5 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.57 (s, 1H), 6.48 (d, *J* = 8.1 Hz, 1H), 5.97 (d, *J* = 3.1 Hz, 2H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.65 (d, *J* = 17.6 Hz, 1H), 3.58 (d, *J* = 17.7 Hz, 1H), 2.46 - 2.35 (m, 2H), 1.93 (dd, *J* = 9.9, 5.4 Hz, 2H).
212 S-isomer		CF_3	H		R^{11} R^{12} =  $R^{13} = OCH_3$	582.3	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.30 (s, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.71 (d, *J* = 8.2 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 4.12 - 4.01 (m, 2H), 3.70 (s, 3H), 3.67 (m, 1H), 3.60 (d, *J* = 17.4 Hz, 1H),

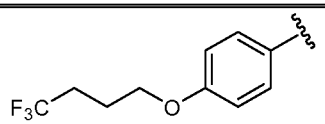
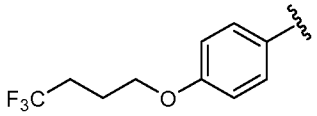
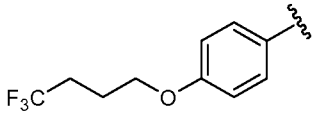
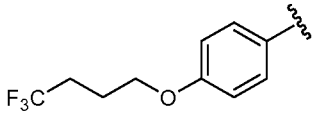
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							2.67 - 2.55 (m, 2H), 2.46 - 2.35 (m, 2H), 2.31 - 2.07 (m, 2H), 1.97 - 1.91 (m, 2H), 1.81 - 1.69 (m, 2H).
213 S-isomer		CHF_2	H		$R^{13} = CH_3$	508.3	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.10 (s, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 7.8 Hz, 2H), 7.02 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 7.9 Hz, 2H), 6.33 (t, J = 55.0 Hz, 1H), 4.07 (t, J = 6.2 Hz, 2H), 3.57 (d, J = 17.9 Hz, 1H), 3.41 (d, J = 18.2 Hz, 1H), 2.44 (ddd, J = 11.4, 8.1, 5.2 Hz, 2H), 1.99 - 1.91 (m, 2H).
214 R-isomer		H	H		$R^{13} = CH_3$	539.4	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.06 (s, 1H), 7.42 (d, J = 8.6 Hz,

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							2H), 7.36 (dd, *J* = 10.3, 8.2 Hz, 4H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 4.82 - 4.73 (m, 1H), 4.05 (t, *J* = 6.2 Hz, 2H), 3.83 - 3.72 (m, 1H), 3.71 (s, 3H), 2.88 (qd, *J* = 17.0, 7.6 Hz, 1H), 2.48 - 2.35 (m, 2H), 2.25 (s, 3H), 1.94 (dq, *J* = 12.5, 6.4 Hz, 2H).
215 S-isomer		CF_3	H	CN	$R^{12} = CH_3$ $R^{13} = OCH_3$	513.1	^{1}H NMR (500 MHz, MeOD) δ 7.61 (s, 1H), 7.58 (s, 1H), 7.54 - 7.41 (m, 1H), 7.30 (dd, J = 8.4, 2.0 Hz, 1H), 7.22 (s, 1H), 7.03 (d, J = 9.4 Hz, 1H), 6.96 (d, J = 8.9 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 4.32 (s,

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							2H), 4.10 - 4.03 (m, 2H), 3.86 (s, 2H), 3.67 - 3.55 (m, 1H), 2.40 - 2.27 (m, 2H), 2.27 - 2.23 (m, 1H), 2.22 (s, 2H), 2.10 - 2.00 (m, 2H)
216 S-isomer		CF_3	H	CN	$R^{12} = OCH_3$ $R^{13} = OCH_3$	529.1	
217 S-isomer		CF_3	H	CN	$R^{12} = CH_3$ $R^{13} = CH_3$	497.1	^{1}H NMR (500 MHz, MeOD) δ 7.61 (s, 1H), 7.49 - 7.43 (m, 2H), 7.35 - 7.23 (m, 3H), 6.99 - 6.94 (m, 2H), 4.32 (s, 2H), 4.06 (t, J = 5.9 Hz, 2H), 3.61 (s, 2H), 2.38 - 2.33 (m, 2H), 2.31 - 2.28 (m, 1H), 2.09 - 2.01 (m, 2H)
218 S-isomer		CF_3	H	CN	$R^{12} = F$ $R^{13} = OCH_3$	517.1	^{1}H NMR (500 MHz, MeOD) δ 7.49 - 7.43 (m, 3H), 7.40 (dd, J = 11.9, 2.0 Hz, 1H),

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							7.14 (t, J = 8.4 Hz, 1H), 7.00 - 6.93 (m, 2H), 4.32 (s, 2H), 4.05 (t, J = 5.9 Hz, 2H), 3.96 (s, 3H), 3.61 (d, J = 3.0 Hz, 2H), 2.39 - 2.27 (m, 2H), 2.09 - 2.01 (m, 2H)
219 S-isomer		CF_3	H	CN	R^{12} = F R^{13} = CH_3	501.1	^{1}H NMR (500 MHz, MeOD) δ 7.49 - 7.43 (m, 2H), 7.39 - 7.32 (m, 1H), 7.30 - 7.21 (m, 2H), 7.00 - 6.93 (m, 2H), 4.29 (s, 1H), 4.08 - 4.04 (m, 2H), 3.60 (d, J = 2.0 Hz, 2H), 2.35 (d, J = 5.4 Hz, 1H), 2.32 - 2.28 (m, 1H), 2.09 - 2.00 (m, 2H)
220 S-isomer		CF_3	H	CN	R^{11} = F R^{13} = Cl	521.0	^{1}H NMR (500 MHz, MeOD) δ 7.48 - 7.43 (m, 2H), 7.36 - 7.28 (m, 3H), 7.00 - 6.95 (m,

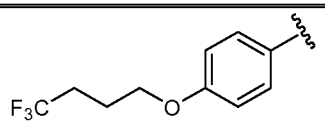
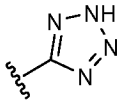
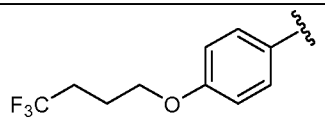
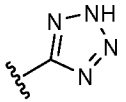
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							2H), 4.07 (t, J = 5.9 Hz, 2H), 3.59 (q, J = 1.0 Hz, 2H), 2.40 - 2.28 (m, 2H), 2.10 - 2.02 (m, 2H)
221 S-isomer		CF_3	H	CN	$R^{12} = CH_3$ $R^{13} = Cl$	517.1	^{1}H NMR (500 MHz, MeOD) δ 7.61 (s, 1H), 7.58 (s, 1H), 7.54 - 7.41 (m, 1H), 7.30 (dd, J = 8.4, 2.0 Hz, 1H), 7.22 (s, 1H), 7.03 (d, J = 9.4 Hz, 1H), 6.96 (d, J = 8.9 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 4.32 (s, 2H), 4.10 - 4.03 (m, 2H), 3.86 (s, 2H), 3.67 - 3.55 (m, 1H), 2.40 - 2.27 (m, 2H), 2.27 - 2.23 (m, 1H), 2.22 (s, 2H), 2.10 - 2.00 (m, 2H)
222 S-isomer		CF_3	H	CN	$R^{12} = Cl$ $R^{13} = Cl$	539.0	

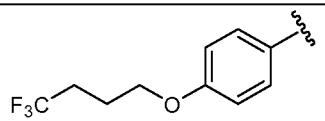
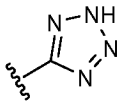
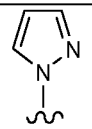
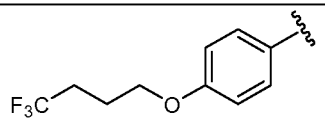
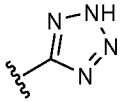
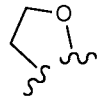
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
223 S-isomer		CF_3	H	CN	R^{11} = Cl R^{13} = OCH_3	532.8	
224 S-isomer		CF_3	H	CN	R^{13} = CN	493.9	
225 S-isomer		CF_3	H	CN	R^{13} = $NHSO_2CH_3$	562.1	
226 S-isomer		CF_3	H	CN	R^{11} = Cl R^{13} = OCH_2CH_3	547.1	^{1}H NMR (500 MHz, MeOD) δ 7.61 - 7.58 (m, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.06 - 7.00 (m, 2H), 7.00 - 6.95 (m, 2H), 6.89 (dd, J = 8.4, 2.5 Hz, 1H), 4.11 - 4.04 (m, 4H), 3.66 (d, J = 18.3 Hz, 1H), 3.43 (d, J = 18.3 Hz, 1H), 2.40 - 2.28 (m, 2H), 2.10 - 2.02 (m, 2H), 1.45 - 1.39 (m, 3H)

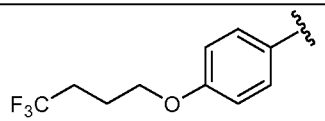
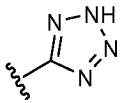
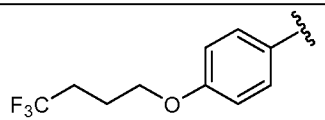
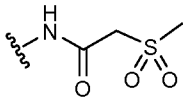
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
227 Rac		CF_3	H	CN	$R^{13} = CH_3$	471.2	
228 Rac		CF_3	H		$R^{13} = CH_3$	609.2	7.86 (s, 1H), 7.66 (s, 1H), 7.37 (d, J = 8.25 Hz, 2H), 7.26 (d, J = 9.08 Hz, 2H), 7.21 (d, J = 7.98 Hz, 2H), 6.82 (d, J = 9.08 Hz, 2H), 4.18 (t, J = 6.88 Hz, 2H), 3.76 (s, 3H), 3.58 (d, J = 17.33 Hz, 1H), 3.35 (d, J = 17.33 Hz, 1H), 2.34 (s, 3H), 2.13 (m, 2H), 1.89 (m, 2H), 1.57 (m, 2H), 1.35 (m, 2H).

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
229 Rac		CF_3	H		$R^{13} = CH_3$	595.2	
230 Rac		CF_3	H	CN	$R^{13} = CH_3$	434.0	
231 S-isomer		CF_3	H		$R^{13} = CH_3$	581.4	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.43 (s, 1H), 9.23 (s, 1H), 7.54 (d, J = 8.80 Hz, 2H), 7.48 (d, J = 1.65 Hz, 1H), 7.29 (d, J = 7.98 Hz, 2H), 7.15 (d, J = 7.98 Hz, 2H), 7.00 (d, J = 8.80 Hz, 2H), 6.34 (d, J = 1.93 Hz, 1H), 4.07 (t, J = 6.05 Hz, 2H), 3.67 (s, 3H), 3.48 (d, J

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							= 17.06 Hz, 1H), 3.39 (d, J = 17.06 Hz, 1H), 2.43 (m, 2H), 2.27 (s, 3H), 1.95 (m, 2H).
232 S-isomer		CF_3	H		$R^{13} = CH_3$	609.1	8.13 (d, J = 9.63 Hz, 1H), 7.54 (d, J = 8.80 Hz, 2H), 7.26 (d, J = 8.25 Hz, 2H), 7.23 (d, J = 9.63 Hz, 1H), 7.17 (d, J = 7.99 Hz, 2H), 6.99 (d, J = 9.08 Hz, 2H), 4.07 (t, J = 6.05 Hz, 2H), 4.01 (s, 3H), 3.67 (d, J = 17.33 Hz, 1H), 3.53 (d, J = 17.06 Hz, 1H), 2.37 (m, 2H), 2.29 (s, 3H), 2.03 (m, 2H).
233 S-isomer		CF_3	H		$R^{13} = CH_3$	479.8	

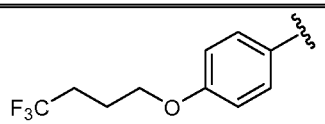
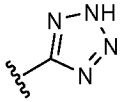
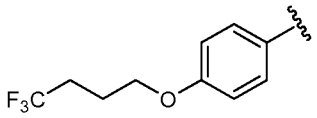
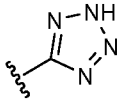
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
234 S-isomer		CF_3	H		R^{13} = Br	589.9	7.54 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 6.97 (dd, *J* = 8.7, 2.3 Hz, 4H), 6.85 (br. s., 1H), 4.04 (t, *J* = 5.8 Hz, 2H), 3.69 - 3.59 (m, 1H), 3.56 - 3.46 (m, 1H), 2.40 - 2.26 (m, 2H), 2.08 (dd, *J* = 9.4, 6.1 Hz, 2H).
235 S-isomer		CF_3	H		R^{13} = 		^{1}H NMR (500 MHz, DMSO) δ 9.55 (br. s., 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.98 - 6.92 (m, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 4.07 (t, *J* = 6.1 Hz, 2H), 3.80 - 3.61 (m, 2H), 2.46 - 2.29 (m, 2H), 2.00 - 1.90 (m, 2H), 1.89 - 1.79 (m, 1H), 1.00 - 0.88 (m, 2H), 0.69 -

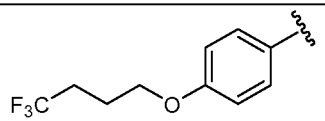
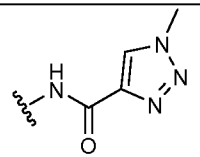
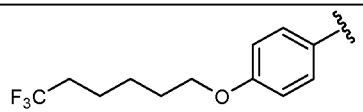
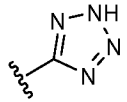
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							0.54 (m, 2H).
236 S-isomer		CF_3	H		R^{13} = 	578.0	^{1}H NMR (500MHz, DMSO) δ 9.42 (br. s., 1H), 8.47 (d, *J* = 2.5 Hz, 1H), 7.73 (d, *J* = 1.1 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 1.9 Hz, 1H), 4.08 (t, *J* = 6.2 Hz, 2H), 3.78 - 3.63 (m, 2H), 2.46 - 2.34 (m, 2H), 2.02 - 1.86 (m, 2H).
237 S-isomer		CF_3	H		R^{12} R^{13} = 	554.0	^{1}H NMR (500MHz, DMSO) δ 9.42 (br. s., 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.97 (s, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 6.59

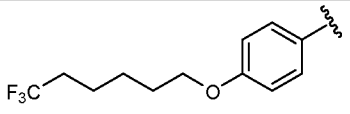
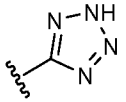
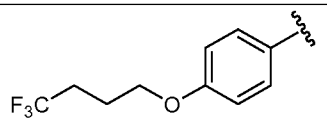
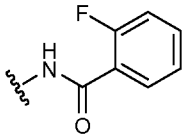
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							(d, *J* = 8.3 Hz, 1H), 4.50 (t, *J* = 8.7 Hz, 2H), 4.07 (t, *J* = 6.2 Hz, 2H), 3.65 (br. s., 2H), 3.06 (t, *J* = 8.7 Hz, 2H), 2.47 - 2.34 (m, 2H), 2.00 - 1.89 (m, 2H).
238 S-isomer		CF_3	H		R^{13} = 	555.1	^{1}H NMR (500 MHz, DMSO) δ 9.41 (br. s., 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 6.52 (d, *J* = 8.8 Hz, 2H), 4.06 (t, *J* = 5.9 Hz, 2H), 3.75 - 3.55 (m, 2H), 2.89 (s, 6H), 2.42 (dd, *J* = 16.5, 11.0 Hz, 2H), 2.02 - 1.84 (m, 2H).
239 S-isomer		CF_3	H		$R^{13} = CH_3$	593.3	^{1}H NMR (400 MHz, MeOD) δ 7.52 (d, *J* = 8.8 Hz, 2H), 7.24 - 7.15 (m, 4H), 6.96 (d,

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							J = 8.8 Hz, 2H), 4.06 (t, J = 6.1 Hz, 2H), 3.97 (s, 2H), 3.67 (d, J = 16.9 Hz, 1H), 3.43 (d, J = 16.9 Hz, 1H), 2.93 (s, 3H), 2.44 - 2.28 (m, 5H), 2.09 - 1.96 (m, 2H).
240 S-isomer		CF_3	H		$R^{13} = OCH_3$	514.3	^{1}H NMR (400 MHz, MeOD) δ 7.65 (d, J = 9.0 Hz, 2H), 7.13 - 7.08 (m, 2H), 6.97 - 6.93 (m, 2H), 6.84 - 6.78 (m, 2H), 4.57 (q, J = 8.4 Hz, 2H), 3.75 (s, 3H), 3.72 (d, J = 2.4 Hz, 2H).
241 S-isomer		CF_3	H		$R^{13} = OCH_3$	528.3	^{1}H NMR (400 MHz, MeOD) δ 7.61 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 9.0 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H),

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							4.25 (t, J = 6.1 Hz, 2H), 3.76 (s, 3H), 3.71 (d, J = 1.5 Hz, 2H), 2.77 - 2.63 (m, 2H).
242 S-isomer		CF_3	H		$R^{13} = OCF_3$	582.2	^{1}H NMR (400 MHz, MeOD) δ 7.62 (d, J = 8.8 Hz, 2H), 7.23 - 7.17 (m, 2H), 7.14 - 7.09 (m, 2H), 7.08 - 7.02 (m, 2H), 4.26 (t, J = 6.2 Hz, 2H), 3.83 - 3.66 (m, 2H), 2.77 - 2.63 (m, 2H).
243 S-isomer		CF_3	H		$R^{13} = OCF_3$	596.3	^{1}H NMR (400 MHz, MeOD) δ 7.61 (d, J = 8.8 Hz, 2H), 7.22 - 7.17 (m, 2H), 7.15 - 7.09 (m, 2H), 7.06 - 7.00 (m, 2H), 4.08 (t, J = 6.1 Hz, 2H), 3.82 - 3.65 (m, 2H), 2.44 - 2.30 (m, 2H), 2.09 - 1.99 (m, 2H).

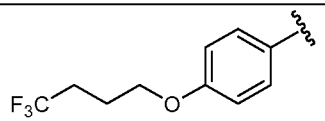
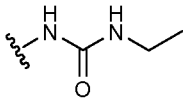
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
244 S-isomer		CF_3	H		$R^{13} = OCH_3$	556.3	^{1}H NMR (400 MHz, MeOD) δ 7.58 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.04 (t, *J* = 6.1 Hz, 2H), 3.76 (s, 3H), 3.70 (d, *J* = 1.3 Hz, 2H), 2.31 - 2.17 (m, 2H), 1.92 - 1.83 (m, 2H), 1.80 - 1.70 (m, 2H).
245 S-isomer		CF_3	H		R^{13} = $OCHCF_2$	592.1	^{1}H NMR (400 MHz, MeOD) δ 7.59 (d, *J* = 8.6 Hz, 2H), 7.05 (s, 4H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.87 (t, *J* = 74.6 Hz, 1H), 4.04 (t, *J* = 6.1 Hz, 2H), 3.74, 3.70 (ABq, *J* = 18.0 Hz, 2H), 2.31 - 2.17 (m, 2H), 1.92 - 1.84 (m, 2H),

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							1.80 - 1.70 (m, 2H)
246 S-isomer		CF_3	H		$R^{13} = CH_3$	582.3	^{1}H NMR (400 MHz, MeOD) δ 8.18 (s, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.25 - 7.19 (m, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 4.09 (s, 3H), 4.07 - 4.03 (m, 2H), 3.71 (d, *J* = 16.9 Hz, 1H), 3.48 (d, *J* = 16.9 Hz, 1H), 2.44 - 2.31 (m, 2H), 2.28 (s, 3H), 2.08 - 1.98 (m, 2H).
247 S-isomer		CF_3	H		$R^{13} = OCH_3$	570.1	^{1}H NMR (400 MHz, MeOD) δ 7.57 (d, *J* = 8.8 Hz, 2H), 7.03 - 6.92 (m, 4H), 6.84 - 6.79 (m, 2H), 4.02 (t, *J* = 6.3 Hz, 2H), 3.76 (s, 3H), 3.70 (d, *J* = 1.5 Hz, 2H), 2.25 -

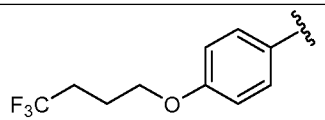
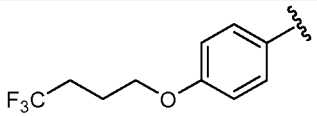
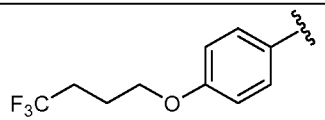
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							2.11 (m, 2H), 1.87 - 1.77 (m, 2H), 1.69 - 1.53 (m, 4H).
248 S-isomer		CF_3	H		R^{13} = $OCHCF_2$	606.3	^{1}H NMR (400 MHz, MeOD) δ 7.61 (d, *J* = 8.8 Hz, 2H), 7.08 (s, 4H), 7.05 - 7.01 (m, *J* = 9.0 Hz, 2H), 6.90 (t, *J* = 73.7 Hz, 1H), 4.05 (t, *J* = 6.2 Hz, 2H), 3.76, 3.73 (ABq, *J* = 18.5 Hz, 2H), 2.28 - 2.14 (m, 2H), 1.89 - 1.81 (m, 2H), 1.72 - 1.56 (m, 4H)
249 S-isomer		CF_3	H		$R^{13} = CH_3$	595.3	^{1}H NMR (400 MHz, MeOD) δ 7.62 - 7.53 (m, 3H), 7.51 - 7.45 (m, 1H), 7.27 - 7.09 (m, 6H), 7.01 - 6.95 (m, 2H), 4.07 (t, *J* = 6.1 Hz, 2H), 3.71 (d, *J* = 16.9 Hz, 1H), 3.48 (d, *J* = 16.9 Hz, 1H), 2.43 - 2.29

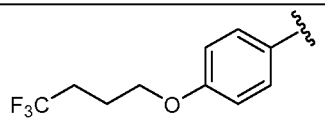
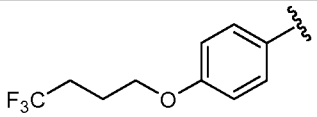
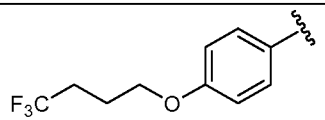
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							(m, 5H), 2.08 - 1.98 (m, 2H).
250 S-isomer		CF_3	H		$R^{13} = CH_3$	543.4	8.35 (br. s., 1H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.18 - 7.13 (m, 2H), 7.11 - 7.06 (m, 2H), 6.96 - 6.90 (m, 2H), 6.30 (s, 1H), 4.03 (t, *J* = 5.9 Hz, 2H), 3.61 (d, *J* = 17.2 Hz, 1H), 3.38 (d, *J* = 17.4 Hz, 1H), 2.41 - 2.25 (m, 8H), 2.11 - 2.02 (m, 2H).
251 S-isomer		CF_3	H		R^{13} = $OCHCF_2$	645.4	^{1}H NMR (400 MHz, MeOD) δ 7.52 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 7.04 - 6.63 (m, 1H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.98 (s, 2H), 3.69 (d, *J* = 16.9 Hz, 1H),

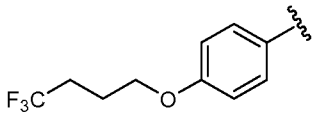
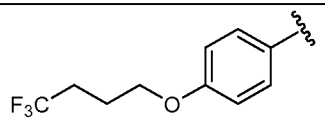
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							3.45 (d, J = 16.9 Hz, 1H), 2.93 (s, 3H), 2.44 - 2.29 (m, 2H), 2.09 - 1.98 (m, 2H).
252 S-isomer		CF_3	H		$R^{13} = OCH_3$	623.3	^{1}H NMR (400 MHz, MeOD) δ 7.51 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 9.0 Hz, 2H), 6.98 - 6.88 (m, 4H), 4.02 (t, J = 6.1 Hz, 2H), 3.99 (s, 2H), 3.79 (s, 3H), 3.66 (d, J = 16.9 Hz, 1H), 3.44 (d, J = 16.7 Hz, 1H), 2.97 (s, 3H), 2.30 - 2.16 (m, 2H), 1.90 - 1.81 (m, 2H), 1.79 - 1.69 (m, 2H).
253 S-isomer		CF_3	H		$R^{13} = CH_3$	545.4	^{1}H NMR (400 MHz, MeOD) δ 7.56 (d, J = 8.8 Hz, 2H), 7.22 - 7.17 (m, 4H), 7.03 - 6.96 (m, 2H), 4.09 (t, J = 6.1

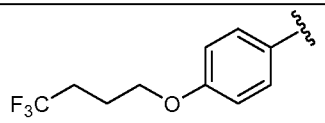
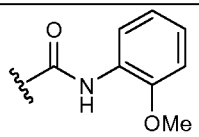
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							Hz, 2H), 4.02 (q, *J* = 6.8 Hz, 1H), 3.66 (d, *J* = 17.2 Hz, 1H), 3.47 (d, *J* = 16.9 Hz, 1H), 2.46 - 2.32 (m, 5H), 2.10 - 2.00 (m, 2H), 1.19 (d, *J* = 6.8 Hz, 3H).
254 S-isomer		CF_3	H		R^{13} = $OCHCF_2$	596.2	^{1}H NMR (400 MHz, MeOD) δ 7.53 (d, *J* = 8.8 Hz, 2H), 7.39 - 7.33 (m, 2H), 7.11 (d, *J* = 8.6 Hz, 2H), 7.00 - 6.95 (m, 2H), 7.02 - 6.63 (m, 1H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.65 (d, *J* = 16.9 Hz, 1H), 3.42 (d, *J* = 16.7 Hz, 1H), 2.96 (q, *J* = 7.3 Hz, 2H), 2.43 - 2.28 (m, 2H), 2.07 - 1.97 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H).

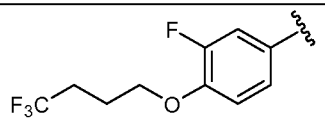
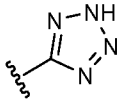
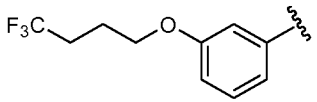
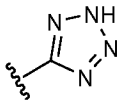
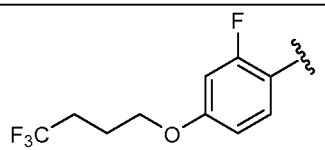
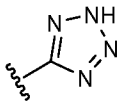
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
255 S-isomer		CF_3	H		$R^{13} = CH_3$	545.3	^{1}H NMR (400 MHz, MeOD) δ 7.53 (d, *J* = 8.8 Hz, 2H), 7.29 - 7.22 (m, 2H), 7.21 - 7.14 (m, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 4.06 (t, *J* = 6.2 Hz, 2H), 3.66 (d, *J* = 16.9 Hz, 1H), 3.45 (d, *J* = 16.7 Hz, 1H), 3.07 (q, *J* = 7.2 Hz, 2H), 2.45 - 2.29 (m, 5H), 2.02 (dd, *J* = 10.2, 5.8 Hz, 2H), 1.06 (t, *J* = 7.2 Hz, 3H).
256 S-isomer		CF_3	H	CN	R^{11} = F $R^{13} = CH_3$	501.1	^{1}H NMR (400 MHz, MeOD) δ 1.96 - 2.13 (m, 2 H) 2.24 - 2.39 (m, 2 H) 2.41 (s, 3 H) 3.49 - 3.68 (m, 2 H) 3.75 (s, 1 H) 4.06 (t, *J* = 5.95 Hz, 2 H) 4.33 (s, 1 H) 6.97 (d, *J* = 1.00 Hz, 2 H) 7.00 - 7.14 (m,

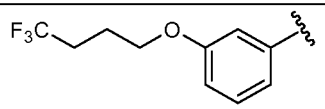
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							2 H) 7.24 (t, *J* = 7.68 Hz, 1 H) 7.45 (d, *J* = 1.00 Hz, 2 H) 7.61 (s, 1 H)
257 S-isomer		CF_3	H	CN	R^{13} = $NHCO_2Me$	541.5	
258 S-isomer		CF_3	H	CN	R^{12} = Cl R^{13} = OCH_3	533.1	
259 S-isomer		CF_3	H	CN	R^{12} = Cl R^{13} = CH_3	[M-H] 515.0	^{1}H NMR (500 MHz, MeOD) δ 2.05 (m, *J* = 9.90, 5.90 Hz, 2 H) 2.22 - 2.41 (m, 2 H) 2.24 - 2.42 (m, 2 H) 2.43 (s, 2 H) 3.62 (br. s., 1 H) 4.06 (t, *J* = 5.95 Hz, 2 H) 4.29 - 4.48 (m, 2 H) 6.98 (d, *J* = 8.92 Hz, 1 H) 7.40 (br. s., 1 H) 7.47 (d, *J* = 8.42 Hz, 1 H) 7.54 (s, 1 H) 7.63 (br. s., 1

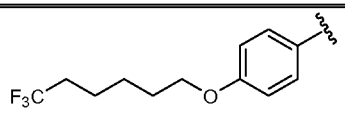
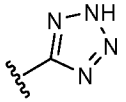
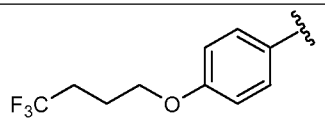
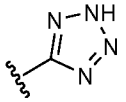
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							H)
260 S-isomer		CF_3	H	CN	R^{13} = CH_2OCH_3	513.1	^{1}H NMR (500 MHz, MeOD) δ 1.97 - 2.11 (m, 2 H) 2.33 (m, *J* = 5.40 Hz, 2 H) 3.43 (s, 3 H) 3.63 (s, 2 H) 4.06 (t, *J* = 5.95 Hz, 2 H) 4.53 (s, 2 H) 6.97 (d, *J* = 1.00 Hz, 2 H) 7.47 (d, *J* = 8.42 Hz, 4 H) 7.55 (d, *J* = 7.93 Hz, 2 H) 7.60 (s, 1 H)
261 S-isomer		CF_3	H	CN	R^{12} = F R^{13} = OCF_3	571.1	
262 S-isomer		CF_3	H	CN	R^{12} = OCH_3 R^{13} = CH_3	513.1	^{1}H NMR (500 MHz, MeOD) δ 1.95 - 2.12 (m, 2 H) 2.25 (s, 3 H) 2.27 - 2.44 (m, 2 H) 3.63 (d, *J* = 2.48 Hz, 2 H) 3.87 (s, 3 H) 4.05 (t, *J* = 5.95 Hz, 2 H) 6.97 (m, *J* = 8.92

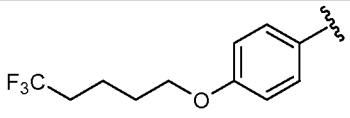
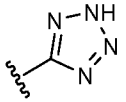
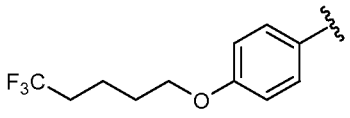
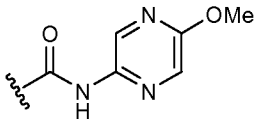
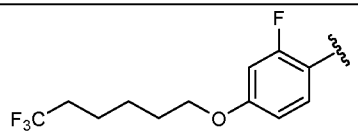
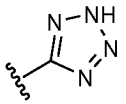
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							Hz, 2 H) 7.08 (d, *J* = 1.49 Hz, 1 H) 7.24 (s, 1 H) 7.47 (m, *J* = 8.92 Hz, 2 H) 7.60 (s, 1 H)
263 S-isomer		CF_3	H	CN	R^{12} = Cl R^{13} = OCH_2CH_3	547.1	^{1}H NMR (500 MHz, MeOD) δ 1.49 (t, *J* = 6.94 Hz, 3 H) 1.95 - 2.12 (m, 2 H) 2.23 - 2.41 (m, 2 H) 3.60 (s, 2 H) 4.05 (t, *J* = 5.95 Hz, 2 H) 4.19 (q, *J* = 6.90 Hz, 2 H) 6.96 (d, *J* = 9.41 Hz, 2 H) 7.08 (d, *J* = 8.92 Hz, 1 H) 7.46 (d, *J* = 8.92 Hz, 2 H) 7.55 (dd, *J* = 1.00 Hz, 1 H) 7.60 (s, 1 H) 7.64 (d, *J* = 1.00 Hz, 1 H)
264 S-isomer		CF_3	H	CN	R^{12} = F R^{13} =	[M-H] 529.1	^{1}H NMR (500 MHz, MeOD) δ 1.47 (t, *J* = 7.18 Hz, 3 H)

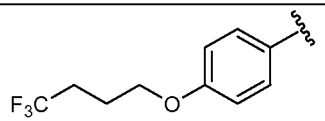
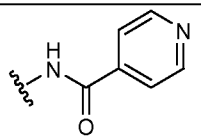
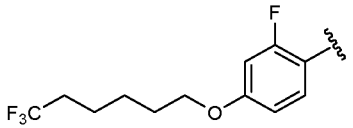
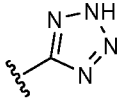
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
					OCH_2CH_3		1.95 - 2.12 (m, 2 H) 2.33 (s, 2 H) 4.06 (t, *J* = 5.95 Hz, 2 H) 4.19 (q, *J* = 6.90 Hz, 2 H) 6.97 (d, *J* = 8.92 Hz, 2 H) 7.12 (t, *J* = 1.00 Hz, 1 H) 7.37 - 7.53 (m, 4 H) 7.62 (s, 1 H)
265 S-isomer		CF_3	H		$R^{13} = CH_3$	607.1	^{1}H NMR (500 MHz, MeOD) δ 7.88 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.05 - 6.97 (m, 3H), 6.89 (d, *J* = 7.4 Hz, 1H), 6.85 - 6.80 (m, 1H), 4.07 (t, *J* = 6.1 Hz, 2H), 3.68 (s, 3H), 3.63 (d, *J* = 17.3 Hz, 1H), 3.51 (d, *J* = 17.3 Hz, 1H),

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							2.43 - 2.32 (m, 2H), 2.31 (s, 3 H), 2.07 - 1.98 (m, 2H).
266 S-isomer		CF_3	H		$R^{13} = CH_3$	544.1	^{1}H NMR (500 MHz, MeOD) δ 7.50 (dd, *J* = 12.7, 2.5 Hz, 1H), 7.45 - 7.38 (m, 1H), 7.18 (t, *J* = 8.7 Hz, 1H), 7.12 - 7.06 (m, 2H), 6.89 (d, *J* = 8.2 Hz, 2H), 4.16 (t, *J* = 6.1 Hz, 2H), 3.74 (d, J = 17.8 Hz, 1H), 3.68 (d, J = 17.8 Hz, 1H), , 2.52 - 2.32 (m, 2H), 2.29 (s, 3H), 2.13 - 1.98 (m, 2H).
267 S-isomer		CF_3	H		$R^{13} = CH_3$	526.2	
268 S-isomer		CF_3	H		$R^{13} = CH_3$	544.2	^{1}HNMR (500 MHz, DMSO-d_6) δ 9.58 (s, 1H), 7.59 (t, *J* = 9.2 Hz, 1H), 7.09 (d, *J* = 8.0

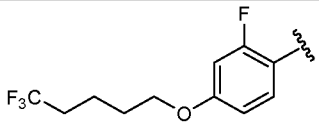
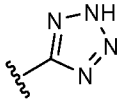
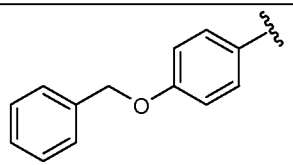
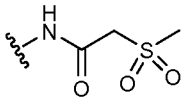
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							Hz, 2H), 6.99 – 6.92 (m, 2H), 6.89 (d, *J* = 8.1 Hz, 2H), 4.11 (t, *J* = 6.1 Hz, 2H), 3.81 (d, *J* = 17.7 Hz, 1H), 3.73 (d, *J* = 17.8 Hz, 1H), 2.49 – 2.30 (m, 2H), 2.25 (s, 3H), 2.03 – 1.78 (m, 2H).
269 S-isomer		CF_3	H	CN	$R^{13} = CH_3$	483.2	^{1}HNMR (400 MHz, MeOD) δ 8.18 (s, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.25 - 7.19 (m, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 4.09 (s, 3H), 4.07 - 4.03 (m, 2H), 3.71 (d, *J* = 16.9 Hz, 1H), 3.48 (d, *J* = 16.9 Hz, 1H), 2.44 - 2.31 (m, 2H), 2.28 (s, 3H), 2.08 - 1.98 (m, 2H).

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
270 R-isomer		CF_3	H		$R^{13} = CH_3$	554.1	^{1}H NMR (400 MHz, MeOD) δ 7.51 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 9.0 Hz, 2H), 6.98 - 6.88 (m, 4H), 4.02 (t, *J* = 6.1 Hz, 2H), 3.99 (s, 2H), 3.79 (s, 3H), 3.66 (d, *J* = 16.9 Hz, 1H), 3.44 (d, *J* = 16.7 Hz, 1H), 2.97 (s, 3H), 2.30 - 2.16 (m, 2H), 1.90 - 1.81 (m, 2H), 1.79 - 1.69 (m, 2H).
271 S-isomer		CF_3	H		$R^{13} = CH_2CF_3$	594.1	^{1}H NMR (500 MHz, 1:1 MeOD/$CDCl_3$) δ 7.52 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.96 (dd, *J* = 8.4, 2.1 Hz, 4H), 4.04 (t, *J* = 6.1 Hz, 2H), 3.73 - 3.64 (m, 1H), 3.60 - 3.49 (m, 1H), 3.35 (d,

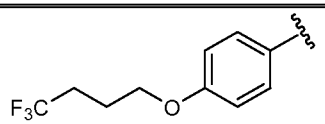
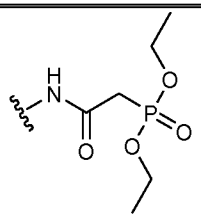
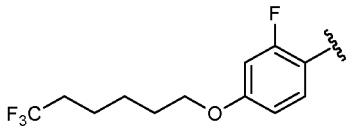
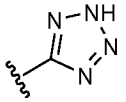
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							J = 10.7 Hz, 2H), 2.39 - 2.23 (m, 2H), 2.13 - 1.91 (m, 2H).
272 S-isomer		CF_3	H		$R^{13} = CH_3$	540.3	
273 S-isomer		CF_3	H		$R^{13} = CH_3$	608.2	1.98 – 2.11 (m, 2H), 2.29 (s, 3H), 2.33 - 2.49 (m, 2H), 3.71 - 3.47 (m, 2H), 3.91 (s, 3H), 4.20 - 4.02 (m, 2H), 6.95 – 7.03 (m, 2H), 7.15 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.86 (d, J = 1.4 Hz, 1H), 8.76 (d, J = 1.4 Hz, 1H).
274 S-isomer		CF_3	H		$R^{13} = OCHF_2$	624.1	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.63 (s, 1H), 7.58 (t, J = 9.3 Hz, 1H), 7.43 – 6.98 (m, 5H), 6.92 (d, J = 12.1

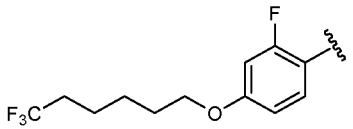
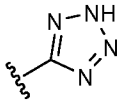
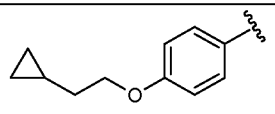
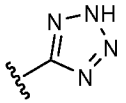
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							Hz, 2H), 4.03 (t, *J* = 6.4 Hz, 2H), 3.80 (d, *J* = 17.8 Hz, 1H), 3.76 (d, *J* = 17.9 Hz, 1H), 2.37 – 2.14 (m, 2H), 1.83 – 1.66 (m, 2H), 1.63 – 1.32 (m, 4H).
275 S-isomer		CF_3	H		$R^{13} = OCHF_2$	630.2	^{1}H NMR (400 MHz, MeOD) δ 8.75 (br. s., 2H), 7.87 (br. s., 2H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 7.04 - 6.62 (m, 3H), 4.08 (t, *J* = 5.8 Hz, 2H), 3.75 (br. s., 1H), 3.52 (d, *J* = 16.9 Hz, 1H), 2.45 - 2.29 (m, 2H), 2.09 - 1.99 (m, 2H).
276 S-isomer		CF_3	H		R^{12} R^{13} =	608.2	^{1}H NMR (500 MHz, MeOD) δ 7.83 – 7.66 (m, 3H), 7.61

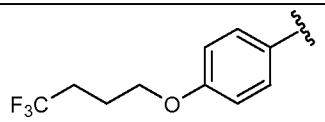
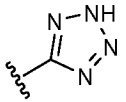
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							(s, 2H), 7.56 – 7.43 (m, 3H), 7.01 (d, *J* = 8.6 Hz, 1H), 6.85 – 6.67 (m, 2H), 4.05 (d, *J* = 18.0 Hz, 1H), 4.01 (t, *J* = 6.4 Hz, 2H), 3.76 (d, *J* = 17.9 Hz, 1H), 2.05-2.20 (m, 2H), 1.91 – 1.72 (m, 2H), 1.74 – 1.45 (m, 4H).
277 S-isomer		CF_3	H			567.1	^{1}H NMR (500 MHz, 1:1 $CDCl_3$:MeOD) δ 7.54 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 6.99 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 4.07 (t, J = 5.9 Hz, 2H), 3.79 - 3.66 (m, 1H), 3.63 - 3.50 (m, 1H), 2.49 (d, J = 6.9 Hz, 2H), 2.40 - 2.25 (m, 2H), 2.13 - 1.97 (m, 2H), 0.97 -

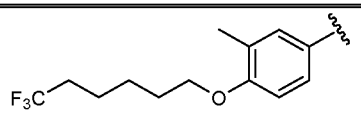
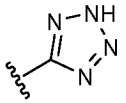
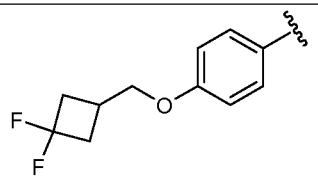
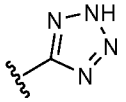
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							0.82 (m, 1H), 0.58 - 0.45 (m, 2H), 0.16 (q, J = 5.0 Hz, 2H).
278 S-isomer		CF_3	H		$R^{13} = CH_3$	558.2	^{1}H NMR (500 MHz, 1:1 $CDCl_3$:MeOD) δ 7.43 (t, *J* = 9.17 Hz, 1H), 7.02 (d, *J* = 7.93 Hz, 2H), 6.87 (d, *J* = 7.93 Hz, 2H), 6.75 (dd, *J* = 2.48, 8.92 Hz, 1H), 6.71 (dd, *J* = 2.23, 14.61 Hz, 1H), 3.99 (t, *J* = 5.95 Hz, 2H), 3.87 (d, *J* = 17.83 Hz, 1H), 3.61 (d, *J* = 17.83 Hz, 1H), 2.26 (s, 3H), 2.11-2.21 (m, 2H), 1.80-1.89 (m, 2H), 1.69-1.78 (m, 2H).
279 S-isomer		CF_3	H		$R^{13} = CH_3$	573.2	7.79 (br. s., 1H), 7.46 - 7.38 (m, 7H), 7.22 - 7.17 (m, 2H), 7.15 - 7.10 (m, 2H), 7.02 (d,

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							J = 9.0 Hz, 2H), 6.69 (br. s., 1H), 5.07 (s, 2H), 3.82 (br. s., 2H), 3.63 (d, *J* = 17.2 Hz, 1H), 3.37 (d, *J* = 17.2 Hz, 1H), 2.95 (s, 3H), 2.36 (s, 3H).
280 S-isomer		CF_3	H		$R^{13} = OCHF_2$	630.2	
281 S-isomer		CF_3	H		$R^{13} = CH_3$	582.2	^{1}H NMR (500MHz, MeOD) δ 7.56 (d, J = 8.92 Hz, 2H), 7.30 (d, J = 8.42 Hz, 2H), 7.10 (d, J = 7.93 Hz, 2H), 6.97 (d, J = 8.92 Hz, 2H), 6.37 (s, 1H), 4.06 (m, 2H), 3.59 (d, J = 17.83 Hz, 1H), 3.43 (d, J = 17.34 Hz, 1H), 2.32 (m, 2H), 2.30 (s, 3H), 2.22 (s, 3H), 2.06 (m, 2H).

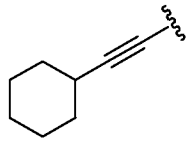
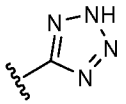
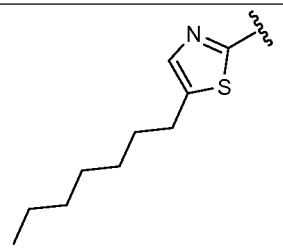
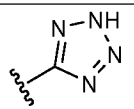
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
282 S-isomer		CF_3	H		$R^{13} = CH_3$	651.2	^{1}H NMR (500MHz, MeOD) δ 7.61 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 5.9 Hz, 4H), 6.93 (d, *J* = 8.9 Hz, 2H), 4.33 (br. s., 1H), 4.07 - 4.02 (m, 2H), 4.02 - 3.94 (m, 4H), 3.67 - 3.56 (m, 1H), 3.37 - 3.34 (m, 1H), 2.94 - 2.78 (m, 2H), 2.33 (s, 5H), 2.09 - 2.00 (m, 2H), 1.22 (d, *J* = 1.5 Hz, 6H).
283 S-isomer		CF_3	H		R^{13} = OCH_2CH_3	602.2	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.39 (s, 1H), 7.56 (t, *J* = 9.3 Hz, 1H), 6.92 (t, *J* = 8.6 Hz, 4H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.03 (t, *J* = 6.4 Hz, 2H), 3.99 (q, *J* = 6.9 Hz , 2H), 3.82 (d, *J* = 17.3 Hz, 1H),

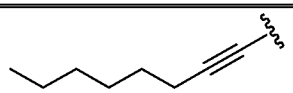
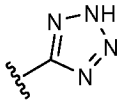
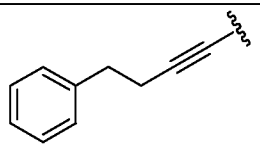
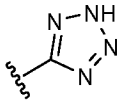
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							3.69 (d, *J* = 17.7 Hz, 1H), 2.34 – 2.15 (m, 2H), 1.85 – 1.70 (m, 2H), 1.65 – 1.42 (m, 4H), 1.29 (t, *J* = 6.9 Hz, 3H).
284 S-isomer		CF_3	H		$R^{13} = CH_2CF_3$	640.1	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.36 (w, 1H), 7.59 (t, *J* = 9.3 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 2H), 7.07 – 6.74 (m, 4H), 4.03 (t, *J* = 6.4 Hz, 2H), 3.76 (d, *J* = 17.4 Hz, 1H), 3.70 (d, *J* = 17.7 Hz, 1H), 3.58 (dd, *J* = 23.3, 11.7 Hz, 2H), 2.33 – 2.16 (m, 2H), 1.86 – 1.68 (m, 2H), 1.545-1.60 (m, 4H).
285 S-isomer		CF_3	H		$R^{13} = CH_3$	484.1	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.58 - 9.48 (m, 1H), 7.65 - 7.55 (m, 2H), 7.07 (d,

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							J = 8.0 Hz, 2H), 7.04 - 6.97 (m, 2H), 6.94 - 6.85 (m, 2H), 4.06 (s, 2H), 3.69 (s, 2H), 2.24 (s, 3H), 1.63 (q, *J* = 6.6 Hz, 2H), 1.35 - 1.08 (m, 1H), 0.94 - 0.77 (m, 1H), 0.51 - 0.38 (m, 2H), 0.16 - 0.06 (m, 2H)
286 S-isomer		CF_3	H		R^{11} = F R^{13} = CH_3	544.2	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.62 (d, J = 8.80 Hz, 2H), 7.02 (d, J = 8.80 Hz, 2H), 7.01 (m, 1H), 6.98 (t, J = 7.98 Hz, 1H), 6.93 (d, J = 11.55 Hz, 1H), 4.08 (t, J = 6.93 Hz, 2H), 3.68 (d, J = 18.16 Hz, 1H), 3.62 (d, J = 17.88 Hz, 1H), 2.42 (m, 2H), 2.28 (s, 3H), 1.95 (m, 2H).

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
287 S-isomer		CF_3	H		$R^{13} = CH_3$	568.2	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.47 (s, 1H), 7.49 (s, 1H), 7.45 (d, J = 8.80 Hz, 1H), 7.07 (d, J = 7.98 Hz, 2H), 6.98 (d, J = 8.80 Hz, 1H), 6.89 (d, J = 8.25 Hz, 2H), 4.00 (t, J = 6.19 Hz, 2H), 3.66 (s, 2H), 2.24 (s, 3H), 2.20-2.32 (m, 2H), 2.17 (s, 3H), 1.71-1.80 (m, 2H), 1.47-1.61 (m, 4H).
288 S-isomer		CF_3	H		$R^{13} = CH_3$	520.0	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.67 (s, 1H), 8.15 (d, J = 4.1 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 4.1 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 4.03 (t, J = 6.2 Hz, 2H), 3.98 (d, J = 17.6 Hz, 1H),

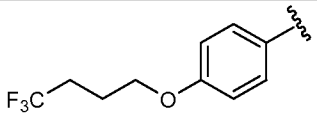
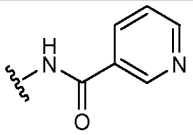
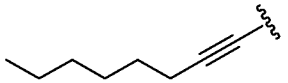
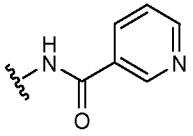
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							3.62 (d, J = 17.3 Hz, 1H), 2.45 - 2.33 (m, 2H), 2.31 - 2.23 (m, 1H), 1.94 - 1.79 (m, 2H), 1.23 - 1.11 (m, 2H), 0.87 - 0.77 (m, 2H).
289 S-isomer		CF_3	H		$R^{13} = CH_3$	444.1	7.17 (d, J = 7.9 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 6.84 (s, 1H), 3.39 (AB quartet, J = 18.7 Hz, 2H), 2.36 (s, 3H), 2.13 (d, J = 6.6 Hz, 2H), 1.77 - 1.60 (m, 5H), 1.55 - 1.42 (m, 1H), 1.29 - 0.88 (m, 5H).
290 S-isomer		CF_3	H		$R^{13} = CH_3$	468.1	7.36 - 7.27 (m, 5H), 7.18 (s, 1H), 7.13 (d, J = 7.9 Hz, 2H), 7.01 (d, J = 8.1 Hz, 2H), 4.57 (AB quartet, J = 11.7 Hz, 2H), 4.22 (s, 2H),

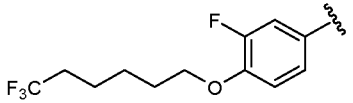
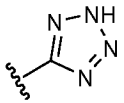
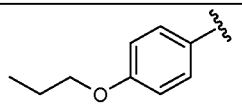
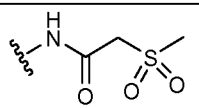
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							3.39 (AB quartet, J = 18.9 Hz, 2H), 2.34 (s, 3H).
291 S-isomer		CF_3	H		$R^{13} = CH_3$	430.1	7.19 (d, J = 7.9 Hz, 2H), 7.06 (d, J = 8.1 Hz, 2H), 6.59 (s, 1H), 3.38 (AB quartet, J = 18.9 Hz, 2H), 2.49 - 2.41 (m, 1H), 2.38 (s, 3H), 1.81 - 1.72 (m, 2H), 1.65 (dd, J = 5.9, 2.4 Hz, 2H), 1.54 - 1.40 (m, J = 12.5, 8.9, 8.9, 8.9 Hz, 3H), 1.38 - 1.28 (m, 3H).
292 Rac		CF_3	H		$R^{13} = CH_3$	394.5	

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
293 S-isomer		CF_3	H		$R^{13} = CH_3$	432.1	7.19 (d, *J* = 7.9 Hz, 2H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.67 (s, 1H), 3.38 (AB quartet, *J* = 18.9 Hz, 2H), 2.37 (s, 3H), 2.23 (t, *J* = 7.0 Hz, 2H), 1.51 (quin, *J* = 7.3 Hz, 2H), 1.40 - 1.22 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H).
294 S-isomer		CF_3	H		$R^{13} = OCH_3$	468.1	1H NMR (500 MHz, MeOD) δ 7.31 - 7.15 (m, 5H), 6.96 (d, J = 8.9 Hz, 2H), 6.81 (d, J = 8.9 Hz, 2H), 3.79 (s, 3H), 3.34 (AB quartet, J = 18.3 Hz, 2H, partially overlapping with solvent), 2.85 (t, J = 7.2 Hz, 2H), 2.58 (t, J = 7.4 Hz, 2H).

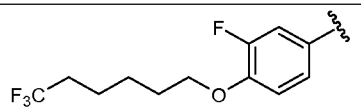
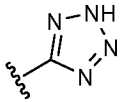
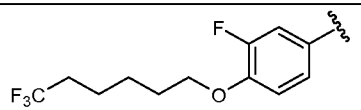
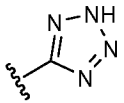
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
295 S-isomer		CF_3	H		$R^{13} = OCH_3$	434.1	1H NMR (500 MHz, MeOD) δ 7.01 (d, J = 8.9 Hz, 2H), 6.78 (d, J = 8.9 Hz, 2H), 3.77 (s, 3H), 3.40 (s, 2H), 2.29 (t, J = 7.4 Hz, 2H), 1.69 (dt, J = 13.5, 6.9 Hz, 1H), 1.45 (q, J = 7.4 Hz, 2H), 0.91 (dd, J = 6.9, 2.0 Hz, 6H).
296 S-isomer		CF_3	H		$R^{11} = F$ $R^{13} = CH_3$	625.2	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.55 (d, J = 8.80 Hz, 2H), 7.31 (d, J = 9.08 Hz, 2H), 7.13 (m, 1H), 7.06 (d, J = 11.83 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 7.70 Hz, 1H), 6.80 (d, J = 9.08 Hz, 2H), 4.08 (m, 2H), 3.70 (m, 2H), 3.68 (s, 3H), 2.43 (m, 2H), 2.27 (s, 3H), 1.95

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							(m, 2H).
297 S-isomer		CF_3	H		$R^{13} = CH_3$	608.1	7.43 (d, J = 8.6 Hz, 2H), 7.20 - 7.16 (m, 2H), 7.15 - 7.10 (m, 2H), 6.93 (d, J = 8.8 Hz, 2H), 6.57 (s, 1H), 5.10 (br. s., 1H), 4.03 (t, J = 5.9 Hz, 2H), 3.72 (br. s., 2H), 3.62 (d, J = 17.6 Hz, 1H), 3.38 (d, J = 17.8 Hz, 1H), 2.80 - 2.74 (m, 3H), 2.40 - 2.24 (m, 5H), 2.12 - 2.02 (m, 2H)
298 S-isomer		CF_3	H		$R^{13} = CH_3$	499.1	7.74 (br. s., 1H), 7.26 - 7.20 (m, 4H), 5.88 (s, 1H), 3.84 (s, 2H), 3.29 (ABq, J = 17.6 Hz, 2H), 2.95 (s, 3H), 2.37 (s, 3H), 2.23 (t, J = 7.0 Hz, 2H), 1.57 - 1.48 (m, 2H),

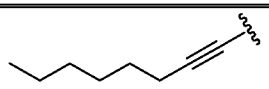
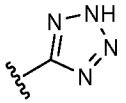
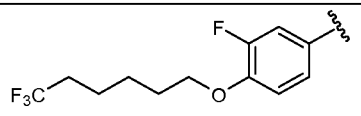
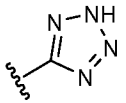
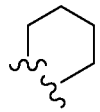
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							1.41 - 1.25 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H)
299 S-isomer		CF_3	H		$R^{13} = CH_3$	578.1	9.08 (br. s., 1H), 8.77 (d, *J* = 4.2 Hz, 1H), 8.37 (br. s., 1H), 8.25 (br. s., 1H), 7.65 (br. s., 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.19 - 7.11 (m, 4H), 6.95 (d, *J* = 9.0 Hz, 2H), 6.88 (s, 1H), 4.04 (t, *J* = 5.9 Hz, 2H), 3.66 (d, *J* = 17.6 Hz, 1H), 3.43 (d, *J* = 17.4 Hz, 1H), 2.40 - 2.25 (m, 5H), 2.12 - 2.03 (m, 2H).
300 S-isomer		CF_3	H		$R^{13} = CH_3$	484.2	^{1}H NMR (400 MHz, MeOD) δ 9.00 (br. s., 1H), 8.79 (dd, *J* = 5.3, 1.3 Hz, 1H), 8.46 (d, *J* = 7.3 Hz, 1H), 7.78 (dd, *J* = 8.0, 5.4 Hz, 1H), 7.33 (d, *J*

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							= 8.1 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 3.38 (s, 2H), 2.35 - 2.27 (m, 5H), 1.60 - 1.50 (m, 2H), 1.48 - 1.38 (m, 2H), 1.35 - 1.27 (m, 4H), 0.93 - 0.87 (m, 3H).
301 S-isomer		CF_3	H		$R^{13} = OCHF_2$	624.2	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.53 (s, 1H), 7.65 (dd, *J* = 13.0, 2.0 Hz, 1H), 7.49 (d, *J* = 7.4 Hz, 1H), 7.46 – 6.88 (m, 6H), 4.11 (t, *J* = 6.3 Hz, 2H), 3.77 (d, *J* = 17.9 Hz, 1H), 3.72 (d, *J* = 17.9 Hz, 1H), 2.36 – 2.08 (m, 2H), 1.88 – 1.71 (m, 2H), 1.67 – 1.34 (m, 4H).
302 S-isomer		CF_3	H		$R^{13} = CH_3$	525.0	^{1}HNMR (400 MHz, MeOD) δ 7.50 (d, *J* = 8.8 Hz, 2H),

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							7.23 - 7.15 (m, 4H), 6.93 (d, J = 9.0 Hz, 2H), 4.00 - 3.92 (m, 4H), 3.66 (d, J = 17.2 Hz, 1H), 3.43 (d, J = 16.9 Hz, 1H), 2.93 (s, 3H), 2.32 (s, 3H), 1.79 (sxt, J = 7.0 Hz, 2H), 1.04 (t, J = 7.4 Hz, 3H).
303 S-isomer		CF_3	H		$R^{13} = CH_3$	572.3	
304 S-isomer		CF_3	H		R^{12} R13 =	608.3	^{1}HNMR (500 MHz, DMSO-d_6) δ 9.57 (br. s., 1H), 7.84 (dd, J = 7.84, 13.34 Hz, 2H), 7.71-7.77 (m, 2H), 7.67 (d, J = 12.93 Hz, 1H), 7.47-7.57 (m, 3H), 7.26 (t, J = 8.94 Hz, 1H), 6.93 (d, J = 8.80 Hz, 1H), 5.56 (d, J = 7.70 Hz,

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							1H), 4.10 (t, *J* = 6.19 Hz, 2H), 3.79-3.92 (m, 2H), 2.20-2.33 (m, 2H), 1.68-1.83 (m, 2H), 1.45-1.65 (m, 4H).
305 S-isomer		CF_3	H		R^{13} = OCH_2CH_3	602.3	^{1}HNMR (500 MHz, DMSO-d_6) δ 9.38-9.54 (m, 1H), 7.63 (d, *J* = 13.20 Hz, 1H), 7.46 (d, *J* = 8.80 Hz, 1H), 7.24 (t, *J* = 8.80 Hz, 1H), 6.96 (d, *J* = 8.53 Hz, 2H), 6.79 (d, *J* = 8.53 Hz, 2H), 4.09 (t, *J* = 6.33 Hz, 2H), 3.98 (q, *J* = 6.88 Hz, 2H), 2.20-2.34 (m, 2H), 1.77 (quin, *J* = 6.81 Hz, 2H), 1.46-1.61 (m, 4H), 1.28 (t, *J* = 7.02 Hz, 3H).
306 S-isomer		CF_3	H		$R^{13} = CH_2CF_3$	640.2	^{1}HNMR (500 MHz, DMSO-d_6) δ 9.56 (br. s., 1H), 7.65

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							(d, J = 12.93 Hz, 1H), 7.49 (d, J = 8.80 Hz, 1H), 7.20-7.28 (m, 3H), 7.03 (d, J = 7.98 Hz, 2H), 4.10 (t, J = 6.33 Hz, 2H), 3.71-3.81 (m, 2H), 3.61 (q, J = 11.55 Hz, 2H), 2.20-2.33 (m, 2H), 1.78 (quin, J = 6.74 Hz, 2H), 1.44-1.61 (m, 4H)
307 S-isomer		CF_3	H		$R^{13} = OCHF_2$	484.1	7.19 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 8.6 Hz, 2H), 6.78 (br. s., 1H), 6.56 (t, J = 73.1 Hz, 1H), 3.37 (AB quartet, J = 18.9 Hz, 2H), 2.24 (t, J = 7.0 Hz, 2H), 1.52 (quin, J = 7.3 Hz, 2H), 1.41 - 1.21 (m, 6H), 0.87 (t, J = 6.8 Hz, 3H).

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
308 S-isomer		CF_3	H		R^{13} = OCH_2CH_3	462.1	7.10 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.72 (s, 1H), 4.04 (q, *J* = 7.0 Hz, 2H), 3.37 (AB quartet, *J* = 18.9 Hz, 2H), 2.22 (t, *J* = 7.2 Hz, 2H), 1.51 (quin, *J* = 7.3 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H), 1.39 - 1.22 (m, 6H), 0.87 (t, *J* = 6.6 Hz, 3H).
309 S-isomer		CF_3	H		R^{12} R13 = 	612.1	^{1}HNMR (500 MHz, DMSO-d_6) δ 9.52 (br. s., 1H), 7.63 (d, *J* = 13.20 Hz, 1H), 7.46 (d, *J* = 8.53 Hz, 1H), 7.25 (t, *J* = 8.94 Hz, 1H), 6.88 (d, *J* = 7.98 Hz, 1H), 6.83 (s, 1H), 6.58 (d, *J* = 7.98 Hz, 1H), 4.09 (t, *J* = 6.19 Hz, 2H), 3.64-3.75 (m, 2H), 2.54-2.67

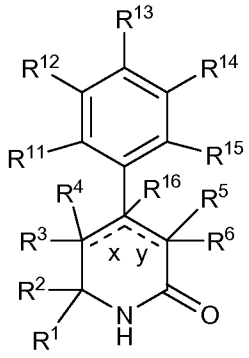
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							(m, 4H), 2.20-2.34 (m, 2H), 1.77 (quin, J = 6.74 Hz, 2H), 1.67 (br. s., 4H), 1.44-1.61 (m, 4H).
310 S-isomer		CF_3	H		$R^{13} = CH_3$	569.0	^{1}HNMR (400 MHz, MeOD) δ 7.56 (d, J = 8.8 Hz, 2H), 7.26 - 7.21 (m, 2H), 7.18 - 7.12 (m, 2H), 6.99 (d, J = 9.0 Hz, 2H), 4.07 (t, J = 6.2 Hz, 2H), 3.73 (d, J = 17.2 Hz, 1H), 3.51 (d, J = 16.9 Hz, 1H), 2.43 - 2.32 (m, 2H), 2.29 (s, 3H), 2.08 - 1.98 (m, 2H).
311 S-isomer		CF_3	H		$R^{13} = CH_3$	475.1	^{1}HNMR (400 MHz, MeOD) δ 7.34 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 3.37 (s, 2H), 2.34 - 2.26 (m,

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							5H), 1.53 (d, J = 7.3 Hz, 2H), 1.42 (br. s., 2H), 1.34 - 1.25 (m, 4H), 0.92 - 0.86 (m, 3H).
312 S-isomer		CF_3	H		R^{13} = OCH_2CH_3	529.4	7.73 (br. s., 1H), 7.31 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 5.91 (s, 1H), 4.06 (q, J = 7.0 Hz, 2H), 3.86 (s, 2H), 3.30, 3.28 (ABq, J = 18.3 Hz, 2H), 2.99 (s, 3H), 2.23 (t, J = 7.0 Hz, 2H), 1.52 (quin, J = 7.3 Hz, 2H), 1.43 (t, J = 6.9 Hz, 3H), 1.41 - 1.22 (m, 7H), 0.89 (t, J = 6.9 Hz, 2H).
313 S-isomer		CF_3	H		$R^{13} = OCHF_2$	551.0	7.85 (br. s., 1H), 7.38 (d, J = 8.6 Hz, 2H), 7.17 (d, J = 8.6 Hz, 2H), 6.55 (t, J = 72.4

Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							Hz, 1H), 5.97 (s, 1H), 3.84 (s, 2H), 3.30, 3.28 (ABq, J = 17.8 Hz, 2H), 2.89 (s, 3H), 2.24 (t, J = 7.0 Hz, 2H), 1.52 (dt, J = 14.6, 7.2 Hz, 2H), 1.43 - 1.23 (m, 6H), 0.89 (t, J = 6.8 Hz, 3H).
314 S-isomer		CF_3	H		$R^{13} = CH_3$	540.3	

What is claimed is:

1. A compound of Formula (I):



(I)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein:

$\overline{---}$ designates a single or double bond;

x and y can be both a single bond; when x is a double bond, then y is a single bond and R^4 and R^{16} are absent; when y is a double bond, then x is a single bond and R^5 and R^{16} are absent;

R^1 is independently selected from the group consisting of: -CONH(C_{4-18} alkyl), -CONHC_{2-8} haloalkyl, -CONH$(CH_2)_{1-8}$Ph, -CONHCH_2COC_{2-8} alkyl, -$(CH_2)_m$-(C_{3-10} carbocycle substituted with 0-2 R^b and 0-2 R^g), -$(CH_2)_m$-(5- to 6-membered heteroaryl comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O and S; wherein said heteroaryl is substituted with 0-1 R^b and 0-2 R^g), and a C_{1-12} hydrocarbon chain substituted with 0-3 R^a; wherein said hydrocarbon chain may be straight or branched, saturated or unsaturated;

R^2 is independently selected from the group consisting of: C_{1-4} alkyl, C_{3-4} cycloalkyl, and C_{1-4} haloalkyl;

R^3 is independently selected from the group consisting of: H, F, Cl, C_{1-4} alkyl and CN;

R^4 and R^5 are independently selected from the group consisting of: H, F, Cl, and C_{1-4} alkyl;

when x is a single bond, R^3 and R^4 may be combined with the carbon atom to which they are attached to form a 3- to 6-membered carbocycle;

R^6 is independently selected from the group consisting of: H, halo, C_{1-4} alkyl, CN, NO_2, R^c, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$, NH_2, $-CONH(C_{1-6}$ alkyl), $-NHCOX_1SO_2R^j$, $-NHCOCH_2PO(OEt)_2$, $-NHCOCOR^j$, $-NHCOCH(OH)R^j$, $-NHCOCH_2COR^j$, $-NHCONHR^j$, and $-OCONR^fR^j$;

X is independently selected from the group consisting of: O, S, NH, CONH, and NHCO;

X_1 is independently C_{1-4} hydrocarbon chain optionally substituted with C_{1-4} alkyl or C_{3-4} cycloalkyl;

when y is a single bond, R^5 and R^6 may be combined with the carbon atom to which they are attached to form a 3- to 6-membered carbocycle;

R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are independently selected from the group consisting of: H, halo, C_{1-4} alkyl substituted with 0-2 R^i, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, $-(CH_2)_m-C_{3-6}$ cycloalkyl, CN, NR^fR^j, OR^j, SR^j, $NHCO_2(C_{1-4}$ alkyl), $NHSO_2(C_{1-4}$ alkyl), and a 4- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S;

alternatively, R^{11} and R^{12}, together with the carbon atoms to which they are attached, combine to form a 5 to 6-membered carbocyclic ring or a 5 to 6-membered heterocyclic ring comprising: carbon atoms and 1-3 heteroatoms selected from N, NR^e, O, and S;

alternatively, R^{12} and R^{13}, together with the carbon atoms to which they are attached, combine to form a 5 to 6-membered carbocyclic ring or a 5 to 6-membered heterocyclic ring comprising: carbon atoms and 1-3 heteroatoms selected from N, NR^e, O, and S;

R^{16} is independently selected from the group consisting of: H and C_{1-4} alkyl;

R^a is, at each occurrence, independently selected from the group consisting of: halo, OH, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $N(C_{1-4}$ alkyl$)_2$, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$, and $-(CH_2)_n-(CH_2O)_m-(CH_2)_nR^f$;

R^b is, at each occurrence, independently selected from the group consisting of: halo, OH, C_{1-10} alkyl, C_{1-10} alkoxy, C_{1-10} haloalkyl, C_{1-10} haloalkoxy, C_{1-10} alkylthio,

C_{1-10} haloalkyltho, $N(C_{1-4}$ alkyl$)_2$, $-CONH(CH_2)_{4-20}H$, $-O(CH_2)_sO(C_{1-6}$ alkyl), R^c, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$, and $-(CH_2)_n-(CH_2O)_m-(CH_2)_nR^f$;

R^c is, at each occurrence, independently selected from the group consisting of: C_{3-6} cycloalkyl substituted with 0-2 R^d, C_{3-6} cycloalkenyl substituted with 0-2 R^d, $-(CH_2)_m$-(phenyl substituted with 0-3 R^d), and a 5- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S; wherein said heterocycle is substituted with 0-2 R^d;

R^d is, at each occurrence, independently selected from the group consisting of: halo, OH, CN, NO_2, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, tetrazolyl, OBn and phenyl substituted with 0-2 R^h;

R^e is, at each occurrence, independently selected from the group consisting of: H, C_{1-8} alkyl, C_{1-8} haloalkyl, benzyl optionally substituted with C_{1-4} alkoxy, $CO(C_{1-4}$ alkyl) and COBn;

R^f is, at each occurrence, independently selected from the group consisting of: H and C_{1-4} alkyl;

R^g, R^h and R^i are, at each occurrence, independently selected from the group consisting of: halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

R^j is, at each occurrence, independently selected from the group consisting of: C_{1-4} alkyl, C_{3-4} cycloalkyl and phenyl;

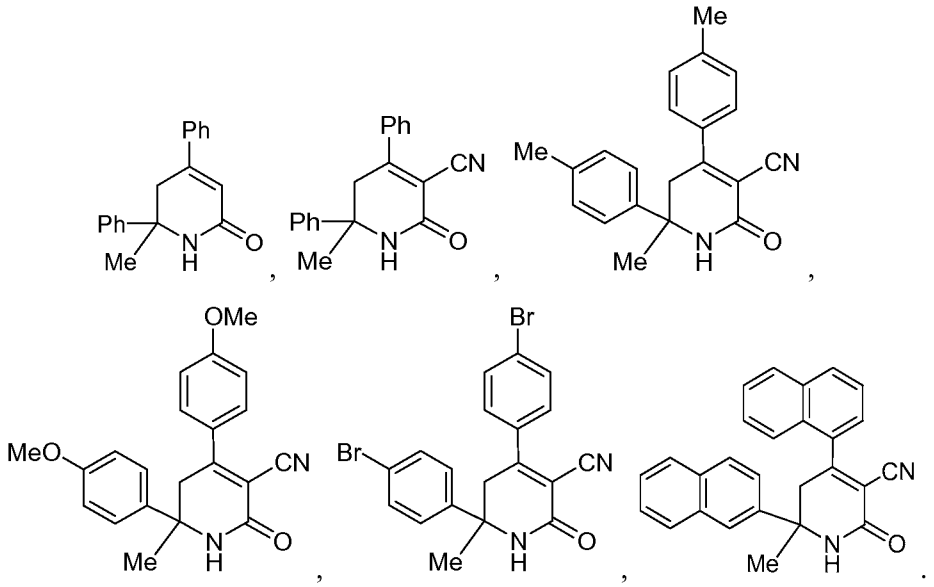
n, at each occurrence, is independently 0 or 1;

m, at each occurrence, is independently 0, 1, 2, 3, or 4

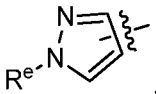
s, at each occurrence, is independently 1, 2, or 3; and

t, at each occurrence, is independently 0 or 1;

provided that the following compounds are excluded:



2. A compound according to claim 1, wherein:

R^1 is independently selected from the group consisting of: -$CONHC_{4-18}$ alkyl, -$CONH(CH_2)_{1-8}$ Ph, C_{1-12} alkyl substituted with 0-2 R^a, C_{1-12} alkenyl substituted with 0-2 R^a, C_{1-12} alkynyl substituted with 0-2 R^a, -$(CH_2)_m$-(phenyl substituted with 0-1 R^b and 0-2 R^g), -$(CH_2)_m$-(C_{3-6} cycloalkyl substituted with 0-1 R^b), and -$(CH_2)_m$-(5- to 6-membered heteroaryl substituted with 0-1 R^b and 0-2 R^g), wherein said heteroaryl is selected from: pyridyl, oxazolyl, thiazolyl and  .

3. A compound according to claim 1 or claim 2, wherein:

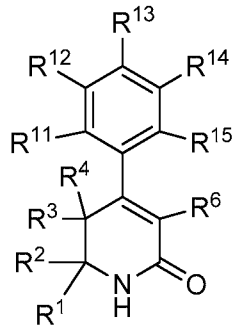
R^{11} and R^{15} are independently selected from the group consisting of: H, C_{1-4} alkyl and halo;

R^{12} and R^{14} are independently selected from the group consisting of: H, halo, C_{1-4} alkyl and C_{1-4} alkoxy; and

R^{13} is independently selected from the group consisting of: H, halo, C_{1-4} alkyl substituted with 0-1 R^i, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, -$(CH_2)_m$-C_{3-4} cycloalkyl, CN, NR^fR^j, SR^j, $NHCO_2(C_{1-4}$ alkyl), $NHSO_2(C_{1-4}$ alkyl), and

a 4- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S.

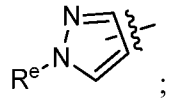
4. A compound according to any one of claims 1 to 3, wherein the compound is of Formula (II):



(II)

or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof.

5. A compound according to any one of claims 1 to 4, wherein:

R^1 is independently selected from the group consisting of: C_{1-6} alkyl, C_{3-6} cycloalkyl, $-CONHC_{4-18}$ alkyl, $-CONHC_{2-8}$ haloalkyl, $-CONH(CH_2)_{1-8}$ Ph, $-(CH_2)_m$-(phenyl substituted with 1 R^b and 0-2 R^g), and a 5- to 6-membered heteroaryl substituted with 0-1 R^b and 0-2 R^g, wherein said heteroaryl is selected from: pyridyl, oxazolyl, thiazolyl and  ;

R^2 is independently selected from the group consisting of: C_{1-4} alkyl and C_{1-4} haloalkyl;

R^3 is independently selected from the group consisting of: H and F;

R^4 is independently selected from the group consisting of: H and F;

R^6 is independently selected from the group consisting of: CN, NH_2, $-CONH(C_{1-6}$ alkyl), R^c, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$, $-NHCO(CH_2)SO_2(C_{1-4}$ alkyl), $-NHCOCH_2PO(OEt)_2$, $-NHCOCO(C_{1-4}$ alkyl), $-NHCOCH(OH)(C_{1-4}$ alkyl), $-NHCOCH_2CO(C_{1-4}$ alkyl), $-NHCONH(C_{1-4}$ alkyl), and $-OCONH(C_{1-4}$ alkyl);

R^{11} and R^{15} are independently selected from the group consisting of: H, C_{1-4} alkyl and halo;

R^{12} and R^{14} are independently selected from the group consisting of: H, halo, C_{1-4} alkyl and C_{1-4} alkoxy;

R^{13} is independently selected from the group consisting of: H, halo, C_{1-4} alkyl substituted with 0-1 C_{1-4} alkoxy, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, $-(CH_2)_m$-C_{3-4} cycloalkyl, CN, $N(C_{1-4}$ alkyl$)_2$, $NHCO_2(C_{1-4}$ alkyl), $NHSO_2(C_{1-4}$ alkyl), pyrazolyl, and morpholinyl;

alternatively, R^{12} and R^{13}, together with the carbon atoms to which they are attached, combine to form a 5 to 6-membered carbocyclic ring or a 5 to 6-membered heterocyclic ring comprising: carbon atoms and 1-3 heteroatoms selected from N, NR^e, O, and S;

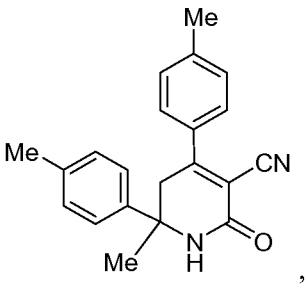
R^b is, at each occurrence, independently selected from the group consisting of: halo, OH, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkyl, C_{1-10} haloalkoxy, $-O(CH_2)_sO(C_{1-6}$ alkyl), $N(C_{1-4}$ alkyl$)_2$, $-CONH(CH_2)_{6-20}H$, $-(CH_2)_m(C_{3-6}$ cycloalkyl), $-(CH_2)_m(C_{4-6}$ cycloalkenyl), $-O(CH_2)_m(C_{3-6}$ cycloalkyl), 4-C_{1-4} alkoxy-Ph, $-O(CH_2)_m$Ph, morpholinyl, pyridyl, 2-C_{1-4} alkoxy-pyridin-5-yl, pyrimidinyl, pyrazinyl, and -O-pyrimidinyl;

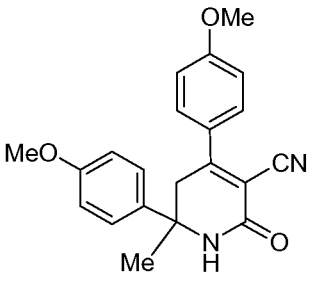
R^g is, at each occurrence, independently selected from the group consisting of: halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

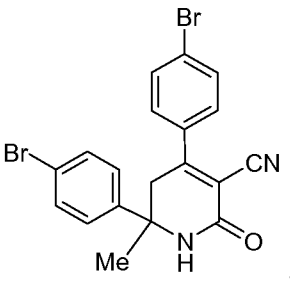
m, at each occurrence, is independently 0, 1, 2 or 3; and

s, at each occurrence, is independently 1, 2, or 3;

provided that the following compounds are excluded:



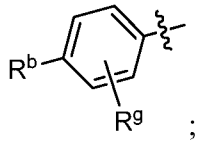
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6. A compound according to any one of claims 1 to 5, wherein:

R^1 is independently selected from the group consisting of: C_{1-6} alkyl,



$-CONHC_{4-18}$ alkyl, $-CONH(CH_2)_{1-8}Ph$, and ;

R^6 is independently selected from the group consisting of: CN, NH_2, $-CONH(C_{1-6}$ alkyl), $-NHCOCH_2PO(OEt)_2$, $-NHCO(CH_2)SO_2(C_{1-4}$ alkyl), R^c, OR^c, $-CONHR^c$, and $-NHCOR^c$;

R^{12} is independently selected from the group consisting of: H, halo, C_{1-4} alkyl and C_{1-4} alkoxy;

R^{13} is independently selected from the group consisting of: H, halo, C_{1-4} alkyl substituted with 0-1 C_{1-4} alkoxy, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, $-(CH_2)_m$-C_{3-4} cycloalkyl, CN, $N(C_{1-4}$ alkyl$)_2$, $NHCO_2(C_{1-4}$ alkyl), $NHSO_2(C_{1-4}$ alkyl), pyrazolyl, and morpholinyl;

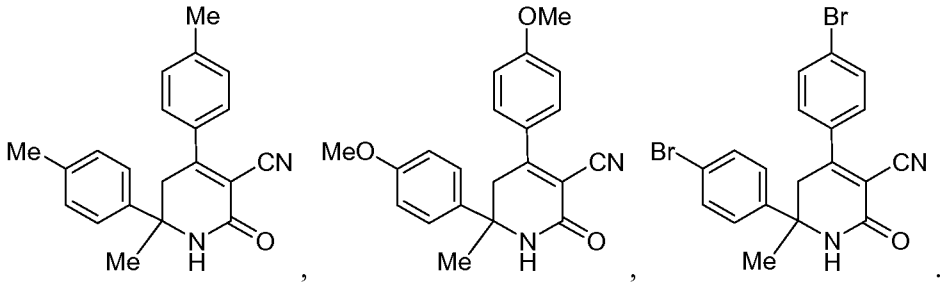
alternatively, R^{12} and R^{13}, together with the carbon atoms to which they are attached, combine to form a 5 to 6-membered carbocyclic ring or a 5 to 6-membered saturated heterocyclic ring comprising: carbon atoms and 1-2 oxygen atoms;

R^{14} is independently selected from the group consisting of: H and C_{1-4} alkoxy;

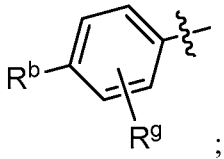
R^b is, at each occurrence, independently selected from the group consisting of: halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-10} haloalkoxy, $-O(CH_2)_sO(C_{1-6}$ alkyl), $-CONH(CH_2)_{6-20}H$, $-(CH_2)_m(C_{3-6}$ cycloalkyl), $-(CH_2)_m(C_{4-6}$ cycloalkenyl), $-O(CH_2)_m(C_{3-6}$ cycloalkyl), phenoxy, benzoxy, morpholinyl, 2-C_{1-4} alkoxy-pyridin-5-yl, pyrimidin-5-yl, pyrazin-2-yl and -O-pyrimidinyl; and

R^c is, at each occurrence, independently selected from the group consisting of: C_{3-6} cycloalkyl substituted with 0-2 R^d, $-(CH_2)_m$-(phenyl substituted with 0-3 R^d), and a heteroaryl selected from: oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, and pyrazinyl; wherein said heteroaryl is substituted with 0-2 R^d; and

provided that the following compounds are excluded:



7. A compound according to any one of claims 1 to 6, wherein:



R^1 is ;

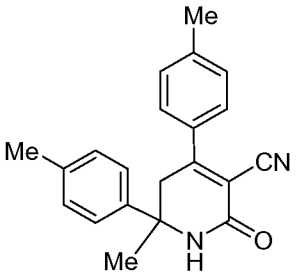
R^6 is independently selected from the group consisting of: NH_2, CN, -CONH(C_{1-4} alkyl), OPh, -CONH(C_{3-6} cycloalkyl), -CONHPh, -CONH-(2-halo-Ph), -CONH-(3-halo-Ph), -CONH-(4-halo-Ph), -CONH-(4-C_{1-4} alkyl-Ph), -CONH(4-OH-Ph), -CONH-(3-C_{1-4} alkoxy-Ph), -CONH-(4-C_{1-4} alkoxy-Ph), -CONH-(4-C_{1-4} haloalkyl-Ph), -CONH-(4-C_{1-4} haloalkoxy-Ph), -CONH-(4-CN-Ph), -CONH-(4-tetrazolyl-Ph), -CONH-(3-halo-4-C_{1-4} alkyl-Ph), -CONH-(3-halo-4-C_{1-4} alkoxy-Ph), -CONH$(CH_2)_2$Ph, -CONH(4-(4-C_{1-4} alkoxy-Ph)-thiazol-2-yl), -CONH(1-C_{1-4} alkyl-pyrazol-3-yl), -CONH(5-C_{1-4} alkoxy-pyrid-2-yl), -CONH(6-C_{1-4} alkoxy-pyrid-3-yl), -CONH(5-C_{1-4} alkoxy-pyrazin-2-yl), -CONH(6-C_{1-4} alkoxy-pyridazin-3-yl), -NHCO$(CH_2)SO_2$(C_{1-4} alkyl), -NHCOPh, -NHCO(2-C_{1-4} alkyl-Ph), -NHCO(3-C_{1-4} alkyl-Ph), -NHCO(4-C_{1-4} alkyl-Ph), -NHCO(2-halo-Ph), -NHCO(3-halo-Ph), -NHCO(2-C_{1-4} haloalkyl-Ph), -NHCO(2-C_{1-4} haloalkoxy-Ph), -NHCO(2-halo-4-halo-Ph), -NHCO(2-halo-5-halo-Ph), -NHCO(oxazolyl), -NHCO(isoxazolyl), -NHCO(3-C_{1-4} alkyl-isoxazol-5-yl), -NHCO(4-C_{1-4} alkyl-isoxazol-5-yl), -NHCO(3-C_{1-4} alkoxy-isoxazol-5-yl), -NHCO(4-C_{1-4} alkoxy-isoxazol-5-yl), -NHCO(3-halo-isoxazol-5-yl), -NHCO(3-OBn-isoxazol-5-yl), -NHCO(3-(2-halo-Ph)-isoxazol-5-yl), -NHCO(3-(3-halo-Ph)-isoxazol-5-yl), -NHCO(5-C_{1-4} alkyl-1*H*-pyrazol-3-yl), imidazolyl,

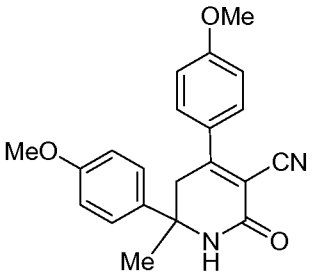
-NHCO(5-C_{1-4} alkyl-1,3,4-oxadiazol-2-yl), -NHCO(1-C_{1-4} alkyl-1,2,3-triazol-4-yl), -NHCO(6-C_{1-4} alkoxy-pyrid-3-yl), -NHCO(pyrazinyl), -NHCO(6-halo-pyridazin-3-yl), 5-C_{1-4} haloalkyl-1,3,4-oxadiazol-2-yl, 3-NO_2-1*H*-1,2,4-triazol-1-yl, tetrazolyl and 5-C_{1-4} alkyl-tetrazol-1-yl;

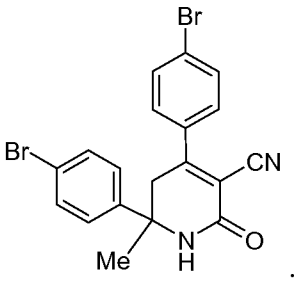
R^b is independently selected from the group consisting of: halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-8} haloalkoxy, -CONH$(CH_2)_{6-20}$H, C_{3-6} cycloalkyl, C_{4-6} cycloalkenyl, -O$(CH_2)_m$(C_{3-6} cycloalkyl), phenoxy, benzoxy, pyrimidinyl, pyrazinyl and -O-pyrimidinyl; and

R^g is independently selected from the group consisting of: halo and C_{1-4} alkyl;

provided that the following compounds are excluded:



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8. A compound according to any one of claims 1-7, wherein:

R^2 is independently selected from the group consisting of: CF_3 and Me;

R^3 is independently selected from the group consisting of: H and F;

R^4 is independently selected from the group consisting of: H and F;

R^6 is independently selected from the group consisting of: NH_2, CN, -CONHMe, OPh, -CONH(cyclopropyl), -CONH(cyclobutyl), -CONH(cyclopentyl), -CONH(cyclohexyl), -CONHPh, -CONH(4-F-Ph), -CONH(2-Cl-Ph), -CONH(4-Cl-Ph), -CONH(4-Me-Ph), -CONH(4-OH-Ph), -CONH(3-OMe-Ph), -CONH(4-OMe-Ph), -CONH(4-CF_3-Ph), -CONH(4-OCF_3-Ph), -CONH(1-Me-pyrazol-3-yl), -CONH(4-(1*H*-tetrazol-2-yl)-Ph), -CONH(4-(2*H*-tetrazol-5-yl)-Ph), -CONH(3-F-4-Me-Ph), -CONH(3-F-4-OMe-Ph), -CONH$(CH_2)_2$Ph, -CONH(5-OMe-pyrid-2-yl), -CONH(6-OMe-pyrid-3-yl), -CONH(5-OMe-pyrazin-2-yl), -CONH(6-OMe-pyridazin-3-yl), -NHCO$(CH_2)SO_2$Me, -NHCOPh, -NHCO(2-Me-Ph), -NHCO(3-Me-Ph), -NHCO(4-Me-Ph), -NHCO(2-Cl-Ph),

-NHCO(3-Cl-Ph), -NHCO(2-Cl-4-F-Ph), -NHCO(2-Cl-5-F-Ph), -NHCO(isoxazol-5-yl), -NHCO(3-Me-isoxazol-5-yl), -NHCO(4-Me-isoxazol-5-yl), -NHCO(3-OMe-isoxazol-5-yl), -NHCO(3-Br-isoxazol-5-yl), -NHCO(3-(2-Cl-Ph)-isoxazol-5-yl), -NHCO(3-(3-F-Ph)-isoxazol-5-yl), -NHCO(3-OBn-isoxazol-5-yl), 1*H*-imidazol-1-yl, -NHCO(5-Me-1,3,4-oxadiazol-2-yl), -NHCO(1-Me-1,2,3-triazol-4-yl), -NHCO(6-OMe-pyrid-3-yl), -NHCO(6-Cl-pyridazin-3-yl), 5-CF_3-1,3,4-oxadiazol-2-yl, 1*H*-tetrazol-1-yl, 1*H*-tetrazol-3-yl, and 2*H*-tetrazol-5-yl;

R^{11} and R^{15} are independently selected from the group consisting of: H, Me, F, and Cl;

R^{12} is independently selected from the group consisting of: H, F, Cl, Me and OMe;

R^{13} is independently selected from the group consisting of: H, F, Cl, Br, Me, OMe, OEt, CH_2OMe, CF_3, CH_2CF_3, $OCHF_2$, OCF_3, CN, $N(Me)_2$, cyclopropyl and cyclopropylmethyl;

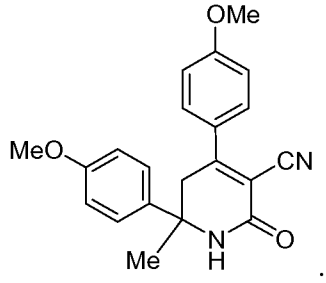
alternatively, R^{12} and R^{13}, together with the carbon atoms to which they are attached, combine to form a 5 to 6-membered carbocyclic ring or a 5 to 6-membered saturated heterocyclic ring comprising: carbon atoms and 1-2 oxygen atoms;

R^{14} is H;

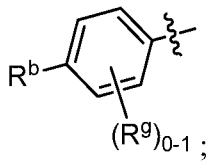
R^b is, at each occurrence, independently selected from the group consisting of: n-pentyl, methoxy, n-butoxy, i-butoxy, i-pentoxy, -$O(CH_2)_{1-6}CF_3$, -$O(CH_2)_{1-4}CF_2CF_3$, -$CONH(CH_2)_{6-20}H$, cyclopropyl, cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, -$O(CH_2)_2$(cyclopentyl), phenoxy, benzoxy, pyrimidin-5-yl, pyrazin-2-yl and -O-pyrimidin-2-yl; and

R^g is F;

provided that the following compound is excluded:



9. A compound according to Claim 4 or Claim 5, wherein:

R^1 is  ;

R^2 is independently selected from CF_3 and CH_3;

R^6 is independently selected from: CN, R^c, -$CONHR^c$, -$NHCOR^c$, and -$NHCOCH_2SO_2$ (C_{1-4} alkyl);

R^b is independently selected from: -$O(CH_2)_{1-6}CF_3$, -$O(CH_2)_{1-4}CF_2CF_3$, -$CONH(CH_2)_{6-20}H$, cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, -$O(CH_2)_2$(cyclopentyl), phenoxy, benzoxy, pyrimidin-5-yl, pyrazin-2-yl and -O-pyrimidin-2-yl;

R^c is, at each occurrence, independently selected from the group consisting of: -$(CH_2)_m$-(phenyl substituted with 0-3 R^d), and a heteroaryl selected from: oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, and pyrazinyl; wherein said heteroaryl is substituted with 0-2 R^d; and

R^d is, at each occurrence, independently selected from the group consisting of: halo, OH, CN, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, tetrazolyl and OBn.

10. A compound according to claim 1, wherein the compound is selected from:

(*S*)-3-(1*H*-tetrazol-5-yl)-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one,

(*S*)-N-(4-methoxyphenyl)-2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxamide,

(*S*)-3-(2*H*-tetrazol-5-yl)-4-(p-tolyl)-6-(4-((6,6,6-trifluorohexyl)oxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one,

(*S*)-2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile,

(*S*)-2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-N-(4-(trifluoromethoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxamide,

(*S*)-N-(6-methoxypyridin-3-yl)-2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxamide,

(*S*)-N-cyclopropyl-2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxamide,

(*S*)-N-(4-hydroxyphenyl)-2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxamide,

(*S*)-4-(4-(difluoromethoxy)phenyl)-2-oxo-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile,

(*S*)-2-oxo-4-(p-tolyl)-6-(trifluoromethyl)-6-(4-(3,3,3-trifluoropropoxy)phenyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile,

(*S*)-4-(4-(difluoromethoxy)phenyl)-3-(1*H*-tetrazol-1-yl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one,

(*S*)-3-methyl-N-(2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridin-3-yl)isoxazole-5-carboxamide,

(*S*)-5-methyl-N-(2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridin-3-yl)-1,3,4-oxadiazole-2-carboxamide,

N^2-heptyl-N^5-(4-methoxyphenyl)-2-methyl-6-oxo-4-(p-tolyl)-1,2,3,6-tetrahydropyridine-2,5-dicarboxamide,

(*S*)-3-(1*H*-tetrazol-1-yl)-4-(p-tolyl)-6-(4-((6,6,6-trifluorohexyl)oxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one,

(*S*)-2-oxo-4-(p-tolyl)-6-(4-((6,6,6-trifluorohexyl)oxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile,

(*S*)-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one,

(*S*)-2-(methylsulfonyl)-N-(2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridin-3-yl)acetamide,

(*S*)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-4-(4-(2,2,2-trifluoroethyl)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one, and

(*S*)-N-(5-methoxypyrazin-2-yl)-2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxamide;

or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a compound of any one of claims 1 to 10, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof.

12. The pharmaceutical composition according to claim 11, further comprising one or more other suitable therapeutic agents useful in the treatment of the aforementioned disorders including: anti-diabetic agents, anti-hyperglycemic agents, anti-hyperinsulinemic agents, anti-retinopathic agents, anti-neuropathic agents, anti-nephropathic agents, anti-atherosclerotic agents, anti-ischemic agents, anti-hypertensive agents, anti-obesity agents, anti-dyslipidemic agents, anti-dyslipidemic agents, anti-hyperlipidemic agents, anti-hypertriglyceridemic agents, anti-hypercholesterolemic agents, anti-restenotic agents, anti-pancreatic agents, lipid lowering agents, anorectic agents, memory enhancing agents, anti-dementia agents, or cognition promoting agents, appetite suppressants, treatments for heart failure, treatments for peripheral arterial disease and anti-inflammatory agents.

13. The pharmaceutical composition according to claim 11, further comprising a dipeptidyl peptidase-IV inhibitor.

14. A compound of any one of claims 1 to 10 for use in preventing, modulating or treating diabetes, hyperglycemia, impaired glucose tolerance, gestational diabetes, insulin resistance, hyperinsulinemia, nonalcoholic fatty liver disease (NAFLD) including nonalcoholic steatohepatitis (NASH), retinopathy, neuropathy, nephropathy, delayed wound healing, atherosclerosis and its sequelae, abnormal heart function, myocardial ischemia, stroke, Metabolic Syndrome, hypertension, obesity, dyslipidemia, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low high-density lipoprotein (HDL), high low-density lipoprotein (LDL), non-cardiac ischemia, lipid disorders, and glaucoma.

15. A compound for use according to claim 14, wherein the compound of any one of of claims 1 to 10 is used simultaneously, separately or sequentially with an additional therapeutic agent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/067173

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D211/86 C07D211/90 C07D401/04 C07D401/10 C07D401/12
C07D401/14 C07D407/14 C07D413/04 C07D413/12 C07D417/04
C07D417/14 C07F9/40 A61K31/4418 A61K31/4427 A61P3/00

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 C07F

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 practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NAGAI: NIPPON KAGAKU ZASSHI, vol. 89, 1968, pages 819-820, XP002693199, ISSN: 0369-5387 compounds with CAS-Registry numbers: 21000-35-1 and 21000-36-2; page 820; compound 3 -----	1
A	AKIO SAKURAI ET AL: "The Cyclization of Ethyl Cyanoacetate and Ketones by Ammonium Acetate", BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, vol. 40, no. 7, 1 January 1967 (1967-01-01), pages 1680-1684, XP055055179, ISSN: 0009-2673, DOI: 10.1246/bcsj.40.1680 page 1681; compound Ie -----	1

-/--

[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 application or patent 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
6 March 2013	12/04/2013

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	Brandstetter, T

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/067173

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	S. M. MCELVAIN ET AL: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 80, no. 15, 5 August 1958 (1958-08-05), pages 3915-3923, XP055055161, ISSN: 0002-7863, DOI: 10.1021/ja01548a030 page 3917; compounds XV, XVI	1
A	ATTIA A ET AL: "Synthesis of some 3-cyano-5,6-dihydropyridin-2-ones and their N-substituted derivatives", EGYPTIAN JOURNAL OF CHEMISTRY, THE EGYPTIAN CHEMICAL SOCIETY, CAIRO, vol. 26, no. 5, 1 January 1983 (1983-01-01), pages 447-452, XP009167683, ISSN: 0367-0422 page 447; compound 2d	1
X	CARRIE: "SUR LA CONDENSATION DE LA BENZALACETOPHENONE ET DE LA DYPNONE AVEC LA CYANACETAMIDE", COMPTES RENDUS HEBDOMADAIRES DES SEANCES DE L'ACADEMIE DES SCIENCES, vol. 257, no. 18, 1963, pages 2849-2851, XP009167680, ISSN: 0001-4036	1-7,11
A	4,6-di-(4-chlorophenyl)-6-methyl-2-oxo-1,2 ,5,6-tetrahydropyridine-3-carbonitrile (analog of compound VII, wherein X is Cl); page 2851	8-10, 12-15
A	US 2010/093771 A1 (NAKAMURA KEIJI [JP] ET AL) 15 April 2010 (2010-04-15) claims 1, 17, 18, 20 paragraph [0453]	1-15
A	WO 2010/095767 A1 (BANYU PHARMA CO LTD [JP]; ARAKAWA KEISUKE [JP]; ITO YOSHIKI [JP]; KAWA) 26 August 2010 (2010-08-26) claims 1, 9-11 page 41; table 20	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/067173

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2010093771 A1	15-04-2010	EP 2078719 A1	15-07-2009
		US 2010093771 A1	15-04-2010
		WO 2008038768 A1	03-04-2008
WO 2010095767 A1	26-08-2010	AU 2010216633 A1	08-09-2011
		CA 2751244 A1	26-08-2010
		EP 2398800 A1	28-12-2011
		JP 2012518597 A	16-08-2012
		US 2011275647 A1	10-11-2011
		WO 2010095767 A1	26-08-2010

(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL TRATADO DE COOPERACION EN MATERIA DE PATENTES (PCT)

VERSIÓN CORREGIDA

(19) Organización Mundial De La Propiedad Intelectual
Oficina Internacional

(10) Número de Publicación Internacional:

(43) Fecha de publicación internacional:

6 junio 2013 (06.06.2013)

PCT WO 2013/082345 A8

(51) Clasificación de patente internacional:

C07D 211/86 (2006.01)	*C07D 413/12 (2006.01)*
C07D 211/90 (2006.01)	*C07D 417/04 (2006.01)*
C07D 401/04 (2006.01)	*C07D 417/14 (2006.01)*
C07D 401/10 (2006.01)	*C07F 9/40 (2006.01)*
C07D 401/12 (2006.01)	*A61K 31/4418 (2006.01)*
C07D 401/14 (2006.01)	*A61K 31/4427 (2006.01)*
C07D 407/14 (2006.01)	*A61P 3/00 (2006.01)*
C07D 413/04 (2006.01)	

(21) Número de solicitud internacional: PCT/US2012/067173

(22) Fecha de presentación internacional: 30 noviembre 2012 (30.11.2012)

(25) Idioma de Presentación: Inglés

(26) Idioma de Publicación: Inglés

(30) Datos de prioridad:

61/566,039	2 diciembre 2011 (02.12.2011)	US
13/688,584	29 noviembre 2012 (29.11.2012)	US

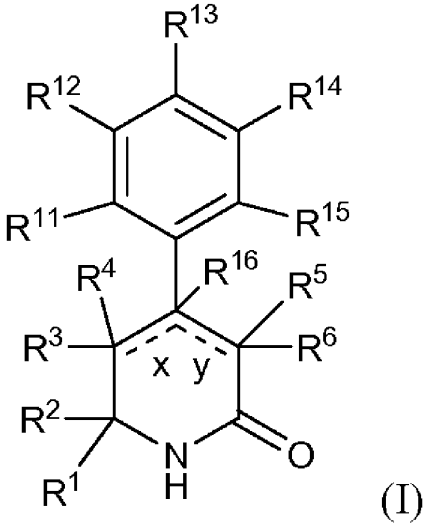
(71) Solicitante: *(para todos los Estados designados excepto US):* **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 (US).

(71) Inventores: TURDI, Huji; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534 (US). **HANGELAND, Jon J.**; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534 (US). **LAWRENCE, R. Michael**; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534 (US). **CHENG, Dong**; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534 (US). **AHMAD, Saleem;** c/o Bristol-Myers Squibb Company, Route 206 & Province Line Road, Princeton, New Jersey 08543 (US). **MENG, Wei**; c/o Bristol-Myers Squibb Company', 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534 (US). **BRIGANCE, Robert Paul**; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534 (US). **DEVASTHALE, Prank**; c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534 (US).

(74) Agente: SUN, Jing G. et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, New Jersey 08543-4000 (US).

[Continua en la siguiente hoja]

(54) Título: ARIL DIHIDROPIRIDINONA Y PIPERIDINONA COMO INHIBIDORES DE MGAT2



(I)

(57) Resumen: La presente invención provee compuestos de la Fórmula (I), o un estereoisómero o una sal de aquel aceptable desde el punto de vista farmacéutico, en donde todas las variables son como se definen en la presente. Estos compuestos son inhibidores de monoacilglicerol aciltransferasa tipo 2 (MGAT2) que se pueden usar como medicamentos.

(81) Estados designados: *(a menos que se indique los contrario, para cada tipo de protección nacional disponible):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, 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, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Estados designados *(a menos que se indique los contrario, para cada tipo de protección regional disponible):* Patente ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Patente Euroasiática (AM, AZ, BY, KG, KZ, RU, TJ, TM), Patente Europea (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaraciones bajo Regla 4.17:

— en cuanto al derecho del solicitante a solicitar y que le sea garantizada una patente (Regla 4.17(ii))

— en cuanto al derecho del solicitante a reclamar la prioridad de la solicitud anterior (Regla 4.17(iii))

— de inventoría (Regla 4.17(iv))

Publicada:

-- con el reporte de búsqueda internacional

(48) Fecha de publicación de esta versión corregida:

23 enero 2014

(15) Información sobre la corrección

Véase Notificación del 23 de enero de 2014

TRATADO DE COOPERACION EN MATERIA DE PATENTES

PCT

REPORTE DE BUSQUEDA INTERNACIONAL

(Artículo 18 y Reglas 43 y 44 del PCT)

Referencia de archivo del solicitante o apoderado: 11841 PCT		**PARA UNA ACCION ADICIONAL** Véase la Notificación de transmisión del reporte de examen preliminar internacional (Forma PCT/ISA/220), así como, cuando sea aplicable, ítem 5 abajo
No. de solicitud internacional: PCT/US2012/067173	Fecha de presentación internacional *(día/mes/año)*: 30/11/2012	Fecha de prioridad (la más inicial) *(día/mes/año):* 02/12/2011
Solicitante: BRISTOL-MYERS SQUIBB COMPANY		

Este reporte de búsqueda internacional ha sido preparado por esta Autoridad de Búsqueda Internacional y se transmite al solicitante de acuerdo al Artículo 18. Una copia se transmite a la Oficina Internacional.
Este reporte de búsqueda internacional consiste de un total de 4 hojas.

[X] También está acompañado de una copia de cada documento de la técnica previa citado en este reporte.

1. **Base del reporte**

a. Con respecto al **idioma**, la búsqueda internacional se llevó a cabo con base en:

☒ la solicitud internacional en el idioma en el cual fue presentada

☐ una traducción de la solicitud internacional en , la cual es la lengua de una traducción presentada para los propósitos de búsqueda internacional (Reglas 12.3(a) y 23.1(b)).

b. ☐ Este reporte de búsqueda se ha establecido tomando en cuenta la **rectificación de un error obvio** autorizado por o Notificado a esta Autoridad bajo la Regla 91 (Regla 43.6*bis*(a)).

c. ☐ Con respecto a cualquier **secuencia de nucleótidos y/o aminoácidos** descrita en la solicitud internacional, véase Bloque I

2. [ ] **Se encontró que ciertas reivindicaciones eran inescrutables** (Véase Bloque No. II).

3. [ ] **Se carece de unidad de la invención** (Véase Bloque No. III).

4. Con respecto al **título**

[ ] el texto está aprobado como se presentó por el solicitante.

[X] el texto ha sido establecido por esta Autoridad para leerse como sigue:
DIHIDROPIRIDINONAS Y PIPERIDONAS DE ARILO COMO INHIBIDORES DE MGAT2

5. Con respecto al **resumen**,

[X] el texto está aprobado como se presentó por el solicitante.

[ ] el texto ha sido establecido, de acuerdo a la Regla 38.2(b), por esta Autoridad como aparece en el Bloque No. IV. El solicitante puede, en el término de un mes a partir de la fecha de envío de este reporte de búsqueda internacional, presentar comentarios a esta Autoridad.

6. Con respecto a los **dibujos,**

a. La figura de los **dibujos** a ser publicada con el extracto es la Figura No.

[ ] Como se sugiere por el solicitante.

[ ] Como se seleccionó por esta Autoridad, debido a que el solicitante fracaso en sugerir una figura.

[ ] Como se seleccionó por esta Autoridad, debido a que esta figura caracteriza mejor la invención.

b. ☐ Ninguna de las figuras será publicada con el resumen.

REPORTE DE BÚSQUEDA INTERNACIONAL

No. de solicitud internacional
PCT/US2012/067173

A. CLASIFICACIÓN DEL TEMA

INV. C07D211/86 C07D211/90 C07D401/04 C07D401/10 C07D401/12
C07D401/14 C07D407/14 C07D413/04 C07D413/12 C07D417/04
C07D417/14 C07F9/40 A61K31/4418 A61K31/4427 A61P3/00

De acuerdo a la Clasificación de Patentes Internacional (IPC) o a la clasificación nacional y a la IPC.

B. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido por los símbolos de clasificación):
C07D C07F

Documentación buscada diferente a la documentación mínima, a la extensión que tales documentos están incluidos en los campos buscados:

Base de datos electrónicos consultados durante la búsqueda internacional (nombre de la base de datos y, en donde sea práctico, términos de búsqueda utilizados):
EPO-Internal, CHEM ABS Data, WPI Data,

C. DOCUMENTOS QUE SE CONSIDERA QUE SON RELEVANTES

Categoría*	Cita del documento, con indicación, en donde sea apropiado, de los pasajes relevantes	Relevante para la Reiv. No.
A	NAGAI: NIPPON KAGAKU ZASSHI, vol. 89, 1968, páginas 819-820, XP002693199, ISSN: 0369-5387 compuestos con números registro CAS: 21000-35-1 y 21000-36-2; página 820; compuesto 3 -----	1
A	AKIO SAKURAI ET AL: "The Cyclization of Ethyl Cyanoacetate and Ketones by Ammonium Acetate", BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, vol. 40, no. 7, 1 enero 1967 (1967-01-01), páginas 1680-1684, XP055055179, ISSN: 0009-2673, DOI: 10.1246/bcsj.40.1680 página 1681; compuesto Ie -----	1
	-/--	

[X] Documentos adicionales se enlistan en la continuación del bloque C [X] Véase familia de patentes anexa.

* Categorías especiales de los documentos citados
"A" documento que define el estado general de la técnica el cual no se considera ser de particular relevancia.
"E" documento anterior publicado en o después de la fecha de presentación internacional.
"L" documento el cual puede arrojar dudas sobre la(s) reivindicacion(es) de prioridad o el cual se cita para establecer la fecha de publicación de otra cita u otra razón especial (como se especifica)
"O" documento que se refiere a una descripción oral, uso, exhibición u otro medio
"P" documento publicado antes de la fecha de presentación internacional pero después de la fecha de prioridad reivindicada.
"T" documento posterior publicado después de la fecha de presentación internacional o fecha de prioridad y no en conflicto con la solicitud, pero citado para entender el principio o teoría fundamental de la invención.
"X" documento de relevancia particular; la invención reivindicada no puede ser considerada nueva o no se puede considerar que involucre una actividad inventiva cuando el documento es considerado de manera A1slada.
"Y" documento de particular relevancia; no se puede considerar que la invención involucre una actividad inventiva cuando el documento es combinado con uno o más de tales documentos, tal combinación sería obvia para una persona experimentada en la técnica.
"&" documento miembro de la misma familia de patentes.

Fecha de la terminación real de la búsqueda internacional	Fecha de envío del reporte de búsqueda internacional
6 marzo 2013	12/04/2013

Nombre y dirección de correspondencia de la ISA	Funcionario Autorizado
Oficina Europea de Patentes, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Brandstetter, T

REPORTE DE BÚSQUEDA INTERNACIONAL

No. de solicitud internacional
PCT/US2012/067173

C. (Continuación) DOCUMENTOS QUE SE CONSIDERA QUE SON RELEVANTES

Categoría	Cita del documento, con indicación, en donde sea apropiado, de los pasajes relevantes	Relevante para la Reiv. No.
A	S. M. MCELVAIN ET AL: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 80, no. 15, 5 Agosto 1958 (1958-08-05), páginas 3915-3923, XP055055161, ISSN: 0002-7863, DOI: 10.1021/ja01548a030 página 3917; compuestos XV, XVI	1

A	ATTIA A ET AL: "Synthesis of some 3-cyano-5,6-dihydropyridin-2-ones and their N-substituted derivatives", EGYPTIAN JOURNAL OF CHEMISTRY, THE EGYPTIAN CHEMICAL SOCIETY, CAIRO, vol. 26, no. 5, 1 enero 1983 (1983-01-01), páginas 447-452, XP009167683, ISSN: 0367-0422 página 447; compuesto 2d	1

X	CARRIE: "SUR LA CONDENSATION DE LA BENZALACETOPHENONE ET DE LA DYPNONE AVEC LA CYANACETAMIDE", COMPTES RENDUS HEBDOMADAIRES DES SEANCES DE L'ACADEMIE DES SCIENCES, vol. 257, no. 18, 1963, páginas 2849-2851, XP009167680, ISSN: 0001-4036	1-7,11
A	4,6-di-(4-chlorophenyl)-6-methy1-2-oxo-1,2,5,6-tetrahydropyridine-3-carbonitrile (análogo de compuesto VII, en donde X es Cl); página 2851	8-10, 12-15

A	US 2010/093771 A1 (NAKAMURA KEIJI [JP] ET AL) 15 Abril 2010 (2010-04-15) reivindicaciones 1, 17, 18, 20 paragraph [0453]	1-15

A	WO 2010/095767 A1 (BANYU PHARMA CO LTD [JP]; ARAKAWA KEISUKE [JP]; ITO YOSHIKI [JP]; KAWA) 26 Agosto 2010 (2010-08-26) reivindicaciones 1, 9-11 página 41; tabla 20	1-15

REPORTE DE BÚSQUEDA INTERNACIONAL

No. de solicitud internacional
PCT/US2008/006768

Información acerca de los miembros de la familia de patentes

Documento de patente citado en el reporte de búsqueda	Fecha de publicación	Miembro(s) de la familia de patentes	Fecha de publicación
US 2010093771 A1	15-04-2010	EP 2078719 A1	15-07-2009
		US 2010093771 A1	15-04-2010
		WO 2008038768 A1	03-04-2008
WO 2010095767 A1	26-08-2010	AU 2010216633 A1	08-09-2011
		CA 2751244 A1	26-08-2010
		EP 2398800 A1	28-12-2011
		JP 2012518597 A	16-08-2012
		US 2011275647 A1	10-11-2011
		WO 2010095767 A1	26-08-2010

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PETITORIO DEL PCT

Original (para **PRESENTACIÓN**)

0 **0-1**	**Para uso de la Oficina receptora únicamente** No. de Solicitud Internacional	**PCT/US12/67173**
0-2	Fecha de Presentación Internacional	**30 NOV 2012 (30.11.2012)**
0-3	Nombre de la Oficina receptora y "Solicitud Internacional de PCT"	**SOLICITUD INTERNACIONAL DEL PCT RO/US**

0-4 0-4-1	**Forma – PCT/RO/101 Petitorio del PCT** Preparado usando	**PCT-SAFE [EASY mode]** **Versión 3.51.056.232 MT/FOP 20121001/0.20.5.19**
0-5	**Petición** El abajo firmante solicita que la presente solicitud internacional sea procesada de conformidad con el Tratado de Cooperación en Materia de Patentes	
0-6	**Oficina Receptora (especificada por el solicitante)**	**Oficina de Patentes y Marcas de Estados Unidos de Norteamérica (USPTO) (RO/US)**
0-7	**Referencia de presentación del solicitante o apoderado**	**11841 PCT**
I	**Título de la invención**	**ARIL DIHIDROPIRIDINONA Y PIPERIDINONA COMO INHIBIDORES DE MGAT2**
II II-1	**Solicitante** Esta persona es:	**Solicitante únicamente**
II-2	Solicitante para:	**Todos los países designados excepto US**
II-4	Nombre	**BRISTOL-MYERS SQUIBB COMPANY**
II-5	Dirección:	**P.O. Box 4000** **Route 206 and Province Line Road** **Princeton, New Jersey 08543-4000** **Estados Unidos de Norteamérica**
II-6	País de nacionalidad	**US**
II-7	País de residencia	**US**
II-8	Teléfono No.	**609-252-4000**
II-9	Fax No.	**609-252-4526**
II-10	Correo electrónico	**patents@bms.com**
II-10(a)	**Autorización para utilizar correo-electrónico** Se autoriza a la Oficina receptora, la Autoridad de Búsqueda Internacional, la Oficina Internacional y la Autoridad de Examen Preliminar Internacional a utilizar la dirección de correo electrónica para enviar con antelación, si la Oficina o Autoridad así lo desea, copias de las notificaciones con respecto a esta solicitud internacional	**exclusivamente en forma electrónica (no se enviarán notificaciones impresas)**

Original (para **PRESENTACIÓN**)

III-1	**Solicitante y/o inventor**	
III-1-1	Esta persona es:	**Inventor solamente**
III-1-4	Nombre (APELLIDO, Nombre)	**TURDI, Huji**
III-1-5	Dirección:	**c/o Bristol-Myers Squibb Company 311 Pennington-Rocky Hill Road Pennington, New Jersey 08534 Estados Unidos de América**
III-2	**Solicitante y/o inventor**	
III-2-1	Esta persona es:	**Inventor solamente**
III-2-4	Nombre (APELLIDO, Nombre)	**RANGELAND, Jon J.**
III-2-5	Dirección:	**c/o Bristol-Myers Squibb Company 311 Pennington-Rocky Hill Road Pennington, New Jersey 08534 Estados Unidos de América**
III-3	**Solicitante y/o inventor**	
III-3-1	Esta persona es:	**Inventor solamente**
III-3-4	Nombre (APELLIDO, Nombre)	**LAWRENCE, R. Michael**
III-3-5	Dirección:	**c/o Bristol-Myers Squibb Company 311 Pennington-Rocky Hill Road Pennington, New Jersey 08534 Estados Unidos de América**
III-4	**Solicitante y/o inventor**	
III-4-1	Esta persona es:	**Inventor solamente**
III-4-4	Nombre (APELLIDO, Nombre)	**CHENG, Dong**
III-4-5	Dirección:	**c/o Bristol-Myers Squibb Company 311 Pennington-Rocky Hill Road Pennington, New Jersey 08534 Estados Unidos de América**
III-5	**Solicitante y/o inventor**	
III-5-1	Esta persona es:	**Inventor solamente**
III-5-4	Nombre (APELLIDO, Nombre)	**ARMAD, Saleem**
III-5-5	Dirección:	**c/o Bristol-Myers Squibb Company 311 Pennington-Rocky Hill Road Pennington, New Jersey 08534 Estados Unidos de América**
III-6	**Solicitante y/o inventor**	
III-6-1	Esta persona es:	**Inventor solamente**
III-6-4	Nombre (APELLIDO, Nombre)	**MENG, Wei**
III-6-5	Dirección:	**c/o Bristol-Myers Squibb Company 311 Pennington-Rocky Hill Road Pennington, New Jersey 08534 Estados Unidos de América**

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PETITORIO DEL PCT

Original (para **PRESENTACIÓN**)

III-7	**Solicitante y/o inventor**	
III-7-1	Esta persona es:	**Inventor solamente**
III-7-4	Nombre (APELLIDO, Nombre)	**BRIGANCE, Robert Paul**
III-7-5	Dirección:	**c/o Bristol-Myers Squibb Company** **311 Pennington-Rocky Hill Road** **Pennington, New Jersey 08534** **Estados Unidos de América**
III-8	**Solicitante y/o inventor**	
III-8-1	Esta persona es:	**Inventor solamente**
III-8-4	Nombre (APELLIDO, Nombre)	**DEVASTHALE, Pratik**
III-8-5	Dirección:	**c/o Bristol-Myers Squibb Company** **311 Pennington-Rocky Hill Road** **Pennington, New Jersey 08534** **Estados Unidos de América**
IV-1	**Apoderado o representante común; o dirección para correspondencia** La persona identificada abajo es en la presente/ha sido asignado para actuar a nombre del(los) solicitante(s) ante las Autoridades Internacionales competentes como:	**agente**
IV-1-1	Nombre	**SUN, Jing G.**
IV-1-2	Dirección:	**Bristol-Myers Squibb Company** **P.O. Box 4000** **Princeton, New Jersey** **08543-4000** **Estados Unidos de América**
IV-1-3	No. telefónico	**609-252-3791**
IV-1-4	No. de facsímil	**609-252-4526**
IV-1-5	Correo electrónico	**patents@bms.com**
IV-1-5 (a)	**Autorización para utilizar correo-electrónico** Se autoriza a la Oficina receptora, la Autoridad de Búsqueda Internacional, la Oficina Internacional y la Autoridad de Examen Preliminar Internacional a utilizar la dirección de correo electrónica para enviar con antelación, si la Oficina o Autoridad así lo desea, copias de las notificaciones con respecto a esta solicitud internacional	**exclusivamente en forma electrónica (no se enviarán notificaciones impresas)**
IV-1-6	No de registro del agente	**45, 914**
IV-2	**Apoderados adicionales**	**Apoderados adicionales con la misma direccion que el primer apoderado nombrado**
IV-2-1	Nombres	**BOGIE, Terence J.(44,544); BERGEN, Briana C.(39,123); CLAUSS, Isabelle M.(47,326); D'AMICO, Stephen C.(46,652); DELAUNEY, Ashton J.(64,286); DUNCAN, Laurelee A.(44,096); FRANK, Eve(46,785); GIBBONS, Maureen S.(44,121); GOLIAN, Paul D.(42,591); GREENBLATT, Gary D.(47,609); GUO, Z. Angela(54,144); HADAD, Henry(35,888); HAI, Bing(35,888); JACOBSEN, Barry(43,689); KORSEN, Elliott (32,705); LIU, Hong(54,891); MILLER, Melissa(52,988); PARLET, Nickki L.(44,996); RODNEY, Burton(22,076); SPALDING, Todd(55,638); VANATTEN, Mary K.(39,408); WALSH, Brian J.(45,543); EPPERSON, James(52,867); LEVIS, John F.(34,210); MINGO, Pamela A.(48,256); VOLLES, Warren(33,810); CHAO, Yuan(32,118)**

V	Designación de Países	
V-1	**La presentación de esta solicitud constituye bajo la Regla 4.9(a), la designación de todos los Estados Contrayentes limitada por el PCT en la fecha de presentación internacional, para garantizar cada tipo de protección disponible y, cuando aplique, para garantizar tanto patentes regionales como nacionales.**	
VI-1	**Reclamo de prioridad de solicitud nacional anterior**	
VI-1-1	Fecha de presentación	**02 diciembre 2011 (02.12.2011)**
VI-1-2	Número	**61/566,039**
VI-1-3	País	**US**
VI-2	**Reclamo de prioridad de solicitud nacional anterior**	
VI-2-1	Fecha de presentación	**29 noviembre 2012 (29.11.2012)**
VI-2-2	Número	**13/688,584**
VI-2-3	País	**US**
VI-3	**Solicitud de documento de prioridad** Se solicita a la Oficina receptora preparar y transmitir a la Oficina Internacional una copia certificada de la solicitud o solicitudes anteriores identificadas arriba como items:	**VI-1, VI-2**
VI-4	**Incorporación por referencia:** cuando un elemento de la solicitud internacional referida en el Artículo 11(1)(iii)(d) o € o una parte de la descripción, reivindicaciones o figuras referidas en la Regla 20.5(a) de otra manera no está contenida en esta solicitud internacional pero está contenida completamente en una solicitud anterior cuya prioridad se reclama en la fecha en la cual uno o más elementos referidos en el Artículo 11(1)(iii) fueron primero recibidos por la Oficina receptora, ese elemento o parte es, sujeto a confirmación bajo la Regla 20.6, incorporada como referencia en esta solicitud internacional para los propósitos de la Regla 20.6	
VII-1	**Autoridad de Búsqueda Internacional Elegida**	**Oficina Europea de Patentes (EPO) (ISA/EP)**

Original (para **PRESENTACIÓN**)

VIII	**Declaraciones**	Número de declaraciones	
VIII-1	Declaración de la identidad del inventor	-	
VIII-2	Declaración del derecho del solicitante, a partir de la fecha de presentación internacional, a solicitar y a que le sea concedida una patente	1	
VIII-3	Declaración del derecho del solicitante, a partir de la fecha de presentación internacional, a reclamar la prioridad de la solicitud anterior	2	
VIII-4	Declaración de inventoría (sólo para propósitos de la designación: de los Estados Unidos de América)	-	
VIII-5	Declaración en cuanto a descripciones no perjudiciales o excepciones a falta de novedad	-	

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PETITORIO DEL PCT

Original (para **PRESENTACIÓN**)

IX	**Lista de verificación**	número de hojas	archivo(s) electrónico(s) anexo(s)
IX-1	Petitorio (incluyendo hojas de declaración)	**9**	✓
IX-2	Descripción	**259**	**-**
IX-3	Reivindicaciones	**13**	**-**
IX-4	Resumen	**1**	✓
IX-5	Dibujos	**0**	**-**
IX-7	TOTAL	**282**	-
	Ítems acompañantes	Documento(s) anexo(s)	archivo(s) electrónico(s) anexo(s)
IX-8	Hoja de cálculo de tarifas	✓	-
IX-19	**Figura de los dibujos que deben acompañar al resumen**		
IX-20	**Idioma de presentación de la solicitud internacional**	**Inglés**	
X-1	Firma del solicitante o apoderado	**/Jing G. Sun, Reg. No. 45, 914/**	
X-1-1	Nombre	**SUN, Jing G.**	
X-1-2	Nombre de signatario		
X-1-3	Función		

PARA USO DE LA OFICINA RECEPTORA ÚNICAMENTE

I0-1	**Fecha de recepción real de la solicitud internacional propuesta**	**30 NOV 202 (30.11.12)**
10-2	**Dibujos:**	
10-2-1	Recibidos	
10-2-2	No recibidos	
10-3	**Fecha de recepción real corregida debido a documentos o dibujos recibidos después pero a tiempo que completan la solicitud internacional propuesta**	
10-4	**Fecha de recepción a tiempo de las correcciones requeridas bajo el Artículo 11(2) del PCT**	
10-5	**Autoridad de Búsqueda Internacional**	**ISA/EP**
10-6	**Transmisión de copia de búsqueda retrasada hasta que se pague la tarifa de búsqueda**	

PARA USO DE LA OFICINA INTERNACIONAL ÚNICAMENTE

11-1	Fecha de recepción de la copia de registro por la Oficina Internacional	

TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES

De la:
AUTORIDAD EXAMINADORA PRELIMINAR INTERNACIONAL

Para:

Véase forma PCT/ISA/220

PCT

OPINIÓN ESCRITA DE LA AUTORIDAD DE BÚSQUEDA INTERNACIONAL
(Regla 43*bis*.1 del PCT)

Fecha de envío
(día/mes/año): véase forma PCT/ISA/220 (segunda hoja)

PARA UNA ACCIÓN ADICIONAL
Véase párrafo 2 abajo.

Referencia de archivo del solicitante o apoderado:
Véase forma PCT/ISA/220

No. de solicitud internacional:	Fecha de presentación internacional *(día/mes/año):*	Fecha de prioridad *(día/mes/año):*
PCT/US2012/067173	30.11.2012	02.12.2011

Clasificación de Patente Internacional (IPC) o clasificación nacional e IPC:
INV. C07D211/86 C07D211/90 C07D401/04 C07D401/10 C07D401/12 C07D401/14 C07D407/14 C07D413/04 C07D413/12 C07D417/04 C07D417/14 C07F9/40 A61K31/4418 A61K31/4427 A61P3/00

Solicitante:
BRISTOL-MYERS SQUIBB COMPANY

1. Esta opinión contiene indicaciones y páginas correspondientes que se relacionan con los siguientes ítems:

- [X] Bloque No. I Base de la opinión
- [ ] Bloque No. II Prioridad
- [ ] Bloque No. III No se establece opinión con respecto a novedad, paso o actividad inventiva y aplicabilidad industrial
- [ ] Bloque No. IV Falta de unidad de la invención
- [X] Bloque No. V Declaración justificada bajo la Regla 43*bis*1(a)(i) con respecto a novedad, etapa o Actividad Inventiva o aplicabilidad industrial; citas y explicaciones que apoyan tal declaración.
- [ ] Bloque No. VI Ciertos documentos citados
- [ ] Bloque No. VII Ciertos defectos en la solicitud internacional
- [X] Bloque No. VIII Ciertas observaciones en la solicitud internacional

2: ACCIÓN ADICIONAL

Si se hace una demanda por un examen preliminar internacional, esta opinión será considerada como una opinión escrita de la Autoridad Examinadora Preliminar internacional ("IPEA") excepto que esto no aplique cuando el solicitante selecciona una Autoridad que no sea esta como la IPEA y la IPEA seleccionada haya notificado a la Oficina Internacional bajo la Regla 66.1 bis(b) que opiniones escritas de esta Autoridad de Búsqueda Internacional no serán consideradas entonces.

Si esta opinión es, como se indicó arriba, considerada como una opinión escrita de la IPEA, se invita al solicitante a presentar a la IPEA una respuesta escrita junto, cuando sea adecuado, enmiendas, antes de la expiración de los 3 meses a partir de a fecha de envío de la Forma PCT/ISA/220 o antes de que expiren los 22 meses a partir de la fecha de prioridad, cualquiera que expire después.

Para opiniones adicionales, véase la Forma PCT/ISA/220.

3. Para detalles adicionales, véase notas a la Forma PCT/ISA/220.

Nombre y dirección de correspondencia de la	Fecha de terminación de esta opinión	Funcionario Autorizado
Oficina Europea de Patentes, D-80298 Munich Tel. +49 89 2399 – 0 Fax: +49 89 2399-4465	Véase forma PCT/ISA/220	Brandstetter, T Teléfono No. +49 89 2399-5847

No. de solicitud internacional
PCT/US2012/067173

OPINIÓN ESCRITA DE LA AUTORIDAD DE BÚSQUEDA INTERNACIONAL

Bloque No. I Base de la opinión

1. Con respecto a la **lengua**, esta opinión ha sido establecida sobre la base de:

   ☒ la solicitud internacional en el idioma en el que se presentó

   ☐ una traducción del idioma original al siguiente idioma ____, el cual es el idioma de una traducción presentada con el propósito de búsqueda internacional (conforme a las Reglas 12.3 y 23.1(b)).

2. ☐ Esta opinión ha sido establecida tomando en cuenta la **rectificación de un error obvio** autorizado por o notificado a esta Autoridad bajo la Regla 91 (Regla 43bis.1 (a)).

3. Con respecto a cualquier **secuencia de nucleótidos y/o aminoácidos** descrita en la solicitud internacional, y necesaria para la invención reclamada, la búsqueda internacional se llevó a cabo con base en:

   a. (medios)

      ☐ en papel

      ☐ en forma electrónica

   b. (tiempo)

      ☐ contenido en la solicitud internacional presentada

      ☐ junto con la solicitud internacional en forma electrónica

      ☐ presentado posteriormente a esta Autoridad con el propósito de búsqueda

4. ☐ Además, en caso de que se haya presentado más de una versión o copia de un listado de secuencias y/o tabla relacionada con el mismo, se presentaron las declaraciones solicitadas de que la información en las copias subsecuentes o adicionales es idéntica a la de la solicitud presentada o no se aleja de la solicitud presentada, según sea adecuado.

5. Comentarios adicionales

Bloque No. V. Declaración razonada conforme a la Regla 43*bis*.1(a)(i) con relación a novedad, actividad inventiva o aplicabilidad industrial; citas y explicaciones que soportan dicha declaración

1. Declaración

Novedad (N)	Sí: Reivindicaciones	8-10, 12-15
	No: Reivindicaciones	1-7, 11
Actividad Inventiva (IA)	Sí: Reivindicaciones	8-10, 12-15
	No: Reivindicaciones	1-7, 11
Aplicabilidad Industrial (AI)	Sí: Reivindicaciones	1-15
	No: Reivindicaciones	

2. Citas y explicaciones:

Véase hoja separada

Bloque No. VIII Ciertas observaciones sobre la solicitud internacional

Se hacen las siguientes observaciones sobre la claridad de las reivindicaciones, descripción y dibujos o sobre la pregunta de si las reivindicaciones están completamente soportadas por la descripción:

Véase hoja separada

Re Ítem V.

1 Se hace referencia a los siguientes documentos:

D1 Nagai, Nippon Kagaku Zasshi, 89, 1968, páginas 819-820

D2 Akio Sakurai et al., Bulletin of the Chemical Society of Japan, 40 (7), 1967, páginas 1680-1684

D3 S. M. MeElvain et al., Journal of the American Chemical Society, 80 (15), 1958, páginas 3915-3923

D4 Attia, A. et al., Egyptian Journal of Chemistry, 26 (5), 1983, páginas 447-452

D5 Carrie, Comptes Rendus Hebdomadaires des Séances de l'Acadérnie des Siences, 257 (18), 1963, páginas 2849-2851

D6 US 2010/093771 A1 (2010-04-15)

D7 WO 2010/095767 A1 (2010-08-26)

2 Novedad

2.1 La presente solicitud se refiere a compuestos de fórmula I (reivindicación 1), composiciones que los comprenden (reivindicación 11) y su uso médico en el tratamiento de la diabetes, hiperglucemia, etc (reivindicación 14).

2.2 D1 (RN-21000-35-1, en RN-21000-36-2, el compuesto 3 en la página 820, en el que X es OCH_3 o Br), D2 (página 1681, compuesto le), D3 (página 3917, compuestos XV y XVI), D4 (página 447, el compuesto 2d, RN 92462-51-6), y D5 (el compuesto VII en la página 2850, y el análogo de compuesto VII, en la que X es CH_3) describe compuestos de fórmula I, que sin embargo han sido excluidos del alcance de las reivindicaciones 1-10, mediante condición.

2.3 Análogo de compuesto VII, en la que X es Cl en la página 2851 de D5 (4,6-di-(4-clorofenil)-6-metil-2-oxo-1,2,5,6-tetrahidropiridina-3-carbonitrilo) sin embargo está dentro del alcance de las actuales reivindicaciones 1-7 y el objeto de las reivindicaciones 1-7 y 11 por lo tanto, no es nueva.

2.4 Los compuestos de las reivindicaciones 8-10, no se han descrito en la técnica anterior y su objeto es, por tanto, nuevo. El uso médico de los compuestos o composiciones que los comprenden y otro agente terapéutico arriba citados no se han descrito en la técnica anterior y por lo tanto el objeto de las reivindicaciones 12-15 es también nuevo.

3 Actividad inventiva

3.1 Las siguientes consideraciones se refieren únicamente a la materia que es nueva.

3.2 D6 o D7 puede ser considerada como la técnica anterior más próxima a la materia objeto de la presente solicitud, y da a conocer compuestos como inhibidores de MGAT2 y su uso médico en el tratamiento de enfermedades, como la diabetes. Los compuestos actualmente reivindicados son estructuralmente lejanos de los compuestos de D6 y D7. El problema a resolver por la presente invención, por tanto, puede ser considerado como la provisión de nuevos inhibidores de MGAT2 que son útiles en el tratamiento de, por ejemplo la diabetes. En vista de los datos de la Tabla 1 (valores de IC_{50} sub-micromolares de la mayoría de los compuestos ensayados) es creíble que los compuestos reivindicados en la presente son una solución del problema anterior.

3.3 Los compuestos reivindicados en la presente no se han propuesto como inhibidores de MGAT2 en D6 o D7 ni de otro modo resultado obvios. En vista de la diferencia estructural significativa para los compuestos de D6 o D7, un experto en la materia no podía esperar que los compuestos reivindicados en el presente inhibirían MGAT2 y la actividad inventiva, por lo tanto puede ser reconocida.

Re ítem VIII

4 Contrariamente a los requisitos de la Regla 5.1 (a) (ii) del PCT, el antecedente relevante de la técnica descrita en D6 y D7 no se menciona en la descripción, ni se identifican estos documentos en el mismo.

5 La afirmación contenida en el párrafo [00195] indica que la presente solicitud abarca profármacos de los compuestos de la invención. Esto está en contradicción con las reivindicaciones, haciendo así poco claro el ámbito para el que se reclama la protección. Además, el término “profármaco” no está claro por sí mismo, ya que se basa en una definición funcional y no proporciona al experto con la enseñanza necesaria para evaluar qué materia objeto es en realidad comprendida en el mismo. Al utilizar el término “profármaco” también se trató de definir la invención por un resultado que debe conseguirse que no es permisible.

ARIL DIHIDROPIRIDINONA Y PIPERIDINONA COMO INHIBIDORES DE MONOACILGLICEROL ACILTRANSFERASA (MGAT2)

Referencia cruzada a solicitudes relacionadas

Esta solicitud reclama el beneficio de prioridad de la Solicitud Provisional de E.U.A. No. 61/566,039 presentada el 2 de diciembre de 2011, y el beneficio de prioridad de la Solicitud No Provisional de E.U.A. No. 13/688,584 presentada el 29 de noviembre de 2012, ambas de las cuales se incorporan completamente en la presente por referencia.

Campo de la Invención

La presente invención provee compuestos novedosos de aril dihidropiridinona y piperidinona y sus análogos, que son inhibidores de MGAT2, composiciones que los contienen y métodos de uso, por ejemplo, para el tratamiento o la profilaxis de la diabetes, la obesidad, la dislipidemia y afecciones relacionadas.

Antecedentes de la Invención

La prevalencia de la obesidad y la diabetes aumentan a una velocidad alarmante. De acuerdo con la OMS, en 2008, el 70% de la población adulta de los Estados Unidos padecía sobrepeso, y el 33% de ellos era obesa. Simultáneamente a la alarmante cantidad de personas que comenzaban a padecer sobrepeso y se volvían obesas, en 2008, se calculó que el 12.3% de la población de los Estados Unidos

tenía altos niveles de glucosa en sangre [http://www.who.int/diabetes/facts/en/]. La epidemia de obesidad/diabetes no ocurre solamente en los Estados Unidos. De acuerdo con la OMS (ficha técnica N.° 312, septiembre de 2012), 347 millones de personas en todo el mundo tienen diabetes. El tratamiento de la obesidad y la mejora del control glucémico de manera eficaz y segura siguen siendo desafíos importantes para la medicina moderna.

Se ha propuesto la monoacilglicerol aciltransferasa 2 (MGAT2) como una diana atractiva para el tratamiento de la obesidad y la diabetes tipo II [Yen, C.L. et al., *Nat. Med.*, 15(4):442-446 (2009)]. MGAT2 se expresa de manera selectiva y en gran medida en el intestino delgado, donde ejerce una función esencial en la vía del monoacilglicerol para la absorción de la grasa alimenticia. Cuando se ingiere grasa alimenticia, la lipasa pancreática digiere los triglicéridos en ácidos grasos libres y 2 monoacilglicerol, que son absorbidos por los enterocitos epiteliales del intestino. Una vez que se encuentran dentro de los enterocitos, los ácidos grasos libres y el 2 monoacilglicerol se usan como bloques de construcción para volver a sintetizar los triglicéridos mediante dos etapas de acilación secuenciales: primero mediante MGAT y luego mediante reacciones enzimáticas DGAT. Luego, los triglicéridos se incorporan en los quilomicrones y se segregan en la linfa a fin de usarse como suministro

energético para el cuerpo. Los ratones con MGAT2 inactivado exhiben un fenotipo metabólico saludable y muestran resistencia a la obesidad inducida por una alimentación alta en grasas, una mejor sensibilidad a la insulina y una menor acumulación de grasas en el tejido adiposo y hepático. Además, la eliminación genética de MGAT2 produce ratones con niveles aumentados de GLP1 [Yen, C.L. et al., *Nat. Med.*, 15(4):442-446 (2009)]. En conjunto, estos datos muestran que los inhibidores de MGAT2 prometen tratar trastornos metabólicos, tales como la obesidad, la diabetes tipo II y la dislipidemia.

Breve Descripción de la Invención

La presente invención provee compuestos de aril dihidropiridinona y piperidinona y sus análogos, que son útiles como inhibidores de MGAT2, que incluyen estereoisómeros, tautómeros, sales aceptables desde el punto de vista farmacéutico o solvatos de estos.

La presente invención también provee procesos e intermediarios para obtener los compuestos de la presente invención o estereoisómeros, tautómeros, sales aceptables desde el punto de vista farmacéutico o solvatos de estos.

La presente invención también provee composiciones farmacéuticas que comprenden un portador aceptable desde el punto de vista farmacéutico y, al menos, uno de los compuestos de la presente invención o estereoisómeros,

tautómeros, sales aceptables desde el punto de vista farmacéutico o solvatos de este.

Los compuestos de la invención se pueden usar para el tratamiento y/o la profilaxis de múltiples enfermedades o trastornos asociados a MGAT2, tales como diabetes, obesidad, dislipidemia y afecciones relacionadas, tales como complicaciones microvasculares y macrovasculares asociadas a la diabetes, enfermedades cardiovasculares, síndrome metabólico y sus afecciones relacionadas, trastornos del metabolismo de la glucosa y de los lípidos, y otras enfermedades.

Los compuestos de la invención se pueden usar en terapia.

Los compuestos de la invención se pueden usar para la fabricación de un medicamento para el tratamiento y/o la profilaxis de múltiples enfermedades o trastornos asociados a MGAT2.

Los compuestos de la invención se pueden usar solos, en combinación con los otros compuestos de la presente invención o en combinación con uno o más de otros agentes.

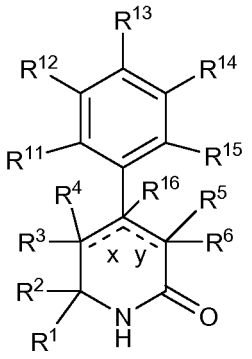
Otras características y ventajas de la invención serán evidentes luego de analizar la siguiente descripción detallada y las reivindicaciones.

Descripción Detallada de la Invención

I.COMPUESTOS DE LA INVENCIÓN

En un primer aspecto, la presente invención provee,

entre otros, un compuesto de la Fórmula (I):



(I)

o un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de aquel, en donde:

--- indica un enlace simple o doble;

x e y pueden ser ambos un enlace simple; en donde x es un enlace doble, y es un enlace simple, y R^4 y R^{16} están ausentes; en donde y es un enlace doble, x es un enlace simple, y R^5 y R^{16} están ausentes;

R^1 se selecciona independientemente del grupo que consiste en: $-CONH(C_{4-18}$ alquilo), $-CONHC_{2-8}$ haloalquilo, $-CONH(CH_2)_{1-8}Ph$, $-(CH_2)_m-(C_{3-10}$ carbociclo sustituido con 0-2 R^b y 0-2 R^g), $-(CH_2)_m-$(heteroarilo de 5 a 6 miembros que comprende átomos de carbono y 1 a 4 heteroátomos seleccionados de N, NR^e, O y S; en donde el heteroarilo se sustituye con 0-1 R^b y 0-2 R^g), y una cadena de hidrocarburos C_{1-12} sustituida con 0-3 R^a; en donde la cadena de hidrocarburos puede ser lineal o ramificada, saturada o insaturada;

R^2 se selecciona independientemente del grupo que

consiste en: C_{1-4} alquilo, C_{3-4} cicloalquilo y C_{1-4} haloalquilo;

R^3 se selecciona independientemente del grupo que consiste en: H, F, Cl, C_{1-4} alquilo y CN;

R^4 y R^5 se seleccionan independientemente del grupo que consiste en: H, F, Cl y C_{1-4} alquilo;

en donde x es un enlace simple, R^3 y R^4 se pueden combinar con el átomo de carbono al que están unidos para formar un carbociclo de 3 a 6 miembros;

R^6 se selecciona independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo, CN, NO_2, R^c, $(CH_2)_n-(X)_t-(CH_2)_mR^c$, NH_2, $-CONH(C_{1-6}$ alquilo), $-NHCOX_1SO_2R^j$, $-NHCOCH_2PO(OEt)_2$, $-NHCOCORj$, $-NHCOCH(OH)R^j$, $-NHCOCH_2COR^j$, $-NHCONHR^j$ y $-OCONR^fR^j$;

X se selecciona independientemente del grupo que consiste en: O, S, NH, -CONH y NHCO;

X_1 es independientemente una cadena de hidrocarburos C_{1-4} opcionalmente sustituida con C_{1-4} alquilo o C_{3-4} cicloalquilo;

en donde y es un enlace simple, R^5 y R^6 se pueden combinar con el átomo de carbono al que están unidos para formar un carbociclo de 3 a 6 miembros;

R^{11}, R^{12}, R^{13}, R^{14} y R^{15} se seleccionan independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo sustituido con 0-2 R^i, C_{1-4} alcoxi, C_{1-4} haloalquilo, C_{1-4} haloalcoxi, C_{3-6} cicloalquilo, CN, NR^fR^j, OR^j, SR^j,

$NHCO_2(C_{1-4}$ alquilo), $NHSO_2(C_{1-4}$ alquilo) y un heterociclo de 4 a 6 miembros que comprende átomos de carbono y 1 a 4 heteroátomos seleccionados de N, NR^e, O y S;

de manera alternativa, R^{11} y R^{12}, junto con los átomos de carbono a los que están unidos, se combinan para formar un anillo carbocíclico de 5 a 6 miembros o un anillo heterocíclico de 5 a 6 miembros, que comprende átomos de carbono y 1 3 heteroátomos seleccionados de N, NR^e, O y S;

de manera alternativa, R^{12} y R^{13}, junto con los átomos de carbono a los que están unidos, se combinan para formar un anillo carbocíclico de 5 a 6 miembros o un anillo heterocíclico de 5 a 6 miembros, que comprende átomos de carbono y 1 3 heteroátomos seleccionados de N, NR^e, O y S;

R^{16} se selecciona independientemente del grupo que consiste en: H y C_{1-4} alquilo;

R^a, en cada caso, se selecciona independientemente del grupo que consiste en halo, OH, C_{1-6} alcoxi, C_{1-6} haloalquilo, C_{1-6} haloalcoxi, $N(C_{1-4}$ alquil$)_2$, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$ y $-(CH_2)_n-(CH_2O)_m-(CH_2)_nR^f$;

R^b, en cada caso, se selecciona independientemente del grupo que consiste en halo, OH, C_{1-10} alquilo, C_{1-10} alcoxi, C_{1-10} haloalquilo, C_{1-10} haloalcoxi, C_{1-10} alquiltio, C_{1-10} haloalquiltio, $N(C_{1-4}$ alquil$)_2$, $-CONH(CH_2)_{4-20}H$, $O(CH_2)_sO(C_{1-6}$ alquilo), R^c, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$ y $-(CH_2)_n-(CH_2O)_m-(CH_2)_nR^f$;

R^c, en cada caso, se selecciona independientemente

del grupo que consiste en: C_{3-6} cicloalquilo sustituido con 0-2 R^d, C_{3-6} cicloalquenilo sustituido con 0-2 R^d, $-(CH_2)_m-$(fenilo sustituido con 0-3 R^d) y un heterociclo de 5 a 6 miembros que comprende átomos de carbono y 1 a 4 heteroátomos seleccionados de N, NR^e, O y S; en donde el heterociclo se sustituye con 0-2 R^d;

R^d, en cada caso, se selecciona independientemente del grupo que consiste en halo, OH, CN, NO_2, C_{1-4} alquilo, C_{1-4} alcoxi, C_{1-4} haloalquilo, C_{1-4} haloalcoxi, tetrazolilo, OBn y fenilo sustituido con 0-2 R^h;

R^e, en cada caso, se selecciona independientemente del grupo que consiste en: H, C_{1-8} alquilo, C_{1-8} haloalquilo, bencilo opcionalmente sustituido con C_{1-4} alcoxi, $CO(C_{1-4}$ alquilo) y COBn;

R^f, en cada caso, se selecciona independientemente del grupo que consiste en: H y C_{1-4} alquilo;

R^g, R^h y R^i, en cada caso, se seleccionan independientemente del grupo que consiste en halo, C_{1-4} alquilo, C_{1-4} alcoxi, C_{1-4} haloalquilo y C_{1-4} haloalcoxi;

R^j, en cada caso, se selecciona independientemente del grupo que consiste en: C_{1-4} alquilo, C_{3-4} cicloalquilo y fenilo;

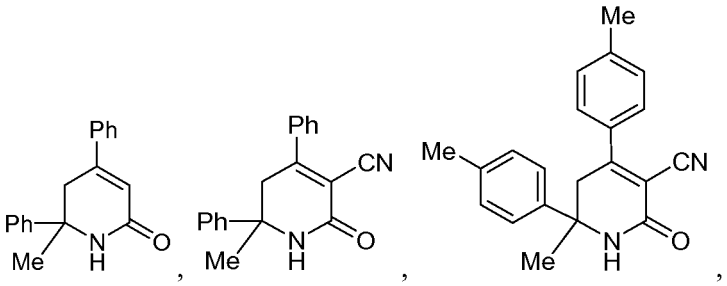
n, en cada caso, es independientemente 0 ó 1;

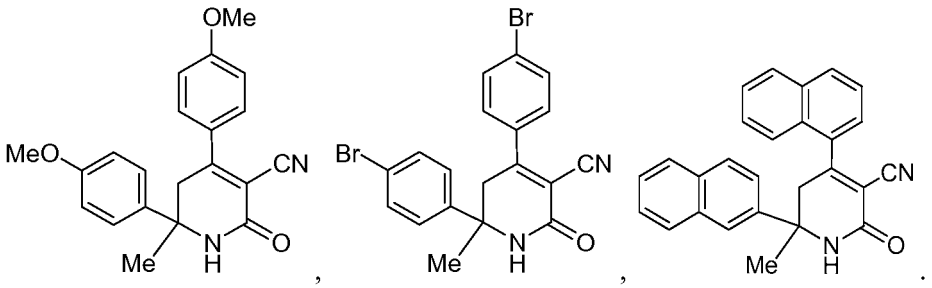
m, en cada caso, es independientemente 0, 1, 2, 3 ó 4;

s, en cada caso, es independientemente 1, 2 ó 3; y

t, en cada caso, es independientemente 0 ó 1;

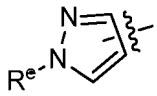
siempre que se excluyan los siguientes compuestos:





En un segundo aspecto, la presente invención incluye un compuesto de la Fórmula (I), un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de aquel, dentro del alcance del primer aspecto, en donde:

R^1 se selecciona independientemente del grupo que consiste en: $-CONHC_{4-18}$ alquilo, $-CONH(CH_2)_{1-8}Ph$, C_{1-12} alquilo sustituido con 0-2 R^a, C_{1-12} alquenilo sustituido con 0-2 R^a, C_{1-12} alquinilo sustituido con 0-2 R^a, $(CH_2)_m$-(fenilo sustituido con 0-1 R^b y 0-2 R^g), $(CH_2)_m$-(C_{3-6} cicloalquilo sustituido con 0-1 R^b) y $-(CH_2)_m$-(heteroarilo de 5 a 6 miembros sustituido con 0-1 R^b y 0-2 R^g), en donde el heteroarilo se selecciona de piridilo, oxazolilo, tiazolilo y



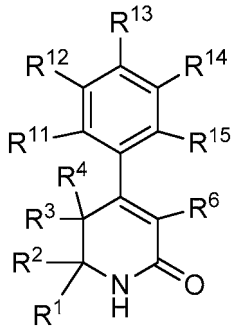
En un tercer aspecto, la presente invención incluye un compuesto de la Fórmula (I), un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de aquel, dentro del alcance del primero o segundo aspecto, en donde:

R^{11} y R^{15} se seleccionan independientemente del grupo que consiste en: H, C_{1-4} alquilo y halo;

R^{12} y R^{14} se seleccionan independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo y C_{1-4} alcoxi; y

R^{13} se selecciona independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo sustituido con 0-1 R^i, C_{1-4} alcoxi, C_{1-4} haloalquilo, C_{1-4} haloalcoxi, $-(CH_2)_m-C_{3-4}$ cicloalquilo, CN, NR^fR^j, SR^j, $NHCO_2(C_{1-4}$ alquilo), $NHSO_2(C_{1-4}$ alquilo) y un heterociclo de 4 a 6 miembros, que comprende: átomos de carbono y 1 a 4 heteroátomos seleccionados de N, NR^e, O y S.

En un cuarto aspecto, la presente invención provee un compuesto de la Fórmula (II):

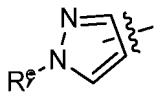


(II)

o un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de aquel, dentro del alcance de cualquiera de los aspectos anteriores.

En un quinto aspecto, la presente invención incluye un compuesto de las Fórmulas (I) o (II), un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de aquel, dentro del alcance de cualquiera de los aspectos anteriores, en donde:

R^1 se selecciona independientemente del grupo que consiste en: C_{1-6} alquilo, C_{3-6} cicloalquilo, $-CONHC_{4-18}$ alquilo, $-CONHC_{2-8}$ haloalquilo, $-CONH(CH_2)_{1-8}Ph$, $(CH_2)_m$-(fenilo sustituido con 1 R^b y 0-2 R^g) y un heteroarilo de 5 a 6 miembros sustituido con 0-1 R^b y 0-2 R^g, en donde el heteroarilo se selecciona de piridilo, oxazolilo, tiazolilo y



R^2 se selecciona independientemente del grupo que consiste en: C_{1-4} alquilo y C_{1-4} haloalquilo;

R^3 se selecciona independientemente del grupo que consiste en: H y F;

R^4 se selecciona independientemente del grupo que consiste en: H y F;

R^6 se selecciona independientemente del grupo que consiste en: CN, NH_2, $-CONH(C_{1-6}$ alquilo), R^c, $(CH_2)_n$-$(X)_t$-

$(CH_2)_mR^c$, $-NHCO(CH_2)SO_2(C_{1-4}$ alquilo), $-NHCOCH_2PO(OEt)_2$, $-NHCOCO(C_{1-4}$ alquilo), $-NHCOCH(OH)(C_{1-4}$ alquilo), $-NHCOCH_2CO(C_{1-4}$ alquilo), $-NHCONH(C_{1-4}$ alquilo) y $-OCONH(C_{1-4}$ alquilo);

R^{11} y R^{15} se seleccionan independientemente del grupo que consiste en: H, C_{1-4} alquilo y halo;

R^{12} y R^{14} se seleccionan independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo y C_{1-4} alcoxi;

R^{13} se selecciona independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo sustituido con 0-1 C_{1-4} alcoxi, C_{1-4} alcoxi, C_{1-4} haloalquilo, C_{1-4} haloalcoxi, C_{3-4} cicloalquilo, CN, $N(C_{1-4}$ alquilo$)_2$, $NHCO_2(C_{1-4}$ alquilo), $NHSO_2(C_{1-4}$ alquilo), pirazolilo y morfolinilo;

de manera alternativa, R^{12} y R^{13}, junto con los átomos de carbono a los que están unidos, se combinan para formar un anillo carbocíclico de 5 a 6 miembros o un anillo heterocíclico de 5 a 6 miembros, que comprende átomos de carbono y 1 3 heteroátomos seleccionados de N, NR^e, O y S;

R^b, en cada caso, se selecciona independientemente del grupo que consiste en halo, OH, C_{1-8} alquilo, C_{1-8} alcoxi, C_{1-8} haloalquilo, C_{1-10} haloalcoxi, $O(CH_2)_sO(C_{1-6}$ alquilo), $N(C_{1-4}$ alquilo$)_2$, $-CONH(CH_2)_{6-20}H$, $(CH_2)_m(C_{3-6}$ cicloalquilo), $(CH_2)_m(C_{4-6}$ cicloalquenilo), $O(CH_2)_m(C_{3-6}$ cicloalquilo), 4-C_{1-4} alcoxi-Ph, $O(CH_2)_mPh$, morfolinilo, piridilo, 2-C_{1-4} alcoxi-piridin-5-ilo, pirimidinilo, pirazinilo y -O-pirimidinilo;

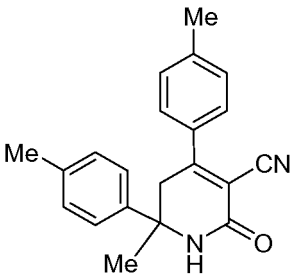
R^g, en cada caso, se selecciona independientemente

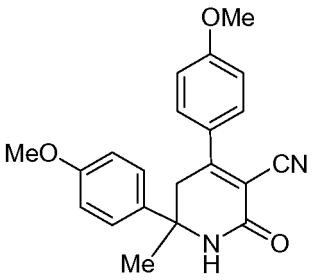
del grupo que consiste en halo, C_{1-4} alquilo, C_{1-4} alcoxi, C_{1-4} haloalquilo y C_{1-4} haloalcoxi;

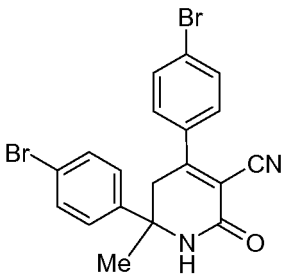
m, en cada caso, es independientemente 0, 1, 2 ó 3; y

s, en cada caso, es independientemente 1, 2 ó 3;

siempre que se excluyan los siguientes compuestos:



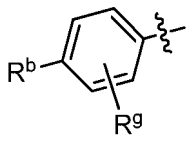
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En un sexto aspecto, la presente invención incluye un compuesto de las Fórmulas (I) o (II), un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de aquel, dentro del alcance de cualquiera de los aspectos anteriores, en donde:

R^1 se selecciona independientemente del grupo que consiste en: C_{1-6} alquilo, $-CONHC_{4-18}$ alquilo, $-CONH(CH_2)_{1-8}Ph$ y



;

R^6 se selecciona independientemente del grupo que consiste en: CN, NH2, $-CONH(C_{1-6}$ alquilo), $-NHCOCH_2PO(OEt)_2$, $-NHCO(CH_2)SO_2(C_{1-4}$ alquilo), R^c, OR^c, $-CONHR^c$ y $-NHCOR^c$;

R^{12} se selecciona independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo y C_{1-4} alcoxi;

R^{13} se selecciona independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo sustituido con 0-1 C_{1-4} alcoxi, C_{1-4} alcoxi, C_{1-4} haloalquilo, C_{1-4} haloalcoxi, C_{3-4} cicloalquilo, CN, $N(C_{1-4}$ alquilo$)_2$, $NHCO_2(C_{1-4}$ alquilo), $NHSO_2(C_{1-4}$ alquilo), pirazolilo y morfolinilo;

de manera alternativa, R^{12} y R^{13}, junto con los átomos de carbono a los que están unidos, se combinan para formar un anillo carbocíclico de 5 a 6 miembros o un anillo heterocíclico saturado de 5 a 6 miembros, que comprende átomos de carbono y 12 átomos de oxígeno;

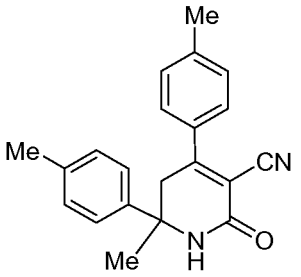
R^{14} se selecciona independientemente del grupo que consiste en: H y C_{1-4} alcoxi;

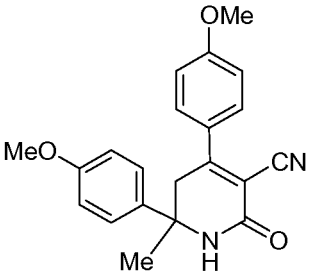
R^b, en cada caso, se selecciona independientemente del grupo que consiste en halo, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} haloalquilo, C_{1-10} haloalcoxi, $O(CH_2)_sO(C_{1-6}$ alquilo), $-CONH(CH_2)_{6-20}H$, $(CH_2)_m(C_{3-6}$ cicloalquilo), $(CH_2)_m(C_{4-6}$ cicloalquenilo), $-O(CH_2)_m(C_{3-6}$ cicloalquilo), fenoxi, benzoxi, morfolinilo, 2-C_{1-4} alcoxi piridin-5-ilo, pirimidin-5-ilo, pirazin-2-ilo y -O-pirimidinilo; y

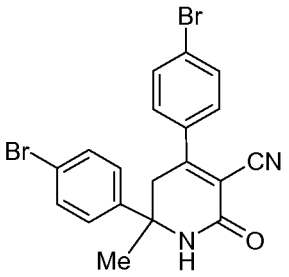
R^c, en cada caso, se selecciona independientemente del grupo que consiste en: C_{3-6} cicloalquilo sustituido con 0-2 R^d, $-(CH_2)_m$-(fenilo sustituido con 0-3 R^d) y un heteroarilo seleccionado de oxazolilo, isoxazolilo, tiazolilo,

pirazolilo, imidazolilo, oxadiazolilo, triazolilo, tetrazolilo, piridilo y pirazinilo; en donde el heteroarilo se sustituye con 0-2 R^d; y

siempre que se excluyan los siguientes compuestos:

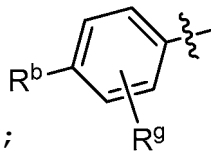


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En un séptimo aspecto, la presente invención incluye un compuesto de las Fórmulas (I) o (II), un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de aquel, dentro del alcance de cualquiera de los aspectos anteriores, en donde:

R^1 es ; 

R^6 se selecciona independientemente del grupo que consiste en: NH_2, CN, -CONH(C_{1-4} alquilo), OPh, -CONH(C_{3-6} cicloalquilo), -CONHPh, -CONH(2-halo-Ph), -CONH(3-halo-Ph), -CONH-(4-halo-Ph), -CONH-(4-C_{1-4} alquil-Ph), -CONH(4-OH-Ph), -CONH-(3-C_{1-4} alcoxi-Ph), -CONH-(4-C_{1-4} alcoxi-Ph), -CONH-(4-C_{1-4} haloalquil-Ph), -CONH-(4-C_{1-4} haloalcoxi-Ph), -CONH-(4-CN-Ph), -CONH-(4-tetrazolil-Ph), -CONH-(3-halo-4-C_{1-4} alquil-Ph), -CONH-(3-halo-4-C_{1-4} alcoxi-Ph), -CONH$(CH_2)_2$Ph, -CONH(4-(4-C_{1-4}

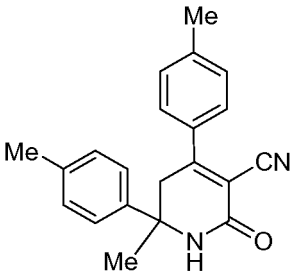
alcoxi-Ph)-tiazol-2-ilo), -CONH(1-C_{1-4} alquil-pirazol-3-ilo), -CONH(5-C_{1-4} alcoxi-pirid-2-ilo), -CONH(6-C_{1-4} alcoxi-pirid-3-ilo), -CONH(5-C_{1-4} alcoxi-pirazin-2-ilo), -CONH(6-C_{1-4} alcoxi-piridazin-3-ilo), -NHCO(CH_2)SO_2(C_{1-4} alquilo), -NHCOPh, -NHCO(2-C_{1-4} alquil-Ph), -NHCO(3-C_{1-4} alquil-Ph), -NHCO(4-C_{1-4} alquil-Ph), -NHCO(2-halo-Ph), -NHCO(3-halo-Ph), -NHCO(2-C_{1-4} haloalquil-Ph), -NHCO(2-C_{1-4} haloalcoxi-Ph), -NHCO(2-halo-4-halo-Ph), -NHCO(2-halo-5-halo-Ph), -NHCO(oxazolilo), -NHCO(isoxazolilo), -NHCO(3-C_{1-4} alquil-isoxazol-5-ilo), -NHCO(4-C_{1-4} alquil-isoxazol-5-ilo), -NHCO(3-C_{1-4} alcoxi-isoxazol-5-ilo), -NHCO(4-C_{1-4} alcoxi-isoxazol-5-ilo), -NHCO(3-halo-isoxazol-5-ilo), -NHCO(3-OBn-isoxazol-5-ilo), -NHCO(3-(2-halo-Ph)-isoxazol-5-ilo), -NHCO(3-(3-halo-Ph)-isoxazol-5-ilo), -NHCO(5-C_{1-4} alquil-1H-pirazol-3-ilo), imidazolilo, -NHCO(5-C_{1-4} alquil-1,3,4-oxadiazol-2-ilo), -NHCO(1-C_{1-4} alquil-1,2,3-triazol-4-ilo), -NHCO(6-C_{1-4} alcoxi-pirid-3-ilo), -NHCO(pirazinilo), -NHCO(6-halo-piridazin-3-ilo), 5-C_{1-4} haloalquil-1,3,4-oxadiazol-2-ilo, 3-NO_2-1*H*-1,2,4-triazol-1-ilo, tetrazolilo y 5-C_{1-4} alquil-tetrazol-1-ilo;

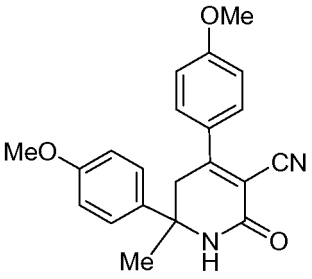
R^b se selecciona independientemente del grupo que consiste en halo, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} haloalquilo, C_{1-8} haloalcoxi, -CONH(CH_2)$_{6-20}$H, C_{3-6} cicloalquilo, C_{4-6} cicloalquenilo, O(CH_2)$_m$(C_{3-6} cicloalquilo), fenoxi, benzoxi, pirimidinilo, pirazinilo y -O-pirimidinilo; y

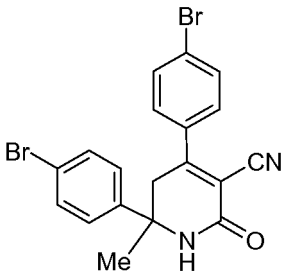
R^g se selecciona independientemente del grupo que

consiste en halo y C_{1-4} alquilo;

siempre que se excluyan los siguientes compuestos:



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En un octavo aspecto, la presente invención incluye un compuesto de las Fórmulas (I) o (II), un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de aquel, dentro del alcance de cualquiera de los aspectos anteriores, en donde:

R^2 se selecciona independientemente del grupo que consiste en: CF_3 y Me;

R^3 se selecciona independientemente del grupo que consiste en: H y F;

R^4 se selecciona independientemente del grupo que consiste en: H y F;

R^6 se selecciona independientemente del grupo que consiste en: NH_2, CN, -CONHMe, OPh, -CONH(ciclopropilo), -CONH(ciclobutilo), -CONH(ciclopentilo), -CONH(ciclohexilo), -CONHPh, -CONH(4-F-Ph), -CONH(2-Cl-Ph), -CONH(4-Cl-Ph), -CONH(4-Me-Ph), -CONH(4-OH-Ph), -CONH(3-OMe-Ph), -CONH(4-OMe-Ph), -CONH(4-CF_3-Ph), -CONH(4-OCF_3-Ph), -CONH(1-Me-pirazol-3-ilo), -CONH(4-(1*H* tetrazol-2-il)-Ph), -CONH(4-(2*H*-tetrazol-5-

il)-Ph), -CONH(3-F-4-Me-Ph), -CONH(3-F-4-OMe-Ph), -CONH$(CH_2)_2$Ph, -CONH(5-OMe-pirid-2-ilo), -CONH(6-OMe-pirid-3-ilo), -CONH(5-OMe-pirazin-2-ilo), -CONH(6-OMe-piridazin-3-ilo), -NHCO$(CH_2)SO_2$Me, -NHCOPh, -NHCO(2-Me-Ph), -NHCO(3-Me-Ph), -NHCO(4-Me-Ph), -NHCO(2-Cl-Ph), -NHCO(3-Cl-Ph), -NHCO(2-Cl-4-F-Ph), -NHCO(2-Cl-5-F-Ph), -NHCO(isoxazol-5-ilo), -NHCO(3-Me-isoxazol-5-ilo), -NHCO(4-Me-isoxazol-5-ilo), -NHCO(3-OMe-isoxazol-5-ilo), -NHCO(3-Br-isoxazol-5-ilo), -NHCO(3-(2-Cl-Ph)-isoxazol-5-ilo), -NHCO(3-(3-F-Ph)-isoxazol-5-ilo), -NHCO(3-OBn-isoxazol-5-ilo), 1H-imidazol-1-ilo, -NHCO(5-Me-1,3,4-oxadiazol-2-ilo), -NHCO(1-Me-1,2,3-triazol-4-ilo), -NHCO(6-OMe-pirid-3-ilo), -NHCO(6-Cl-piridazin-3-ilo), 5-CF3-1,3,4-oxadiazol-2-ilo, 1*H*-tetrazol-1-ilo, 1*H*-tetrazol-3-ilo y 2*H*-tetrazol-5-ilo;

R^{11} y R^{15} se seleccionan independientemente del grupo que consiste en: H, Me, F y Cl;

R^{12} se selecciona independientemente del grupo que consiste en: H, F, Cl, Me y OMe;

R^{13} se selecciona independientemente del grupo que consiste en: H, F, Cl, Br, Me, OMe, OEt, CH_2OMe, CF_3, CH_2CF_3, $OCHF_2$, OCF_3, CN, $N(Me)_2$, ciclopropilo y ciclopropilmetilo;

de manera alternativa, R^{12} y R^{13}, junto con los átomos de carbono a los que están unidos, se combinan para formar un anillo carbocíclico de 5 a 6 miembros o un anillo heterocíclico saturado de 5 a 6 miembros, que comprende

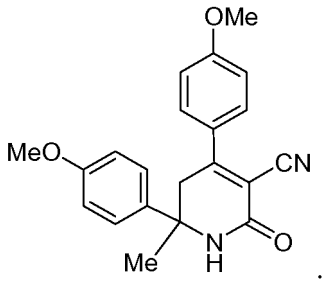
átomos de carbono y 1-2 átomos de oxígeno;

R^{14} es H;

R^b, en cada caso, se selecciona independientemente del grupo que consiste en n-pentilo, metoxi, n-butoxi, i-butoxi, i-pentoxi, $O(CH_2)_{1-6}CF_3$, $O(CH_2)_{1-4}CF_2CF_3$, $-CONH(CH_2)_{6-20}H$, ciclopropilo, ciclopent-1-en-1-ilo, ciclohex-1-en-1-ilo, $O(CH_2)_2$(ciclopentilo), fenoxi, benzoxi, pirimidin-5-ilo, pirazin-2-ilo y -O-pirimidin-2-ilo; y

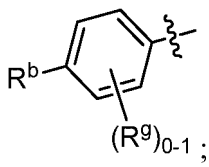
R^g es F;

siempre que se excluya el siguiente compuesto:



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En un noveno aspecto, la presente invención incluye un compuesto de las Fórmulas (I) o (II), un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de aquel, dentro del alcance de cualquiera del primer, segundo, tercer, cuarto, quinto y sexto aspectos anteriores, en donde:

R^1 es 

;

R^2 se selecciona independientemente de CF_3 y CH_3;

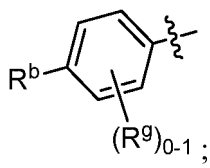
R^6 se selecciona independientemente de: CN, R^c, -$CONHR^c$, -$NHCOR^c$ y -$NHCOCH_2SO_2(C_{1-4}$ alquilo);

R^b se selecciona independientemente de: $O(CH_2)_{1-6}CF_3$, $O(CH_2)_{1-4}CF_2CF_3$, $-CONH(CH_2)_{6-20}H$, ciclopent-1-en-1-ilo, ciclohex-1-en-1-ilo, $O(CH_2)_2$(ciclopentilo), fenoxi, benzoxi, pirimidin-5-ilo, pirazin-2-ilo y -O-pirimidin-2-ilo;

R^c, en cada caso, se selecciona independientemente del grupo que consiste en: $-(CH_2)_m$-(fenilo sustituido con 0-3 R^d), y un heteroarilo seleccionado de oxazolilo, isoxazolilo, pirazolilo, imidazolilo, oxadiazolilo, triazolilo, tetrazolilo, piridilo y pirazinilo; en donde el heteroarilo se sustituye con 0-2 R^d; y

R^d, en cada caso, se selecciona independientemente del grupo que consiste en halo, OH, CN, C_{1-4} alquilo, C_{1-4} alcoxi, C_{1-4} haloalquilo, C_{1-4} haloalcoxi, tetrazolilo y OBn.

En otro aspecto, la presente invención incluye un compuesto de las Fórmulas (I) o (II), un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de aquel, dentro del alcance de cualquiera del primer, segundo, tercer, cuarto, quinto, sexto y noveno aspectos anteriores, en donde:

R^1 es 

;

R^2 se selecciona independientemente de CF_3 y CH_3;

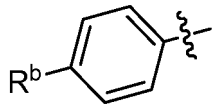
R^6 se selecciona independientemente de: CN, R^c, -$CONHR^c$, -$NHCOR^c$ y -$NHCOCH_2SO_2(C_{1-4}$ alquilo);

R^{11}, R^{12}, R^{14} y R^{15} son H;

R^{13} se selecciona independientemente del grupo que consiste en: H, C_{1-4} alquilo, C_{1-4} haloalquilo, C_{1-4} alcoxi y C_{1-4} haloalcoxi; y

R^b se selecciona independientemente de: $O(CH_2)_{1-6}CF_3$ y $O(CH_2)_{1-4}CF_2CF_3$.

En otro aspecto, la presente invención incluye un compuesto de la Fórmula (II), o un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de aquel, dentro del alcance del cuarto o quinto aspecto, en donde:

R^1 es  ;

R^2 se selecciona independientemente de CF_3 y CH_3;

R^3 y R^4 son H;

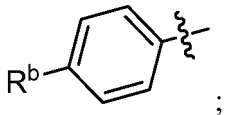
R^6 es independientemente un heteroarilo de nitrógeno de 5 miembros;

R^{11}, R^{12}, R^{14} y R^{15} son H;

R^{13} se selecciona independientemente del grupo que consiste en: H, C_{1-4} alquilo, C_{1-4} haloalquilo, C_{1-4} alcoxi y C_{1-4} haloalcoxi; y

R^b se selecciona independientemente de: $O(CH_2)_{1-6}CF_3$ y $O(CH_2)_{1-4}CF_2CF_3$.

En otro aspecto, la presente invención incluye un compuesto de la Fórmula (II), un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de aquel, dentro del alcance del cuarto o quinto aspecto, en donde:

R^1 es  ;

R^2 se selecciona independientemente de CF_3 y CH_3;

R^3 y R^4 son H;

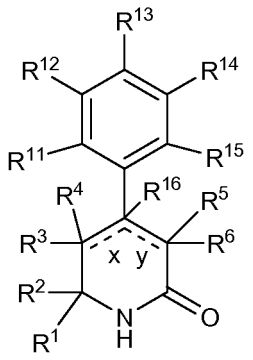
R^6 se selecciona independientemente de: 1*H*-imidazol-1-ilo, 1*H* tetrazol-1-ilo, 1*H*-tetrazol-3-ilo y 2*H*-tetrazol-5-ilo;

R^{11}, R^{12}, R^{14} y R^{15} son H;

R^{13} se selecciona independientemente del grupo que consiste en: H, Me, OMe y $OCHF_2$; y

R^b se selecciona independientemente de: $O(CH_2)_{1-6}CF_3$ y $O(CH_2)_{1-4}CF_2CF_3$.

En un décimo aspecto, la presente invención provee, entre otros, un compuesto de la Fórmula (I):



(I)

o un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de aquel, en donde:

--- indica un enlace simple o doble;

x e y pueden ser ambos un enlace simple; en donde x es un enlace doble, y es un enlace simple, y R^4 y R^{16} están ausentes; en donde y es un enlace doble, x es un enlace simple, y R^5 y R^{16} están ausentes;

R^1 se selecciona independientemente del grupo que consiste en:

$-(CH_2)_m-(C_{3-10}$ carbociclo sustituido con 0-3 R^b) o una cadena de hidrocarburos C_{1-12} sustituida con 0-3 R^a; en donde la cadena de hidrocarburos puede ser lineal o ramificada, saturada o insaturada;

R^2 se selecciona independientemente del grupo que consiste en: C_{1-4} alquilo y C_{1-4} haloalquilo;

R^3 se selecciona independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo y CN;

R^4 y R^5 se seleccionan independientemente del grupo que consiste en: H, halo y C_{1-4} alquilo;

en donde x es un enlace simple, R^3 y R^4 se pueden combinar con el átomo de carbono al que están unidos para formar un carbociclo de 3 a 6 miembros;

R^6 se selecciona independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo, CN, NO_2 y $-(CH_2)_n-(X)_t-$

$(CH_2)_mR^c$;

X se selecciona independientemente del grupo que consiste en: O, S, NH, -CONH y NHCO;

en donde y es un enlace simple, R^5 y R^6 se pueden combinar con el átomo de carbono al que están unidos para formar un carbociclo de 3 a 6 miembros;

R^{11}, R^{12}, R^{13}, R^{14} y R^{15} se seleccionan independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo, C_{1-4} alcoxi, C_{1-4} haloalquilo, C_{1-4} haloalcoxi, CN y un heterociclo de 5 a 6 miembros que comprende átomos de carbono y 1 a 4 heteroátomos seleccionados de N, NR^e, O y S;

R^{16} se selecciona independientemente del grupo que consiste en: H y C_{1-4} alquilo;

R^a, en cada caso, se selecciona independientemente del grupo que consiste en halo, OH, C_{1-6} alcoxi, C_{1-6} haloalquilo, C_{1-6} haloalcoxi, $N(C_{1-4}$ alquil$)_2$, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$ y $-(CH_2)_n-(CH_2O)_m-(CH_2)_nR^f$;

R^b, en cada caso, se selecciona independientemente del grupo que consiste en halo, OH, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} haloalquilo, C_{1-6} haloalcoxi, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$ y $-(CH_2)_n-(CH_2O)_m-(CH_2)_nR^f$;

R^c se selecciona independientemente del grupo que consiste en: C_{3-6} cicloalquilo sustituido con 0-2 R^d, fenilo sustituido con 0-3 R^d y un heterociclo de 5 a 6 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de

N, NR^e, O y S; en donde el heterociclo se sustituye con 0-2 R^d;

R^d, en cada caso, se selecciona independientemente del grupo que consiste en halo, OH, CN, C_{1-4} alquilo, C_{1-4} alcoxi, C_{1-4} haloalquilo y C_{1-4} haloalcoxi;

R^e se selecciona independientemente del grupo que consiste en: H, C_{1-4} alquilo, bencilo, CO(C_{1-4} alquilo) y COBn;

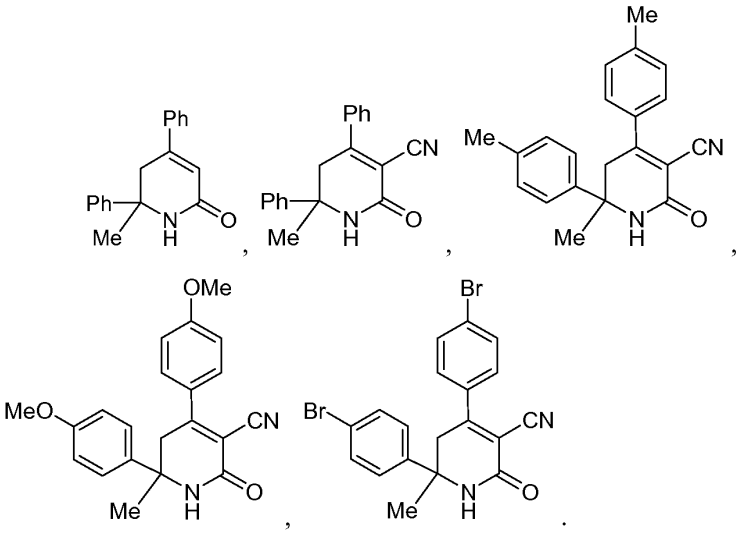
R^f se selecciona independientemente del grupo que consiste en: H y C_{1-4} alquilo;

n, en cada caso, es independientemente 0 ó 1;

m, en cada caso, es independientemente 0, 1, 2, 3 ó 4; y

t, en cada caso, es independientemente 0 ó 1;

siempre que los siguientes compuestos estén excluidos



En un undécimo aspecto, la presente invención incluye un compuesto de la Fórmula (I), un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un

solvato de aquel, dentro del alcance del décimo aspecto, en donde:

R^1 se selecciona independientemente del grupo que consiste en: C_{1-6} alquilo sustituido con 0-2 R^a, $(CH_2)_m$-(fenilo sustituido con 0-3 R^b) y -$(CH_2)_m$-(C_{3-6} cicloalquilo sustituido con 0-2 R^b).

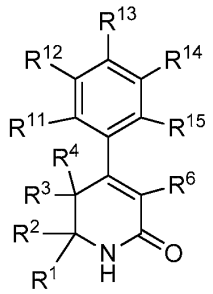
En un duodécimo aspecto, la presente invención incluye un compuesto de la Fórmula (I), un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de aquel, dentro del alcance del décimo y undécimo aspecto, en donde:

R^{11} y R^{15} se seleccionan independientemente del grupo que consiste en: H y halo;

R^{12} y R^{14} se seleccionan independientemente del grupo que consiste en: H, C_{1-4} alquilo y C_{1-4} alcoxi; y

R^{13} se selecciona independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo, C_{1-4} alcoxi, C_{1-4} haloalquilo, C_{1-4} haloalcoxi, CN y morfolinilo.

En un décimo tercer aspecto, la presente invención provee un compuesto de la Fórmula (II)

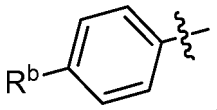


(II)

o un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de aquel, dentro del alcance de cualquiera del décimo, undécimo y duodécimo aspectos anteriores.

En un décimo cuarto aspecto, la presente invención incluye un compuesto de las Fórmulas (I) o (II), un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de aquel, dentro del alcance del décimo, undécimo, duodécimo y décimo tercer aspectos, en donde:

R^1 se selecciona independientemente del grupo que consiste en: C_{1-6} alquilo, C_{3-6} cicloalquilo, $(CH_2)_mPh$ y



;

R^2 se selecciona independientemente del grupo que consiste en: C_{1-4} alquilo y C_{1-4} haloalquilo;

R^3 es H;

R^4 es H;

R^6 se selecciona independientemente del grupo que consiste en: CN, NO_2, -CONH(C_{1-6} alquilo), -CONHPh, -CONH-(3-halo-Ph), -CONH-(4-halo-Ph), -CONH-(4-C_{1-4} alquil-Ph), -CONH-(3-C_{1-4} alcoxi-Ph), -CONH-(4-C_{1-4} alcoxi-Ph), -CONH-(4-C_{1-4} haloalquil-Ph), -CONH-(4-C_{1-4} haloalcoxi-Ph), -CONH-(3-halo-4-C_{1-4} alquil-Ph), -CONH-(3-halo-4-C_{1-4} alcoxi-Ph), -CONH$(CH_2)_2$Ph

y 2H-tetrazol-5-ilo;

R^{11} y R^{15} se seleccionan independientemente del grupo que consiste en: H y halo;

R^{12} y R^{14} se seleccionan independientemente del grupo que consiste en: H, C_{1-4} alquilo y C_{1-4} alcoxi;

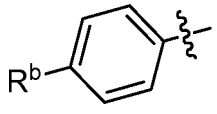
R^{13} se selecciona independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo, C_{1-4} alcoxi, C_{1-4} haloalquilo, C_{1-4} haloalcoxi, CN y morfolinilo;

R^b se selecciona independientemente del grupo que consiste en halo, OH, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} haloalquilo, C_{1-6} haloalcoxi, $O(CH_2)_mO(C_{1-4}$ alquilo), $N(C_{1-4}$ alquilo$)_2$, $O(CH_2)_m(C_{3-6}$ cicloalquilo), 4-C_{1-4} alcoxi-Ph, $O(CH_2)_mPh$, piridin-2-ilo, 2-C_{1-4} alcoxi-piridin-5-ilo, pirimidin-5-ilo, pirazin-2-ilo y -O-pirimidin-2-ilo; y

m, en cada caso, es independientemente 0, 1, 2 ó 3.

En un décimo quinto aspecto, la presente invención incluye un compuesto de las Fórmulas (I) o (II), un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de aquel, dentro del alcance del décimo, undécimo, duodécimo, décimo tercer y décimo cuarto aspectos, en donde:

R^1 se selecciona independientemente del grupo que consiste en: C_{1-6} alquilo y



;

R^6 se selecciona independientemente del grupo que consiste en: CN, -CONH(C_{1-6} alquilo), -CONHPh, -CONH-(3-halo-Ph), -CONH-(4-halo-Ph), -CONH-(4-C_{1-4} alquil-Ph), -CONH-(3-C_{1-4} alcoxi-Ph), -CONH-(4-C_{1-4} alcoxi-Ph), -CONH-(4-C_{1-4} haloalquil-Ph), -CONH-(4-C_{1-4} haloalcoxi-Ph), -CONH-(3-halo-4-C_{1-4} alcoxi-Ph), -CONH$(CH_2)_2$Ph y 2*H*-tetrazol-5-ilo;

R^{12} se selecciona independientemente del grupo que consiste en: H, C_{1-4} alquilo y C_{1-4} alcoxi;

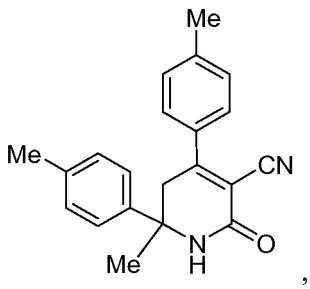
R^{14} se selecciona independientemente del grupo que consiste en: H y C_{1-4} alcoxi;

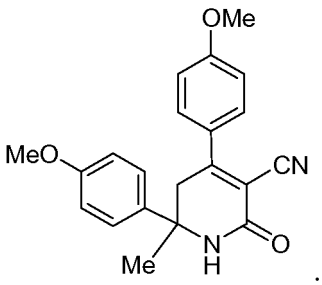
R^{13} se selecciona independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo, C_{1-4} alcoxi, C_{1-4} haloalquilo, C_{1-4} haloalcoxi y CN;

R^b se selecciona independientemente del grupo que consiste en: C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} haloalquilo, C_{1-6} haloalcoxi, $O(CH_2)_mO(C_{1-4}$ alquilo), $-O(CH_2)_m(C_{3-6}$ cicloalquilo), fenoxi, benzoxi, 2-C_{1-4} alcoxi-piridin-5-ilo, pirimidin-5-ilo, pirazin-2-ilo y -O-pirimidin-2-ilo; y

m, en cada caso, es independientemente 0, 1, 2 ó 3;

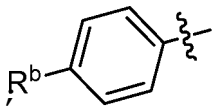
siempre que se excluyan los siguientes compuestos:



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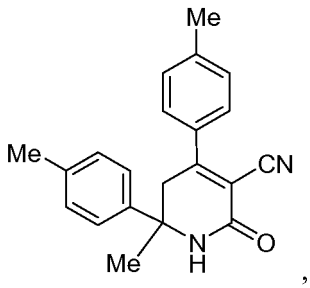
En un décimo sexto aspecto, la presente invención incluye un compuesto de las Fórmulas (I) o (II), un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de aquel, dentro del alcance del noveno, décimo, undécimo, duodécimo, décimo tercer, décimo cuarto y décimo quinto aspectos, en donde:

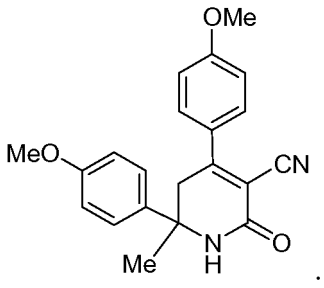
R^1 es  ;

R^6 se selecciona independientemente del grupo que consiste en: CN, -CONHPh, -CONH-(4-halo-Ph), -CONH-(4-C_{1-4} alquil-Ph), -CONH-(3-C_{1-4} alcoxi-Ph), -CONH-(4-C_{1-4} alcoxi-Ph), -CONH-(4-C_{1-4} haloalquil-Ph), -CONH-(4-C_{1-4} haloalcoxi-Ph), -CONH-(3-halo-4-C_{1-4} alcoxi-Ph), -CONH$(CH_2)_2$Ph y 2*H*-tetrazol-5-ilo; y

R^b se selecciona independientemente del grupo que consiste en: C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} haloalquilo, C_{1-6} haloalcoxi, O$(CH_2)_m$(C_{3-6} cicloalquilo), fenoxi, benzoxi, pirimidin-5-ilo, pirazin-2-ilo y -O-pirimidin-2-ilo;

siempre que los siguientes compuestos estén excluidos



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En un décimo séptimo aspecto, la presente invención incluye un compuesto de las Fórmulas (I) o (II), un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de aquel, dentro del alcance del noveno, décimo, undécimo, duodécimo, décimo tercer, décimo cuarto, décimo quinto y décimo sexto aspectos, en donde:

R^2 se selecciona independientemente del grupo que consiste en: CF_3 y Me;

R^6 se selecciona independientemente del grupo que consiste en: CN, -CONHPh, -CONH-(4-F-Ph), -CONH-(4-Cl-Ph), -CONH-(4-Me-Ph), -CONH-(3-OMe-Ph), -CONH-(4-OMe-Ph), -CONH-(4-CF_3-Ph), -CONH-(4-OCF_3-Ph), -CONH-(3-F-4-OMe-Ph), -$CONH(CH_2)_2$Ph y 2*H*-tetrazol-5-ilo;

R^{11} y R^{15} se seleccionan independientemente del grupo que consiste en: H y F;

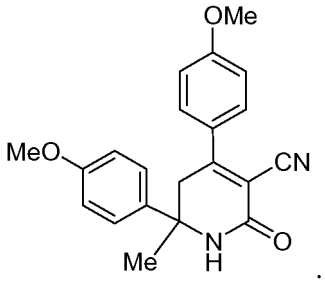
R^{12} se selecciona independientemente del grupo que consiste en: H, Me y OMe;

R^{13} se selecciona independientemente del grupo que consiste en: H, F, Cl, Me, OMe, OEt, CF_3, $OCHF_2$, OCF_3 y CN;

R^{14} es H; y

R^b se selecciona independientemente del grupo que consiste en n-pentilo, metoxi, n-butoxi, i-butoxi, $O(CH_2)_{1-3}CF_3$, $O(CH_2)_2$(ciclopentilo), fenoxi, benzoxi, pirimidin-5-ilo, pirazin-2-ilo y -O-pirimidin-2-ilo;

siempre que se excluyan los siguientes compuestos:



.

En una décimo octavo aspecto, la presente invención provee un compuesto seleccionado de los ejemplos o un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de aquel.

En otro aspecto, la presente invención provee un compuesto seleccionado de cualquier lista de subconjuntos de compuestos o un solo compuesto de los ejemplos, dentro del alcance de cualquiera de los aspectos anteriores.

En otro aspecto, la presente descripción provee un compuesto seleccionado de:

(*S*)-3-(1*H*-tetrazol-5-il)-4-(p-tolil)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-5,6-dihidropiridin-2(1*H*)-ona,

(*S*)-N-(4-metoxifenil)-2-oxo-4-(p-tolil)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carboxamida,

(*S*)-3-(2*H*-tetrazol-5-il)-4-(p-tolil)-6-(4-((6,6,6-trifluorohexil)oxi)fenil)-6-(trifluorometil)-5,6-dihidropiridin-2(1*H*)-ona,

(*S*)-2-oxo-4-(p-tolil)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carbonitrilo,

(*S*)-2-oxo-4-(p-tolil)-6-(4-(4,4,4-trifluorobutoxi)fenil)-N-(4-(trifluorometoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carboxamida,

(*S*)-N-(6-metoxipiridin-3-il)-2-oxo-4-(p-tolil)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carboxamida,

(*S*)-N-ciclopropil-2-oxo-4-(p-tolil)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carboxamida,

(*S*)-N-(4-hidroxifenil)-2-oxo-4-(p-tolil)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carboxamida,

(*S*)-4-(4-(difluorometoxi)fenil)-2-oxo-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carbonitrilo,

(*S*)-2-oxo-4-(p-tolil)-6-(trifluorometil)-6-(4-(3,3,3-trifluoropropoxi)fenil)-1,2,5,6-tetrahidropiridin-3-carbonitrilo,

(*S*)-4-(4-(difluorometoxi)fenil)-3-(1*H*-tetrazol-1-il)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-5,6-dihidropiridin-2(1*H*)-ona,

(*S*)-3-metil-N-(2-oxo-4-(p-tolil)-6-(4-(4,4,4-

trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-il)isoxazol-5-carboxamida,

(*S*)-5-metil-N-(2-oxo-4-(p-tolil)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-il)-1,3,4-oxadiazol-2-carboxamida,

N^2-heptil-N^5-(4-metoxifenil)-2-metil-6-oxo-4-(p-tolil)-1,2,3,6-tetrahidropiridin-2,5-dicarboxamida,

(*S*)-3-(1*H*-tetrazol-1-il)-4-(p-tolil)-6-(4-((6,6,6-trifluorohexil)oxi)fenil)-6-(trifluorometil)-5,6-dihidropiridin-2(1*H*)-ona,

(*S*)-2-oxo-4-(p-tolil)-6-(4-((6,6,6-trifluorohexil)oxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carbonitrilo,

(*S*)-4-(5,6,7,8-tetrahidronaftalen-2-il)-3-(1*H*-tetrazol-5-il)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-5,6-dihidropiridin-2(1*H*)-ona,

(*S*)-2-(metilsulfonil)-N-(2-oxo-4-(p-tolil)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-il)acetamida,

(*S*)-3-(1*H*-tetrazol-5-il)-6-(4-(4,4,4-trifluorobutoxi)fenil)-4-(4-(2,2,2-trifluoroetil)fenil)-6-(trifluorometil)-5,6-dihidropiridin-2(1*H*)-ona, y

(*S*)-N-(5-metoxipirazin-2-il)-2-oxo-4-(p-tolil)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carboxamida;

o una sal de aquel aceptable desde el punto de vista farmacéutico.

En otra modalidad, R^1 es independientemente -$CONH(C_{4-18}$ alquilo), -$CONHC_{2-8}$ haloalquilo o -$CONH(CH_2)_{1-8}$Ph.

En otra modalidad, R^1 es -$(CH_2)_m$-(C_{3-10} carbociclo sustituido con 0-2 R^b y 0-2 R^g) o -$(CH_2)_m$-(heteroarilo de 5 a 6 miembros que comprende átomos de carbono y 1 a 4 heteroátomos seleccionados de N, NR^e, O y S; en donde el heteroarilo se sustituye con 0-1 R^b y 0-2 R^g).

En otra modalidad, R^1 es -$(CH_2)_m$-(C_{3-10} carbociclo sustituido con 0-2 R^b y 0-2 R^g).

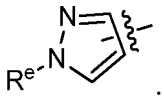
En otra modalidad, R^1 es -$(CH_2)_m$-(fenilo sustituido con 0-2 R^b y 0-2 R^g).

En otra modalidad, R^1 es -$(CH_2)_m$-(heteroarilo de 5 a 6 miembros que comprende átomos de carbono y 1 a 4 heteroátomos seleccionados de N, NR^e, O y S; en donde el heteroarilo se sustituye con 0-1 R^b y 0-2 R^g).

En otra modalidad, R^1 es una cadena de hidrocarburos C_{1-12} sustituida con 0-3 R^a; en donde la cadena de hidrocarburos puede ser lineal o ramificada, saturada o insaturada.

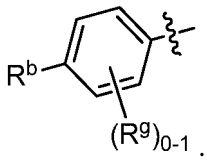
En otra modalidad, R^1 es independientemente: C_{1-6} alquilo, C_{3-6} cicloalquilo, -$CONHC_{4-18}$ alquilo, -$CONHC_{2-8}$ haloalquilo, -$CONH(CH_2)_{1-8}$-Ph, $(CH_2)_m$-(fenilo sustituido con 1 R^b y 0-2 R^g), o un heteroarilo de 5 a 6 miembros sustituido

con 0-1 R^b y 0-2 R^g, en donde el heteroarilo se selecciona de piridilo, oxazolilo, tiazolilo y

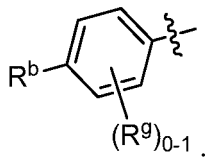


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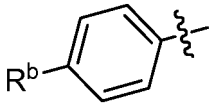
En otra modalidad, R^1 es independientemente: C_{1-6} alquilo, $-CONHC_{4-18}$ alquilo, $-CONH(CH_2)_{1-8}Ph$ o



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En otra modalidad, R^1 es  .

En otra modalidad, R^1 es independientemente



.

En otra modalidad, R^2 es independientemente C_{1-4} alquilo o C_{1-4} haloalquilo.

En otra modalidad, R^2 es C_{1-4} alquilo.

En otra modalidad, R^2 es C_{1-4} haloalquilo.

En otra modalidad, R^2 es independientemente CF_3 o Me.

En otra modalidad, R^2 es CF_3.

En otra modalidad, R^2 es Me.

En otra modalidad, R^3 es independientemente H o F.

En otra modalidad, R^3 es H.

En otra modalidad, R^3 es F.

En otra modalidad, R^4 es independientemente H o F.

En otra modalidad, R^4 es H.

En otra modalidad, R^4 es F.

En otra modalidad, R^5 es independientemente H o F.

En otra modalidad, R^5 es H.

En otra modalidad, R^5 es F.

En otra modalidad, R^6 es independientemente C_{1-4} alquilo, CN, R^c o $(CH_2)_n-(X)_t-(CH_2)_mR^c$.

En otra modalidad, R^6 es independientemente $-CONH(C_{1-6}$ alquilo), $-NHCOX_1SO_2R^j$, $-NHCOCOR^j$, $-NHCOCH(OH)R^j$, $-NHCOCH_2COR^j$, $-NHCONHR^j$ u $-OCONR^fR^j$.

En otra modalidad, R^6 es independientemente CN, NH_2, $-CONH(C_{1-6}$ alquilo), R^c, $(CH_2)_n-(X)_t-(CH_2)_mR^c$, $-NHCO(CH_2)SO_2(C_{1-4}$ alquilo), $-NHCOCO(C_{1-4}$ alquilo), $-NHCOCH(OH)(C_{1-4}$ alquilo), $-NHCOCH_2CO(C_{1-4}$ alquilo), $-NHCONH(C_{1-4}$ alquilo) o $-OCONH(C_{1-4}$ alquilo).

En otra modalidad, R^6 es independientemente CN, NH_2, $-CONH(C_{1-6}$ alquilo), $-NHCO(CH_2)SO_2(C_{1-4}$ alquilo), R^c, OR^c, $-CONHR^c$ o $-NHCOR^c$.

En otra modalidad, R^6 es independientemente CN, NH_2, $-CONH(C_{1-6}$ alquilo), $-NHCO(CH_2)SO_2(C_{1-4}$ alquilo), R^c, OR^c, $-CONHR^c$ o $-NHCOR^c$.

En otra modalidad, R^6 es independientemente CN, R^c, $-CONHR^c$, $-NHCOR^c$ o $-NHCOCH_2SO_2(C_{1-4}$ alquilo).

En otra modalidad, R^6 es independientemente un heteroarilo de nitrógeno de 5 miembros.

En otra modalidad, R^6 es independientemente: 1*H*-imidazol-1-ilo, 1*H* tetrazol-1-ilo, 1*H*-tetrazol-3-ilo o 2*H*-tetrazol-5-ilo.

En otra modalidad, R^{11} es independientemente H, C_{1-4} alquilo o halo.

En otra modalidad, R^{11} es independientemente H, Me, F o Cl.

En otra modalidad, R^{11} es H.

En otra modalidad, R^{11} es C_{1-4} alquilo.

En otra modalidad, R^{11} es Me.

En otra modalidad, R^{11} es halo.

En otra modalidad, R^{11} es independientemente F o Cl.

En otra modalidad, R^{12} es independientemente H, halo, C_{1-4} alquilo o C_{1-4} alcoxi.

En otra modalidad, R^{12} es independientemente H, F, Cl, Me y OMe.

En otra modalidad, R^{12} es H.

En otra modalidad, R^{12} es C_{1-4} alquilo.

En otra modalidad, R^{12} es Me.

En otra modalidad, R^{12} es C_{1-4} alcoxi.

En otra modalidad, R^{12} es OMe.

En otra modalidad, R^{12} es halo.

En otra modalidad, R^{12} es independientemente F o Cl.

En otra modalidad, R^{13} es independientemente: H, halo, C_{1-4} alquilo sustituido con 0-1 R^i, C_{1-4} alcoxi, C_{1-4}

haloalquilo, C_{1-4} haloalcoxi, C_{3-4} cicloalquilo, CN, NR^fR^j, SR^j, $NHCO_2(C_{1-4}$ alquilo), $NHSO_2(C_{1-4}$ alquilo) o un heterociclo de 4 a 6 miembros, que comprende átomos de carbono y 1 a 4 heteroátomos seleccionados de N, NR^e, O y S.

En otra modalidad, R^{13} es independientemente: H, halo, C_{1-4} alquilo sustituido con 0-1 C_{1-4} alcoxi, C_{1-4} alcoxi, C_{1-4} haloalquilo, C_{1-4} haloalcoxi, CN, C_{3-4} cicloalquilo, $N(C_{1-4}$ alquilo)$_2$, $NHCO_2(C_{1-4}$ alquilo), $NHSO_2(C_{1-4}$ alquilo), pirazolilo o morfolinilo.

En otra modalidad, R^{13} es independientemente: H, halo, C_{1-4} alquilo sustituido con 0-1 C_{1-4} alcoxi, C_{1-4} alcoxi, C_{1-4} haloalquilo, C_{1-4} haloalcoxi, CN o C_{3-4} cicloalquilo.

En otra modalidad, R^{13} es independientemente: NR^fR^j, $NHCO_2(C_{1-4}$ alquilo), $NHSO_2(C_{1-4}$ alquilo) o un heterociclo de 4 a 6 miembros, que comprende átomos de carbono y 1 a 4 heteroátomos seleccionados de N, NR^e, O y S.

En otra modalidad, R^{14} es independientemente H, halo, C_{1-4} alquilo o C_{1-4} alcoxi.

En otra modalidad, R^{14} es independientemente H, F, Cl, Me y OMe.

En otra modalidad, R^{14} es H.

En otra modalidad, R^{14} es C_{1-4} alquilo.

En otra modalidad, R^{14} es Me.

En otra modalidad, R^{14} es C_{1-4} alcoxi.

En otra modalidad, R^{14} es OMe.

En otra modalidad, R^{14} es halo.

En otra modalidad, R^{14} es independientemente F o Cl.

En otra modalidad, R^{15} es independientemente H, C_{1-4} alquilo o halo.

En otra modalidad, R^{15} es independientemente H, Me, F o Cl.

En otra modalidad, R^{15} es H.

En otra modalidad, R^{15} es C_{1-4} alquilo.

En otra modalidad, R^{15} es Me.

En otra modalidad, R^{15} es halo.

En otra modalidad, R^{15} es independientemente F o Cl.

En otra modalidad, R^{16} es H.

En otra modalidad, R^{16} es C_{1-4} alquilo.

En otra modalidad, X es independientemente O, S o NH.

En otra modalidad, X es independientemente O o S.

En otra modalidad, X es O.

En otra modalidad, X es independientemente CONH o NHCO.

En otra modalidad, X es CONH.

En otra modalidad, X es NHCO.

En otra modalidad, R^b, en cada caso, es independientemente: C_{1-10} alquilo, C_{1-10} alcoxi, C_{1-10} haloalquilo, C_{1-10} haloalcoxi, C_{1-10} alquiltio, C_{1-10} haloalquiltio, $-CONH(CH_2)_{4-20}H$, $O(CH_2)_sO(C_{1-6}$ alquilo), R^c, -

$(CH_2)_n-(X)_t-(CH_2)_mR^c$ o $-(CH_2)_n-(CH_2O)_m-(CH_2)_nR^f$.

En otra modalidad, R^b, en cada caso, es independientemente halo, OH, C_{1-8} alquilo, C_{1-8} alcoxi, C_{1-8} haloalquilo, C_{1-10} haloalcoxi, $O(CH_2)_sO(C_{1-6}$ alquilo), $N(C_{1-4}$ alquilo)$_2$, $-CONH(CH_2)_{6-20}H$, $(CH_2)_m(C_{3-6}$ cicloalquilo), $(CH_2)_m(C_{4-6}$ cicloalquenilo), $O(CH_2)_m(C_{3-6}$ cicloalquilo), 4-C_{1-4} alcoxi-Ph, $O(CH_2)_mPh$, morfolinilo, piridilo, 2-C_{1-4} alcoxi piridin-5-ilo, pirimidinilo, pirazinilo o -O-pirimidinilo.

En otra modalidad, R^b, en cada caso, es independientemente halo, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} haloalquilo, C_{1-10} haloalcoxi, $O(CH_2)_sO(C_{1-6}$ alquilo), $-CONH(CH_2)_{6-20}H$, $(CH_2)_m(C_{3-6}$ cicloalquilo), $(CH_2)_m(C_{4-6}$ cicloalquenilo), $O(CH_2)_m(C_{3-6}$ cicloalquilo), fenoxi, benzoxi, morfolinilo, 2-C_{1-4} alcoxi-piridin-5-ilo, pirimidin-5-ilo, pirazin-2-ilo o -O-pirimidinilo.

En otra modalidad, R^b, en cada caso, es independientemente halo, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} haloalquilo, C_{1-8} haloalcoxi, $-CONH(CH_2)_{6-20}H$, C_{3-6} cicloalquilo, C_{4-6} cicloalquenilo, $O(CH_2)_m(C_{3-6}$ cicloalquilo), fenoxi, benzoxi, pirimidinilo, pirazinilo y -O-pirimidinilo.

En otra modalidad, R^b, en cada caso, es independientemente:

$-O(CH_2)_{1-6}CF_3$ y $O(CH_2)_{1-4}CF_2CF_3$.

En otra modalidad, R^c, en cada caso, es independientemente:

C_{3-6} cicloalquilo sustituido con 0-2 R^d, C_{3-6} cicloalquenilo sustituido con 0-2 R^d o $-(CH_2)_m$-(fenilo sustituido con 0-3 R^d).

En otra modalidad, R^c, en cada caso, es independientemente:

C_{3-6} cicloalquilo sustituido con 0-2 R^d o C_{3-6} cicloalquenilo sustituido con 0-2 R^d.

En otra modalidad, R^c, en cada caso, es independientemente $-(CH_2)_m$-(fenilo sustituido con 0-3 R^d).

En otra modalidad, R^c, en cada caso, es independientemente C_{3-6} cicloalquilo sustituido con 0-2 R^d.

En otra modalidad, R^c, en cada caso, es independientemente C_{3-6} cicloalquenilo sustituido con 0-2 R^d.

En otra modalidad, R^c, en cada caso, es independientemente un heterociclo de 5 a 6 miembros que comprende átomos de carbono y 1 a 4 heteroátomos seleccionados de N, NR^e, O y S; en donde el heterociclo se sustituye con 0-2 R^d.

En otra modalidad, R^c, en cada caso, es independientemente $-(CH_2)_m$-(fenilo sustituido con 0-3 R^d) o un heteroarilo seleccionado de oxazolilo, isoxazolilo, pirazolilo, imidazolilo, oxadiazolilo, triazolilo, tetrazolilo, piridilo y pirazinilo; en donde el heteroarilo se sustituye con 0-2 R^d.

En otra modalidad, R^c, en cada caso, es

independientemente un heteroarilo seleccionado de oxazolilo, isoxazolilo, pirazolilo, imidazolilo, oxadiazolilo, triazolilo, tetrazolilo, piridilo y pirazinilo; en donde el heteroarilo se sustituye con 0-2 R^d.

En otra modalidad, los compuestos de la presente invención tienen valores IC_{50} de hMGAT2 ≤ 10 μM, mediante el uso del ensayo MGAT2 SPA.

En otra modalidad, los compuestos de la presente invención tienen valores IC_{50} de hMGAT2 ≤ 5 μM, mediante el uso del ensayo SPA de MGAT2.

En otra modalidad, los compuestos de la presente invención tienen valores IC_{50} de hMGAT2 ≤ 1 μM, mediante el uso del ensayo SPA de MGAT2.

En otra modalidad, los compuestos de la presente invención tienen valores IC_{50} de hMGAT2 ≤ 0.5 μM, mediante el uso del ensayo SPA de MGAT2.

En otra modalidad, los compuestos de la presente invención tienen valores IC_{50} de hMGAT2 ≤ 10 μM, mediante el uso del ensayo LCMS de MGAT2.

En otra modalidad, los compuestos de la presente invención tienen valores IC_{50} de hMGAT2 ≤ 5 μM, mediante el uso del ensayo LCMS de MGAT2.

En otra modalidad, los compuestos de la presente invención tienen valores IC_{50} de hMGAT2 ≤ 2.5 μM, mediante el uso del ensayo LCMS de MGAT2.

En otra modalidad, los compuestos de la presente invención tienen valores IC_{50} de hMGAT2 ≤ 1 μM, mediante el uso del ensayo LCMS de MGAT2.

En otra modalidad, los compuestos de la presente invención tienen valores IC_{50} de hMGAT2 ≤ 0.5 μM, mediante el uso del ensayo LCMS de MGAT2.

En otra modalidad, los compuestos de la presente invención tienen valores IC_{50} de hMGAT2 ≤ 0.1 μM, mediante el uso del ensayo LCMS de MGAT2.

II. OTRAS MODALIDADES DE LA INVENCIÓN

En otra modalidad, la presente invención provee una composición que comprende, al menos, uno de los compuestos de la presente invención o un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de este.

En otra modalidad, la presente invención provee una composición farmacéutica que comprende un portador aceptable desde el punto de vista farmacéutico y, al menos, uno de los compuestos de la presente invención o un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de este.

En otra modalidad, la presente invención provee una composición farmacéutica que comprende: un portador aceptable desde el punto de vista farmacéutico y una cantidad terapéuticamente eficaz de, al menos, uno de los compuestos

de la presente invención o un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de este.

En otra modalidad, la presente invención provee un proceso para elaborar un compuesto de la presente invención o un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de este.

En otra modalidad, la presente invención provee un intermediario para elaborar un compuesto de la presente invención o un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de este.

En otra modalidad, la presente invención provee una composición que también comprende agentes terapéuticos adicionales. En una modalidad preferida, la presente invención provee una composición farmacéutica, en donde el agente terapéutico adicional es, por ejemplo, un inhibidor de dipeptidil peptidasa-IV (DPP4) (por ejemplo, un miembro seleccionado de saxagliptin, sitagliptin, vildagliptin y alogliptin).

En otra modalidad, la presente invención provee un método para el tratamiento y/o la profilaxis de varias enfermedades o trastornos asociados a MGAT2, que comprende administrar a un paciente que necesita el tratamiento y/o la profilaxis una cantidad terapéuticamente eficaz de al menos

uno de los compuestos de la presente invención solo u, opcionalmente, en combinación con otro compuesto de la presente invención y/o al menos otro tipo de agente terapéutico.

Los ejemplos de enfermedades o trastornos asociados a la actividad de MGAT2 que se pueden prevenir, modular o tratar de acuerdo con la presente invención incluyen, entre otros, diabetes, hiperglucemia, intolerancia a la glucosa, diabetes gestacional, resistencia a la insulina, hiperinsulinemia, hepatopatía grasa no alcohólica (NAFLD, por sus siglas en inglés), que incluye esteatohepatitis no alcohólica (NASH, por sus siglas en inglés), retinopatía, neuropatía, nefropatía, cicatrización tardía, ateroesclerosis y sus secuelas, actividad cardíaca anormal, isquemia de miocardio, apoplejía, síndrome metabólico, hipertensión, obesidad, dislipidemia, dislipidemia, hiperlipidemia, hipertrigliceridemia, hipercolesterolemia, niveles reducidos de lipoproteínas de baja densidad (HDL, por sus siglas en inglés), niveles elevados de lipoproteínas de alta densidad (LDL, por sus siglas en inglés), isquemia no cardíaca, trastornos lipídicos y glaucoma.

En otra modalidad, la presente invención provee un método para el tratamiento y/o la profilaxis de la diabetes, la hiperglucemia, la diabetes gestacional, la obesidad, la dislipidemia y la hipertensión, que comprende administrar a

un paciente que necesita el tratamiento y/o la profilaxis una cantidad terapéuticamente eficaz de al menos uno de los compuestos de la presente invención solo u, opcionalmente, en combinación con otro compuesto de la presente invención y/o al menos otro tipo de agente terapéutico.

En otra modalidad, la presente invención provee un método para el tratamiento y/o la profilaxis de la diabetes, que comprende administrar a un paciente que necesita el tratamiento y/o la profilaxis una cantidad terapéuticamente eficaz de al menos uno de los compuestos de la presente invención solo u, opcionalmente, en combinación con otro compuesto de la presente invención y/o al menos otro tipo de agente terapéutico.

En otra modalidad, la presente invención provee un método para el tratamiento y/o la profilaxis de la hiperglucemia, que comprende administrar a un paciente que necesita el tratamiento y/o la profilaxis una cantidad terapéuticamente eficaz de al menos uno de los compuestos de la presente invención solo u, opcionalmente, en combinación con otro compuesto de la presente invención y/o al menos otro tipo de agente terapéutico.

En otra modalidad, la presente invención provee un método para el tratamiento y/o la profilaxis de la obesidad, que comprende administrar a un paciente que necesita el tratamiento y/o la profilaxis una cantidad terapéuticamente

eficaz de al menos uno de los compuestos de la presente invención solo u, opcionalmente, en combinación con otro compuesto de la presente invención y/o al menos otro tipo de agente terapéutico.

En otra modalidad, la presente invención provee un método para el tratamiento y/o la profilaxis de la dislipidemia, que comprende administrar a un paciente que necesita el tratamiento y/o la profilaxis una cantidad terapéuticamente eficaz de al menos uno de los compuestos de la presente invención solo u, opcionalmente, en combinación con otro compuesto de la presente invención y/o al menos otro tipo de agente terapéutico.

En otra modalidad, la presente invención provee un método para el tratamiento y/o la profilaxis de la hipertensión, que comprende administrar a un paciente que necesita el tratamiento y/o la profilaxis una cantidad terapéuticamente eficaz de al menos uno de los compuestos de la presente invención solo u, opcionalmente, en combinación con otro compuesto de la presente invención y/o al menos otro tipo de agente terapéutico.

En otra modalidad, la presente invención provee un compuesto de la presente invención para usar en la terapia.

En otra modalidad, la presente invención provee un compuesto de la presente invención para usar en la terapia para el tratamiento y/o la profilaxis de varias enfermedades

o trastornos asociados a MGAT2.

En otra modalidad, la presente invención también provee el uso de un compuesto de la presente invención para la fabricación de un medicamento para el tratamiento y/o la profilaxis de varias enfermedades o trastornos asociados a MGAT2.

En otra modalidad, la presente invención provee un método para el tratamiento y/o la profilaxis de varias enfermedades o trastornos asociados a MGAT2, que comprende administrar a un paciente que lo necesita una cantidad terapéuticamente eficaz de un primer y un segundo agente terapéutico, en donde el primer agente terapéutico es un compuesto de la presente invención. Preferentemente, el segundo agente terapéutico es, por ejemplo, un inhibidor de dipeptidil peptidasa-IV (DPP4) (por ejemplo, un miembro seleccionado de saxagliptin, sitagliptin, vildagliptin, linagliptin y alogliptin).

En otra modalidad, la presente invención provee una preparación combinada de un compuesto de la presente invención y agentes terapéuticos adicionales para el uso simultáneo, separado o consecutivo en la terapia.

En otra modalidad, la presente invención provee una preparación combinada de un compuesto de la presente invención y agentes terapéuticos adicionales para el uso simultáneo, separado o consecutivo en el tratamiento y/o la

profilaxis de varias enfermedades o trastornos asociados a MGAT2.

Si se desea, el compuesto de la presente invención se puede usar en combinación con uno o más de otros tipos de agentes contra la diabetes y/o uno o más de otros tipos de agentes terapéuticos que se pueden administrar por vía oral en la misma forma de dosificación, en una forma de dosificación oral diferente o mediante inyección. El otro tipo de agente contra la diabetes que se puede usar opcionalmente en combinación con el inhibidor de MGAT2 de la presente invención puede ser 1, 2, 3 o más agentes contra la diabetes o agentes antihiperglucémicos que se pueden administrar por vía oral en la misma forma de dosificación, en una forma de dosificación oral diferente o mediante inyección para producir un beneficio farmacológico adicional.

Los agentes contra la diabetes que se usan en combinación con el inhibidor de MGAT2 de la presente invención incluyen, entre otros, secretagogos de insulina o sensibilizadores de insulina, otros inhibidores de MGAT2 u otros agentes contra la diabetes. Estos agentes incluyen, entre otros, inhibidores de dipeptidil peptidasa IV (DP4) (por ejemplo, sitagliptin, saxagliptin, alogliptin, linagliptin y vildagliptin), biguanidas (por ejemplo, metformin y phenformin), sulfonilureas (por ejemplo, glyburide, glimepiride y glipizide), inhibidores de

glucosidasa (por ejemplo, acarbose, miglitol), agonistas de PPARγ, tales como tiazolidinedionas (por ejemplo, rosiglitazone y pioglitazone), agonistas duales de PPAR α/γ (por ejemplo, muraglitazar, tesaglitazar y aleglitazar), activadores de glucoquinasa, moduladores del receptor de GPR^{40} (por ejemplo, TAK-875), moduladores del receptor de GPR^{119} (por ejemplo, MBX 2952, PSN821 y APD597), inhibidores del transportador de sodio-glucosa 2 (SGLT2) (por ejemplo, dapagliflozin, canagliflozin y remagliflozin), inhibidores de 11b-HSD-1 (por ejemplo, MK-0736, BI35585, BMS-823778 y LY2523199), análogos de amilina, tales como pramlintide y/o insulina.

El inhibidor de MGAT2 de la presente invención también se puede usar opcionalmente en combinación con uno o más agentes hipofágicos y/o para la pérdida de peso, tales como diethylpropion, phendimetrazine, phentermine, orlistat, sibutramine, lorcaserin, pramlintide, topiramate, antagonistas del receptor de $MCHR^{1}$, oxyntomodulin, naltrexone, péptido amilina, moduladores del receptor de NPY Y5, moduladores del receptor de NPY Y2, moduladores del receptor de NPY Y4, cetilistat, moduladores del receptor de 5HT2c y similares. Los compuestos de la presente invención también se puede usar en combinación con un agonista del receptor de péptido 1 tipo glucagón (GLP-1 R), tal como exenatide, liraglutide, amida GPR-1 (1-36), amida GLP 1(7-

36), GLP 1(7-37), que se puede administrar mediante inyección, por vía intranasal o mediante dispositivos transdérmicos o bucales.

El inhibidor de MGAT2 de la presente invención también se puede usar opcionalmente en combinación con uno o más de otros tipos de agentes terapéuticos, tales como inhibidores de DGAT, fármacos reductores de LDL, tales como estatinas (inhibidores de HMG CoA reductasa) o inhibidores de la absorción del colesterol, moduladores de PCSK9 y fármacos que aumentan HDL, tales como inhibidores de CETP.

La presente invención se puede realizar en otras formas específicas sin apartarse del espíritu ni de sus atributos esenciales. Esta invención abarca todas las combinaciones de aspectos preferidos de la invención expuestos en la presente. Cabe destacar que todas las modalidades de la presente invención pueden tomarse en conjunto con cualquier otra modalidad, a fin de describir modalidades adicionales. Además, cabe destacar que cada elemento individual de las modalidades es su propia modalidad independiente. Asimismo, cualquier elemento de una modalidad tiene como fin que se lo combine con cualquier otro elemento de cualquiera de las modalidades para describir una modalidad adicional.

III. QUÍMICA

En toda la descripción y las reivindicaciones

adjuntas, un nombre o una fórmula química determinada abarca todos los estereoisómeros, isómeros ópticos y racematos de estos, en caso de que existan los isómeros. A menos que se indique los contrario, todas las formas quirales (enantioméricas y diastoméricas) y racémicas se encuentran dentro del alcance de la invención. Muchos isómeros geométricos de enlaces dobles C=C, enlaces dobles C=N, sistemas de anillos y similares también pueden estar presentes en los compuestos, y todos esos isómeros estables se contemplan en la presente invención. Los isómeros geométricos cis y trans (o *E* y *Z*) de los compuestos de la presente invención se describen y se pueden aislar como una mezcla de isómeros o como formas isoméricas separadas. Los compuestos de la presente se pueden aislar en formas ópticamente activas o racémicas. Las formas ópticamente activas se pueden preparar mediante la resolución de formas racémicas o mediante síntesis de materiales de inicio ópticamente activos. Todos los procesos usados para preparar compuestos de la presente invención y los intermediarios allí elaborados se consideran parte de la presente invención. Cuando se preparan productos enantioméricos o diastoméricos, se pueden separar mediante métodos convencionales, por ejemplo, mediante cromatografía o cristalización fraccional. En función de las condiciones del proceso, los productos finales de la presente invención se obtienen en forma libre

(neutral) o salina. Tanto la forma libre como las sales de estos productos finales se encuentran dentro del alcance de la invención. Si se desea, una forma de un compuesto puede convertirse en otra forma. Un ácido o base libre se puede convertir en una sal; una sal se puede convertir en el compuesto libre o en otra sal; una mezcla de compuestos isoméricos de la presente invención se puede separar en los isómeros individuales. Los compuestos de la presente invención, la forma libre y las sales de estos, pueden existir en múltiples formas tautoméricas, en donde los átomos de hidrógeno se transponen a otras partes de las moléculas, y los enlaces químicos entre los átomos de las moléculas se redisponen, en consecuencia. Cabe destacar que todas las formas tautoméricas, en caso de que existan, están incluidas en la invención.

Como se usan en la presente, los términos "alquilo" o "alquileno" incluyen grupos de hidrocarburo saturados alifáticos de cadena lineal o ramificada que tienen la cantidad especificada de átomos de carbono. Por ejemplo, "C_1 a C_{12} alquilo" o "C_{1-12} alquilo" (o alquileno) incluye grupos C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11} y C_{12} alquilo; "C_4 a C_{18} alquilo" o "C_{4-18} alquilo" (o alquileno) incluye grupos C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17} y C_{18} alquilo. De manera adicional, por ejemplo, "C_1 a C_6 alquilo" o "C_{1-6} alquilo" indican un alquilo que tiene de 1 a 6 átomos de

carbono. El grupo alquilo puede ser no sustituido o sustituido con, al menos, un hidrógeno que se reemplaza por otro grupo químico. Los ejemplos de grupos alquilo incluyen, entre otros, metilo (Me), etilo (Et), propilo (por ejemplo, n-propilo e isopropilo), butilo (por ejemplo, n-butilo, isobutilo, t-butilo) y pentilo (por ejemplo, n-pentilo, isopentilo, neopentilo). Cuando se usan "C_0 alquilo" o "C_0 alquileno", denotan un enlace directo.

Los términos "alquenilo" o "alquenileno" incluyen cadenas de hidrocarburos de configuración lineal o ramificada que tienen la cantidad especificada de átomos de carbono y uno o más, preferentemente, uno o dos, enlaces dobles de carbono-carbono que pueden ocurrir en cualquier punto estable de la cadena. Por ejemplo, "C_2 a C_6 alquenilo" o "C_{2-6} alquenilo" (o alquenileno) incluyen grupos C_2, C_3, C_4, C_5 y C_6 alquenilo. Los ejemplos de alquenilo incluyen, entre otros, etenilo, 1-propenilo, 2-propenilo, 2-butenilo, 3-butenilo, 2-pentenilo, 3-pentenilo, 4-pentenilo, 2-hexenilo, 3-hexenilo, 4 hexenilo, 5-hexenilo, 2-metil-2-propenilo y 4-metil-3-pentenilo.

Los términos "alquinilo" o "alquinileno" incluyen cadenas de hidrocarburos de configuración lineal o ramificada que tienen uno o más, preferentemente, de uno a tres, enlaces triples de carbono-carbono que pueden ocurrir en cualquier punto estable de la cadena. Por ejemplo, "C_2 a C_6 alquinilo" o

"C_{2-6} alquinilo" (o alquinileno) incluyen grupos C_2, C_3, C_4, C_5 y C_6 alquinilo; tales como etinilo, propinilo, butinilo, pentinilo y hexinilo.

Cuando se usa la expresión "cadena de hidrocarburos", esta incluye "alquilo", "alquenilo" y "alquinilo", a menos que se especifique de otro modo.

El término "alcoxi" o "alquiloxi" se refiere a un grupo -O-alquilo. Por ejemplo, "C_1 a C_6 alcoxi" o "C_{1-6} alcoxi" (o alquiloxi) incluyen grupos C_1, C_2, C_3, C_4, C_5 y C_6 alcoxi. Los ejemplos de grupos alcoxi incluyen, entre otros, metoxi, etoxi, propoxi (por ejemplo, n-propoxi y isopropoxi) y t-butoxi. De manera similar, "alquiltio" o "tioalcoxi" representan un grupo alquilo como se definió anteriormente con una cantidad de átomos de carbono unidas a través de un puente de azufre; por ejemplo, metil-S- y etil-S-.

"Halo" o "halógeno" incluyen fluoro, cloro, bromo y yodo. El término "haloalquilo" incluye grupos de hidrocarburos alifáticos saturados de cadena lineal o ramificada que tienen la cantidad especificada de átomos de carbono, sustituidos con 1 o más halógenos. Los ejemplos de haloalquilo incluyen, entre otros, fluorometilo, difluorometilo, trifluorometilo, triclorometilo, pentafluoroetilo, pentacloroetilo, 2,2,2-trifluoroetilo, heptafluoropropilo y heptacloropropilo. Los ejemplos de haloalquilo también incluyen "fluoroalquilo", que incluye

grupos de hidrocarburos alifáticos saturados de cadena lineal o ramificada que tienen la cantidad especificada de átomos de carbono, sustituidos con 1 o más átomos de flúor.

Los términos "haloalcoxi" o "haloalquiloxi" representan un grupo haloalquilo, como se definió anteriormente, con la cantidad indicada de átomos de carbono unidos a través de un puente de oxígeno. Por ejemplo, "C_{1-6} haloalcoxi" incluye grupos C_1, C_2, C_3, C_4, C_5 y C_6 haloalcoxi. Los ejemplos de haloalcoxi incluyen, entre otros, trifluorometoxi, 2,2,2-trifluoroetoxi y pentafluorotoxi. De manera similar, "haloalquiltio" o "tiohaloalcoxi" representan un grupo haloalquilo, como se definió anteriormente, con la cantidad indicada de átomos de carbono unidos a través de un puente de azufre; por ejemplo, trifluorometil-S- y pentafluoroetil-S-.

El término "cicloalquilo" se refiere a grupos alquilo ciclizados, que incluyen sistemas de anillos monocíclicos, bicíclicos o policíclicos. Por ejemplo, "C_3 a C_6 cicloalquilo" o "C_{3-6} cicloalquilo" incluyen grupos C_3, C_4, C_5 y C_6 cicloalquilo. Los ejemplos de grupos cicloalquilo incluyen, entre otros, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y norbornilo. Los grupos cicloalquilo ramificados, tales como 1-metilciclopropilo y 2-metilciclopropilo, se incluyen en la definición de "cicloalquilo". El término "cicloalquenilo" se refiere a

grupos alquenilo ciclizados. C_{4-6} cicloalquenilo incluye grupos C_4, C_5 y C_6 cicloalquenilo. Los ejemplos de grupos cicloalquenilo incluyen, entre otros, ciclobutenilo, ciclopentenilo y ciclohexenilo.

Como se usan en la presente, "carbociclo", "carbociclilo" o "residuo carbocíclico" incluyen cualquier anillo monocíclico o bicíclico estable de 3, 4, 5, 6, 7 u 8 miembros, o cualquier anillo bicíclico o tricíclico de 7, 8, 9, 10, 11, 12 ó 13 miembros; y cualquiera de ellos puede ser saturado, parcialmente insaturado, insaturado o aromático. Los ejemplos de carbociclos incluyen, entre otros, ciclopropilo, ciclobutilo, ciclobutenilo, ciclopentilo, ciclopentenilo, ciclohexilo, cicloheptenilo, cicloheptilo, cicloheptenilo, adamantilo, ciclooctilo, ciclooctenilo, ciclooctadienilo, [3.3.0]biciclooctano, [4.3.0]biciclononano, [4.4.0]biciclodecano (decalin), [2.2.2]biciclooctano, fluorenilo, fenilo, naftilo, indanilo, adamantilo, antracenilo y tetrahidronaftilo (tetralin). Como se indicó anteriormente, los anillos en puente también se incluyen en la definición de carbociclo (por ejemplo, [2.2.2]biciclooctano). A menos que se especifique lo contrario, los carbociclos preferidos son ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, fenilo, indanilo y tetrahidronaftilo. Cuando se usa el término "carbociclo", este incluye "arilo". Un anillo con puente se produce cuando

uno o más, preferentemente de 1 a 3, átomos de carbono se unen a dos átomos de carbono no adyacentes. Los puentes preferidos son uno o dos átomos de carbono. Cabe destacar que un puente siempre se convierte un anillo monocíclico en un anillo tricíclico. Cuando un anillo está en puente, los sustituyentes enumerados para el anillo también pueden estar presentes en el puente.

Como se usan en la presente, las expresiones "carbociclo bicíclico" o "grupo carbociclo bicíclico" significan un sistema de anillos carbocíclicos estables de 9 o 10 miembros que contiene dos anillos fusionados y consiste en átomos de carbono. De los dos anillos fusionados, un anillo es un anillo de benzo fusionado a un segundo anillo; y el segundo anillo es un anillo de carbono de 5 ó 6 miembros saturado, parcialmente insaturado o insaturado. El grupo carbocíclico bicíclico se puede unir a su grupo colgante en cualquier átomo de carbono que genere una estructura estable. El grupo carbocíclico bicíclico descrito en la presente se puede sustituir en cualquier carbono si el compuesto resultante es estable. Los ejemplos de grupos carbocíclicos bicíclicos son, entre otros, naftilo, 1,2-dihidronaftilo, 1,2,3,4 tetrahidronaftilo e indanilo.

Los grupos "arilo" se refieren a hidrocarburos monocíclicos o bicíclicos aromáticos que incluyen, por ejemplo, fenilo y naftilo. Las porciones arilo son conocidas

y se describen, por ejemplo, en *Hawley's Condensed Chemical Dictionary* (15.ta ed.), R.J. Lewis, ed., J. Wiley & Sons, Inc., Nueva York, 2007. "C_{6-10} arilo" se refiere a fenilo y naftilo.

Como se usa en la presente, el término "bencilo" se refiere a un grupo metilo en el que uno de los átomos de hidrógeno se reemplaza por un grupo fenilo.

Como se usa en la presente, "heterociclo", "heterociclilo" o "grupo heterocíclico" significan un anillo monocíclico o bicíclico estable de 3, 4, 5, 6 ó 7 miembros, o un anillo heterocíclico policíclico de 7, 8, 9, 10, 11, 12, 13 ó 14 miembros, que es saturado, parcialmente insaturado o totalmente insaturado, que contiene átomos de carbono y 1, 2, 3 ó 4 heteroátomos seleccionados independientemente del grupo que consiste en N, O y S; e incluyen cualquier grupo policíclico en los que se fusiona cualquiera de los anillos heterocíclicos antes definidos a un anillo de benceno. Los heteroátomos de nitrógeno y de azufre se pueden oxidar opcionalmente (es decir, N→O y $S(O)_p$, en donde p es 0, 1 ó 2). El átomo de nitrógeno puede ser sustituido o no sustituido (es decir, N o NR, en donde R es H u otro sustituyente, si se define). El anillo heterocíclico se puede unir a su grupo colgante en cualquier heteroátomo o átomo de carbono que genere una estructura estable. Los anillos heterocíclicos descritos en la presente se pueden sustituir

en un átomo de carbono o de nitrógeno si el compuesto resultante es estable. Opcionalmente, se puede cuaternizar un nitrógeno en el heterociclo. Se prefiere que cuando la cantidad total de átomos de S y O en el heterociclo exceda 1, estos heteroátomos no sean adyacentes entre sí. Se prefiere que la cantidad total de átomos de S y O en el heterociclo no sea mayor de 1. Cuando se usa el término "heterociclo", se pretende incluir heteroarilo.

Los ejemplos de heterociclos incluyen, entre otros, acridinilo, azetidinilo, azocinilo, bencimidazolilo, benzofuranilo, benzotiofuranilo, benzotiofenilo, benzoxazolilo, benzoxazolinilo, benztiazolilo, benztriazolilo, benztetrazolilo, bencisoxazolilo, bencisotiazolilo, bencimidazolinilo, carbazolilo, 4a*H*-carbazolilo, carbolinilo, cromanilo, cromenilo, cinnolinilo, decahidroquinolinilo, 2*H*,6*H*-1,5,2-ditiazinilo, dihidrofuro[2,3-*b*]tetrahidrofurano, furanilo, furazanilo, imidazolidinilo, imidazolinilo, imidazolilo, 1*H*-indazolilo, imidazolopiridinilo, indolenilo, indolinilo, indolizinilo, indolilo, 3*H*-indolilo, isatinoílo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo, isotiazolilo, isotiazolopiridinilo, isoxazolilo, isoxazolopiridinilo, metilendioxifenilo, morfolinilo, naftiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, oxazolidinilo, oxazolilo, oxazolopiridinilo,

oxazolidinilperimidinilo, oxindolilo, pirimidinilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, piperidonilo, 4-piperidonilo, piperonilo, pteridinilo, purinilo, piranilo, pirazinilo, pirazolidinilo, pirazolinilo, pirazolopiridinilo, pirazolilo, piridazinilo, piridooxazolilo, piridoimidazolilo, piridotiazolilo, piridinilo, pirimidinilo, pirrolidinilo, pirrolinilo, 2-pirrolidonilo, 2*H*-pirrolilo, pirrolilo, quinazolinilo, quinolinilo, 4*H*-quinolizinilo, quinoxalinilo, quinuclidinilo, tetrazolilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, 6*H*-1,2,5-tiadiazinilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tiantrenilo, tiazolilo, tienilo, tiazolopiridinilo, tienotiazolilo, tienooxazolilo, tienoimidazolilo, tiofenilo, triazinilo, 1,2,3-triazolilo, 1,2,4-triazolilo, 1,2,5-triazolilo, 1,3,4-triazolilo y xantenilo. También se incluyen compuestos spiro y de anillos fusionados que contienen, por ejemplo, los heterociclos anteriores.

Los ejemplos de heterociclos de 5 a 10 miembros incluyen, entre otros, piridinilo, furanilo, tienilo, pirrolilo, pirazolilo, pirazinilo, piperazinilo, piperidinilo, imidazolilo, imidazolidinilo, indolilo, tetrazolilo, isoxazolilo, morfolinilo, oxazolilo,

oxadiazolilo, oxazolidinilo, tetrahidrofuranilo, tiadiazinilo, tiadiazolilo, tiazolilo, triazinilo, triazolilo, bencimidazolilo, 1*H*-indazolilo, benzofuranilo, benzotiofuranilo, benztetrazolilo, benzotriazolilo, bencisoxazolilo, benzoxazolilo, oxindolilo, benzoxazolinilo, benztiazolilo, bencisotiazolilo, isatinoilo, isoquinolinilo, octahidroisoquinolinilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, isoxazolopiridinilo, quinazolinilo, quinolinilo, isotiazolopiridinilo, tiazolopiridinilo, oxazolopiridinilo, imidazolopiridinilo y pirazolopiridinilo.

Los ejemplos de heterociclos de 5 a 6 miembros incluyen, entre otros, piridinilo, furanilo, tienilo, pirrolilo, pirazolilo, pirazinilo, piperazinilo, piperidinilo, imidazolilo, imidazolidinilo, indolilo, tetrazolilo, isoxazolilo, morfolinilo, oxazolilo, oxadiazolilo, oxazolidinilo, tetrahidrofuranilo, tiadiazinilo, tiadiazolilo, tiazolilo, triazinilo y triazolilo. También se incluyen compuestos spiro y de anillos fusionados que contienen, por ejemplo, los heterociclos anteriores.

Como se usan en la presente, las expresiones "heterociclo bicíclico" o "grupo heterocíclico bicíclico" significan un sistema de anillos heterocíclicos estable de 9 o 10 miembros que contiene dos anillos fusionados y consiste en átomos de carbono y 1, 2, 3 ó 4 heteroátomos seleccionados

independientemente del grupo que consiste en N, O y S. De los dos anillos fusionados, un anillo es un anillo aromático monocíclico de 5 ó 6 miembros que comprende un anillo de heteroarilo de 5 miembros, un anillo de heteroarilo de 6 miembros o un anillo de benzo, cada uno fusionado a un segundo anillo. El segundo anillo es un anillo monocíclico de 5 ó 6 miembros que es saturado, parcialmente insaturado o insaturado y comprende un heterociclo de 5 miembros; un heterociclo de 6 miembros o un carbociclo (siempre que el primer anillo no sea benzo cuando el segundo anillo es un carbociclo).

El grupo heterocíclico bicíclico se puede unir a su grupo colgante en cualquier heteroátomo o átomo de carbono que genere una estructura estable. El grupo heterocíclico bicíclico descrito en la presente se puede sustituir en un átomo de carbono o de nitrógeno si el compuesto resultante es estable. Se prefiere que cuando la cantidad total de átomos de S y O en el heterociclo exceda 1, estos heteroátomos no sean adyacentes entre sí. Se prefiere que la cantidad total de átomos de S y O en el heterociclo no sea mayor de 1.

Los ejemplos de un grupo heterocíclico bicíclico son, entre otros, quinolinilo, isoquinolinilo, ftalazinilo, quinazolinilo, indolilo, isoindolilo, indolinilo, 1*H*-indazolilo, bencimidazolilo, 1,2,3,4-tetrahidroquinolinilo, 1,2,3,4-tetrahidroisoquinolinilo, 5,6,7,8-tetrahidro-

quinolinilo, 2,3-dihidro-benzofuranilo, cromanilo, 1,2,3,4-tetrahidro-quinoxalinilo y 1,2,3,4-tetrahidro quinazolinilo.

Como se usan en la presente, "grupo heterocíclico aromático" o "heteroarilo" significan hidrocarburos aromáticos monocíclicos o policíclicos que incluyen, al menos, un miembro del anillo heteroátomo, tal como azufre, oxígeno o nitrógeno. Los grupos heteroarilo incluyen, entre otros, piridilo, pirimidinilo, pirazinilo, piridazinilo, triazinilo, furilo, quinolilo, isoquinolilo, tienilo, imidazolilo, tiazolilo, indolilo, pirroilo, oxazolilo, benzofurilo, benzotienilo, benztiazolilo, isoxazolilo, pirazolilo, triazolilo, tetrazolilo, indazolilo, 1,2,4-tiadiazolilo, isotiazolilo, purinilo, carbazolilo, bencimidazolilo, indolinilo, benzodioxolanilo y benzodioxano. Los grupos heteroarilo son sustituidos o no sustituidos. El átomo de nitrógeno es sustituido o no sustituido (es decir, N o NR, en donde R es H u otro sustituyente, si se define). Los heteroátomos de nitrógeno y de azufre se pueden oxidar opcionalmente (es decir, N→O y $S(O)_p$, en donde p es 0, 1 o 2).

Los ejemplos de heteroarilos de 5 a 6 miembros incluyen, entre otros, piridinilo, furanilo, tienilo, pirrolilo, pirazolilo, pirazinilo, imidazolilo, imidazolidinilo, tetrazolilo, isoxazolilo, oxazolilo, oxadiazolilo, oxazolidinilo, tiadiazinilo, tiadiazolilo, tiazolilo, triazinilo y triazolilo.

Los anillos en puente también se incluyen en la definición de heterociclo. Un anillo con puente se produce cuando uno o más, preferentemente de 1 a 3, átomos (es decir, C, O, N o S) se unen a dos átomos de carbono o de nitrógeno no adyacentes. Los ejemplos de anillos en puente incluyen, entre otros, un átomo de carbono, dos átomos de carbono, un átomo de nitrógeno, dos átomos de nitrógeno y un grupo carbono-nitrógeno. Cabe destacar que un puente siempre se convierte un anillo monocíclico en un anillo tricíclico. Cuando un anillo está en puente, los sustituyentes enumerados para el anillo también pueden estar presentes en el puente.

El término "contraión" se usa para representar una especie con carga negativa, tal como cloro, bromo, hidróxido, acetato y sulfato, o una especie con carga positiva, tal como sodio (Na+), potasio (K+), amonio (R_nNH_m+ en donde n=0 4 y m=0 4) y similares.

Cuando un anillo punteado se usa en una estructura anular, esto indica que la estructura anular puede ser saturada, parcialmente saturada o insaturada.

Como se usa en la presente, la expresión "grupo protector de amina" significa cualquier grupo conocido en el ámbito de la síntesis orgánica para la protección de grupos amina, que es estable para un agente reductor de ésteres, una hidrazina disustituida, R4-M y R7-M, un nucleófilo, un agente reductor de hidrazinas, un activador, una base fuerte, una

base de amina impedida y un agente de ciclización. Los grupos protectores de amina que cumplen estos criterios incluyen los que se enumeran en Wuts, P. G. M. y Greene, T.W. *Protecting Groups in Organic Synthesis*, 4.ta edición, Wiley (2007) y *The Peptides: Analysis, Synthesis, Biology*, Vol. 3, Academic Press, Nueva York (1981), cuya descripción se incorpora en la presente por referencia. Los ejemplos de grupos protectores de amina incluyen, entre otros, los siguientes: (1) tipos de acilo, tales como formilo, trifluoroacetilo, ftalilo y p toluensulfonilo; (2) tipos de carbamatos aromáticos, tales como benciloxicarbonilo (Cbz) y benciloxicarbonilos sustituidos, 1-(p-bifenil)-1-metiletoxicarbonilo y 9-fluorenilmetiloxicarbonilo (Fmoc); (3) tipos de carbamatos alifáticos, tales como *ter*-butiloxicarbonilo (Boc), etoxicarbonilo, diisopropilmetoxicarbonilo y aliloxicarbonilo; (4) tipos de carbamatos de alquilo cíclicos, tales como ciclopentiloxicarbonilo y adamantiloxicarbonilo; (5) tipos de alquilo, tales como trifenilmetilo y bencilo; (6) trialquilsilano, tal como trimetilsilano; (7) tipos que contienen tiol, tales como feniltiocarbonilo y ditiasuccinoílo; y (8) tipos de alquilo, tales como trifenilmetilo, metilo y bencilo; y tipos de alquilo sustituido, tales como 2,2,2-tricloroetilo, 2-feniletilo y *t*-butilo; y tipos de trialquilsilano, tales como trimetilsilano.

Como se indica en la presente, el término "sustituido" significa que, al menos, un átomo de hidrógeno se reemplaza por un grupo que no es de hidrógeno, siempre que se mantengan las valencias normales y que la sustitución resulte en un compuesto estable. Los enlaces dobles del anillo, como se usa en la presente, son enlaces dobles que se forman entre dos átomos del anillo adyacentes (por ejemplo, C=C, C=N o N=N).

Cuando existan átomos de nitrógeno (por ejemplo, aminas) en compuestos de la presente invención, estos se pueden convertir a N-óxidos mediante el tratamiento con un agente oxidante (por ejemplo, mCPBA y/o peróxidos de hidrógeno) para obtener otros compuestos de esta invención. Por ello, se considera que los átomos de nitrógeno indicados y reivindicados incluyen el nitrógeno indicado y su derivado de N-óxido (N→O).

Cuando cualquier variable ocurre más de una vez en cualquier constituyente o fórmula de un compuesto, su definición en cada caso es independiente de su definición en cada uno de los otros casos. Por ello, por ejemplo, si un grupo se muestra sustituido con 0-3 R, entonces, el grupo se puede sustituir opcionalmente con hasta 3 grupos R y, en cada caso, R se selecciona independientemente de la definición de R.

Cuando se muestra que un enlace a un sustituyente cruza un enlace que conecta dos átomos en un anillo, el

sustituyente puede unirse a cualquier átomo en el anillo. Cuando se enumera un sustituyente sin indicar el átomo en el cual el sustituyente está unido al resto del compuesto de una fórmula determinada, el sustituyente puede unirse mediante cualquier átomo en el sustituyente.

Las combinaciones de los sustituyentes y/o las variables se permiten solo si las combinaciones resultan en compuestos estables.

La frase "aceptable desde el punto de vista farmacéutico" se usa en la presente para referirse a aquellos compuestos, materiales, composiciones y/o formas de dosificación que, dentro del alcance del criterio médico sensato, son adecuados para usar en contacto con los tejidos de seres humanos y animales sin provocar excesiva toxicidad, irritación, respuesta alérgica ni otros problemas o complicaciones proporcionales con una relación riesgo/beneficio razonable.

Como se usa en la presente, “sales aceptables desde el punto de vista farmacéutico” se refiere a derivados de los compuestos descritos, en donde el compuesto de origen se modifica elaborando las sales ácidas o básicas de este. Los ejemplos de sales aceptables desde el punto de vista farmacéutico incluyen, entre otras, sales de ácidos orgánicos o minerales de grupos básicos, tales como aminas; y sales alcalinas u orgánicas de grupos ácidos, tales como ácidos

carboxílicos. Las sales aceptables desde el punto de vista farmacéutico incluyen las sales no tóxicas convencionales o las sales de amonio cuaternario del compuesto de origen formado, por ejemplo, de ácidos orgánicos o inorgánicos no tóxicos. Por ejemplo, las sales no tóxicas convencionales incluyen las que derivan de ácidos inorgánicos, tales como ácido clorhídrico, bromhídrico, sulfúrico, sulfámico, fosfórico y nítrico; y las sales preparadas de ácidos orgánicos, tales como ácido acético, propiónico, succínico, glicólico, esteárico, láctico, málico, tartárico, cítrico, ascórbico, pamoico, maleico, hidroximaleico, fenilacético, glutámico, benzoico, salicílico, sulfanílico, 2-acetoxibenzoico, fumárico, toluensulfónico, metansulfónico, etandisulfónico, oxálico e isetiónico y similares.

Las sales aceptables desde el punto de vista farmacéutico de la presente invención se pueden sintetizar del compuesto de origen que contiene una porción básica o ácida mediante métodos químicos convencionales. En general, las sales se pueden preparar haciendo reaccionar las formas básicas o ácidas libres de estos compuestos con una cantidad estoiquiométrica de la base o del ácido adecuados en agua, en un solvente orgánico o en una mezcla de los dos; en general, se prefieren medios no acuosos, como éter, acetato de etilo, etanol, isopropanol o acetonitrilo. Se pueden hallar listas de sales adecuadas en *Remington: The Science and Practice of*

Pharmacy, 22.a edición, Allen, L. V. Jr., Ed.; Pharmaceutical Press, Londres, Reino Unido (2012), cuya descripción se incorpora en la presente por referencia.

Además, los compuestos de la Fórmula I pueden tener forma de profármaco. Todo compuesto que se convertirá *in vivo* para proporcionar el agente bioactivo (es decir, un compuesto de la Fórmula I) es un profármaco dentro del alcance y espíritu de la invención. En el estado de la técnica se conocen varias formas de profármacos. Para obtener ejemplos de los derivados de profármacos, véase:

a) Bundgaard, H., ed., *Design of Prodrugs*, Elsevier (1985) y Widder, K. et al., eds., *Methods in Enzymology*, 112:309 396, Academic Press (1985);

b) Bundgaard, H., capítulo 5, "Design and Application of Prodrugs," *A Textbook of Drug Design and Development*, pp. 113 191, Krosgaard-Larsen, P. et al., eds., Harwood Academic Publishers (1991);

c) Bundgaard, H., *Adv. Drug Deliv. Rev.*, 8:1 38 (1992);

d) Bundgaard, H. et al., *J. Pharm. Sci.*, 77:285 (1988);

e) Kakeya, N. et al., *Chem. Pharm. Bull.*, 32:692 (1984); y

f) Rautio, J (Editor). *Prodrugs and Targeted Delivery (Methods and Principles in Medicinal Chemistry)*, Vol

47, Wiley-VCH, 2011.

Los compuestos que contienen un grupo carboxi pueden formar ésteres fisiológicamente hidrolizables que funcionan como profármacos hidrolizándose en el cuerpo para obtener los compuestos de la Fórmula I *per se*. Preferentemente, tales profármacos se administran de manera oral, dado que la hidrólisis ocurre en muchos casos principalmente con la influencia de las enzimas digestivas. La administración parenteral puede usarse cuando el éster per se está activo, o cuando la hidrólisis se produce en la sangre. Los ejemplos de ésteres fisiológicamente hidrolizables de los compuestos de la Fórmula I incluyen C_{1-6}alquilo, C_{1-6}alquilbencilo, 4-metoxibencilo, indanilo, ftalilo, metoximetilo, C_{1-6} alcanoiloxi-C_{1-6}alquilo (por ejemplo, acetoximetilo, pivaloiloximetilo o propioniloximetilo), C_{1-6}alcoxicarboniloxi-C_{1-6}alquilo (por ejemplo, metoxicarbonil-oximetilo o etoxicarboniloximetilo, gliciloximetilo, fenilgliciloximetilo, (5-metil-2-oxo-1,3-dioxolen-4-il)-metilo) y otros ésteres fisiológicamente hidrolizables conocidos que se usan, por ejemplo, con penicilina y cefalosporina. Tales ésteres se pueden preparar mediante técnicas convencionales conocidas en el estado de la técnica.

La preparación de profármacos es conocida en el estado de la técnica y se describe, por ejemplo, en King, F.D., ed., *Medicinal Chemistry: Principles and Practice*, The

Royal Society of Chemistry, Cambridge, UK (2.da edición, reproducida, 2006); Testa, B. et al., *Hydrolysis in Drug and Prodrug Metabolism. Chemistry, Biochemistry and Enzymology*, VCHA and Wiley-VCH, Zúrich, Suiza (2003); Wermuth, C.G., ed., *The Practice of Medicinal Chemistry*, 3.ra edición, Academic Press, San Diego, CA (2008).

Se pretende que la presente invención incluya todos los isótopos de átomos que ocurren en estos compuestos. Los isótopos incluyen aquellos átomos que tienen el mismo número atómico, pero diferentes números másicos. A fin de brindar ejemplos generales y sin limitación, los isótopos de hidrógeno incluyen deuterio y tritio. Los isótopos de carbono incluyen ^{13}C y ^{14}C. Por lo general, los compuestos de la invención rotulados de manera isotópica se pueden preparar mediante técnicas convencionales conocidas por las personas del oficio de nivel medio o mediante procesos análogos a los que se describen en la presente, usando un reactivo adecuado rotulado de manera isotópica en lugar de un reactivo no rotulado.

El término "solvato" significa una asociación física de un compuesto de esta invención con una o más moléculas solventes, orgánicas o inorgánicas. Esta asociación física incluye la unión al hidrógeno. En ciertos casos, el solvato es capaz de aislarse, por ejemplo, cuando una o más moléculas solventes se incorporan en la red cristalina del sólido cristalino. Las moléculas solventes en el solvato

pueden estar presentes en una disposición regular y/o una disposición no ordenada. El solvato puede comprender una cantidad estoiquiométrica o no estoiquiométrica de las moléculas solventes. El "solvato" abarca tanto solvatos de solución-fase como solvatos que se pueden aislar. Los solvatos de ejemplo incluyen, entre otros, hidratos, etanolatos, metanolatos e isopropanolatos. En el estado de la técnica se conocen varios métodos de solvatación.

Las abreviaturas que se usan en la presente se definen de la siguiente manera: "1 x" para una vez, "2 x" para dos veces, "3 x" para tres veces, "°C" para grados Celsius, "eq" para equivalente o equivalentes, "g" para gramo o gramos, "mg" para miligramo o miligramos, "l" para litro o litros, "ml" para mililitro o mililitros, "µl" para microlitro o microlitros, "N" para normal, "M" para molar, "mmol" para milimol o milimoles, "min" para minuto, "h" para hora, "rt" para temperatura ambiente, "RT" para tiempo de retención, "atm" para atmósfera, "psi" para libras por pulgada cuadrada, "conc." para concentrado, "ac." para acuoso, "sat." para saturado, "MW" para peso molecular, "mp" para punto de fusión, "MS" o "esp. de masa" para espectrometría de masa, "ESI" para espectroscopía de masa por ionización de electrospray, "HR" para alta resolución, "HRMS" para espectrometría de masa de alta resolución, "LCMS" para cromatografía de líquidos/espectrometría de masa, "HPLC" para

cromatografía de líquidos de alta presión, "RP HPLC" para HPLC de fase inversa, "TLC" o "tlc" para cromatografía de capa delgada, "NMR" para espectroscopía de resonancia magnética nuclear, "nOe" para espectroscopía de efecto nuclear Overhauser, "^{1}H" para protón, "δ" para delta, "s" para singulete, "d" para doblete, "t" para triplete, "q" para cuarteto, "m" para multiplete, "br" para amplio, "Hz" para hertz, y "α", "β", "R", "S", "E", "Z" y "ee" son designaciones estereoquímicas conocidas por las personas del oficio de nivel medio.

Me	metilo
Et	etilo
Pr	propilo
i-Pr	isopropilo
Bu	butilo
i-Bu	isobutilo
t-Bu	*ter*-butilo
Ph	fenilo
Bn	bencilo
Hex	hexanos
MeOH	metanol
EtOH	etanol
i-PrOH o IPA	isopropanol
AcOH o HOAc	ácido acético
Ag_2CO_3	carbonato de plata

AgOAc	acetato de plata
$CDCl_3$	deutero-cloroformo
$CHCl_3$	cloroformo
cADN	ADN complementario
DCC	N,N'-diciclohexilcarbodiimida
DIAD	azodicarboxilato de diisopropilo
DMA	dimetilamina
DME	dimetiléter
DMF	dimetilformamida
DMSO	sulfóxido de dimetilo
DMAP	4-dimetilaminopiridina
EDTA	ácido etilendiaminotetraacético
EtOAc	acetato de etilo
Et_2O	dietiléter
$AlCl_3$	cloruro de aluminio
Boc	*ter*-butiloxicarbonilo
CH_2Cl_2	diclorometano
CH_3CN o ACN	acetonitrilo
Cs_2CO_3	carbonato de cesio
HCl	ácido clorhídrico
H_2SO_4	ácido sulfúrico
K_2CO_3	carbonato de potasio
KCN	cianuro de potasio
mCPBA o m-CPB	Aácido *meta*-cloroperbenzoico
Pd/C	paladio sobre carbón

$PhSO_2Cl$	cloruro de bencensulfonilo
i-PR_2NEt	diisopropiletilamina
PS	poliestireno
SFC	Cromatografía de fluido supercrítico
SiO_2	óxido de sílice
$SnCl_2$	cloruro de estaño(II)
TBAT	trifenidifluorosilicato de tetrabutilamonio
TEA	trietilamina
TFA	ácido trifluoroacético
THF	tetrahidrofurano
KOAc	acetato de potasio
$MgSO_4$	sulfato de magnesio
NaCl	cloruro de sodio
NaH	hidruro de sodio
$NaHCO_3$	bicarbonato de sodio
NaOH	hidróxido de sodio
Na_2SO_3	sulfito de sodio
Na_2SO_4	sulfato de sodio
NH_3	amoníaco
NH_4Cl	cloruro de amonio
NH_4OH	hidróxido de amonio
LG	grupo de salida
Pd_2dba_3	tris(dibencilidenacetona) dipaladio(0)

selectFluor bis(tetrafluoroborato) de N-fluoro-N'-metil-trietilendiamina

Los compuestos de la presente invención pueden prepararse de varias maneras conocidas por las personas del oficio de nivel medio en el área de la síntesis orgánica. Los compuestos de la presente invención se pueden sintetizar con los métodos descritos a continuación, junto con los métodos de síntesis conocidos en el arte de la química orgánica sintética o sus variaciones consideradas por la persona del oficio de nivel medio. Los métodos preferidos incluyen, entre otros, los que se describen a continuación. Las reacciones se realizan en un solvente o en una mezcla de solventes adecuados para los reactivos y materiales usados, y son adecuadas para las transformaciones que se llevan a cabo. Una persona del oficio de nivel medio en el área de la síntesis orgánica comprenderá que la funcionalidad presente en la molécula debe ser compatible con las transformaciones que se proponen. En ocasiones, esto requerirá cierto criterio para modificar el orden de las etapas de síntesis o para seleccionar un cronograma particular del proceso en lugar de otro, a fin de obtener el compuesto deseado de la invención.

Los compuestos novedosos de la presente invención se pueden preparar con las reacciones y técnicas descritas en esta sección. Además, en la descripción de los métodos de síntesis indicados a continuación, se debe tener en cuenta

que todas las condiciones de reacción propuestas, incluso la elección del solvente, la atmósfera de reacción, la temperatura de reacción, la duración del experimento y los procedimientos de preparación se eligen por ser condiciones estándares para esa reacción, que debe reconocer fácilmente un experto en el arte. Las restricciones a los sustituyentes que son compatibles con las condiciones de reacción serán evidentes para una persona del oficio de nivel medio y, por ello, se deben usar métodos alternativos.

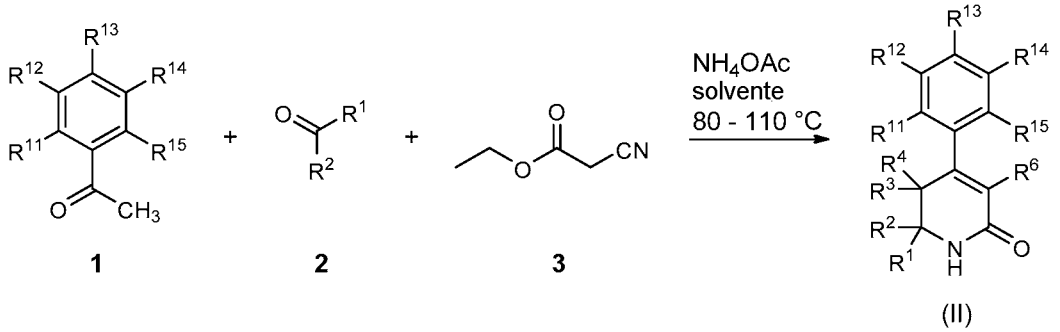
SÍNTESIS

Los compuestos de la Fórmula (I) se pueden preparar mediante los procesos ilustrativos descritos en los siguientes esquemas y ejemplos de trabajo, así como mediante los procedimientos pertinentes de la literatura publicada que usan las personas del oficio de nivel medio. Los reactivos y procedimientos ilustrativos para estas reacciones se indican a continuación y en los ejemplos de trabajo. La protección y la desprotección en los siguientes procesos se pueden realizar mediante procedimientos conocidos en general en el estado de la técnica (véase, por ejemplo, Wuts, P. G. M. y Greene, T.W. *Protecting Groups in Organic Synthesis*, 4.ta edición, Wiley (2007)). Los métodos generales de síntesis orgánicas y las transformaciones de grupos funcionales se pueden hallar en: Trost, B.M. y Fleming, I., eds., *Comprehensive Organic Synthesis: Selectivity, Strategy &*

Efficiency in Modern Organic Chemistry, Pergamon Press, Nueva York, NY (1991); Smith, M. B. y March, J., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*. 6.ta edición, Wiley & Sons, Nueva York, NY (2007); Katritzky, A.R. y Taylor, R. J. K., eds., *Comprehensive Organic Functional Groups Transformations II*, 2.da edición, Elsevier Science Inc., Tarrytown, NY (2004); Larock, R.C., *Comprehensive Organic Transformations*, VCH Publishers, Inc., Nueva York, NY (1999) y las referencias allí citadas.

Por ejemplo, los compuestos de la Fórmula (II), en donde $R^3 = R^4 = H$ y $R^6 = CN$, se pueden obtener de acuerdo con el Esquema 1. Las cetonas 1 y 2 y el acetato de 2 cianoetilo (3) se calientan entre 80°C y 110°C con acetato de amonio en un solvente, tal como DMF o DMSO. Las cetonas 1 y 2 pueden ser diferentes o iguales.

Esquema 1



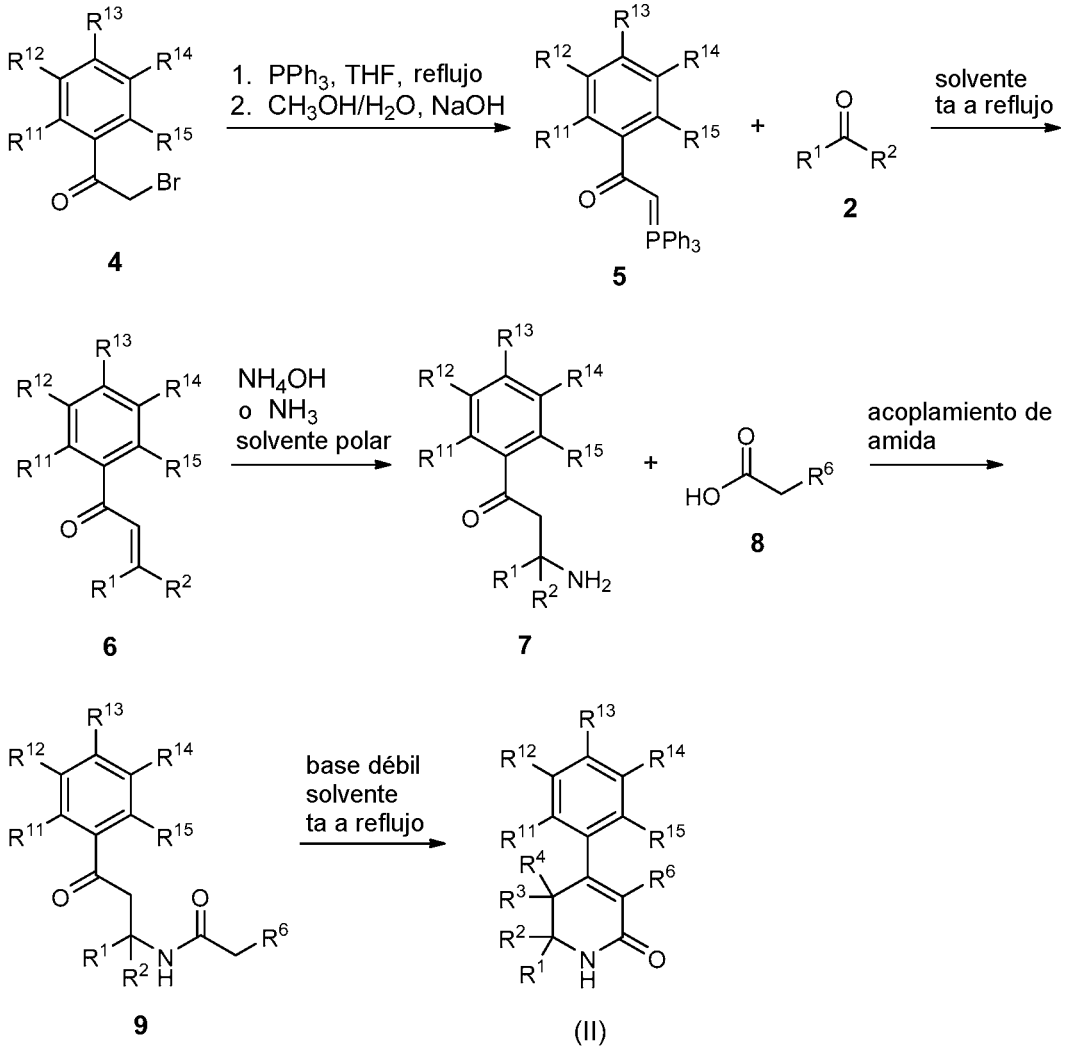
1 **2** **3** (II)

De manera alternativa, los compuestos de la Fórmula (II), en donde $R^3 = R^4 = H$, se pueden obtener de acuerdo con el Esquema 2. Se combina α-bromocetona **4** con trifenilfosfina en un solvente, tal como THF, CH_2Cl_2 o 1,4-dioxano, a

temperaturas entre temperatura ambiente y de reflujo. El intermediario bromuro de trifenilfosfonio se trata con una base, tal como NaOH, en un solvente, tal como metanol y agua para formar el iluro de fósforo **5**. El iluro de fósforo **5** se calienta a 80°C con cetona **2** en un solvente adecuado, tal como THF o DMSO, para obtener la α,β-cetona insaturada **6**, que puede existir como una mezcla de isómeros E/Z. Se puede usar irradiación de microondas para acortar el tiempo de reacción. La α,β-cetona insaturada 6 se trata con NH_4OH acuoso concentrado en un solvente, tal como DMSO, en un recipiente sellado para obtener la amina **7**. De manera alternativa, el alqueno **6** se puede tratar con NH_3 en un solvente, tal como DMSO o DMSO, y metanol en un recipiente sellado para obtener la amina **7**. La amina **7** se acopla con el ácido carboxílico **8** mediante varias reacciones formadoras de enlaces de amida. Por ejemplo, el ácido carboxílico **8** se puede convertir en el cloruro ácido correspondiente usando cloruro de oxalilo en un solvente, tal como CH_2Cl_2 y DMF catalítica. De manera alternativa, cuando R^6 es una amida o un heterociclo, el ácido carboxílico **8** se puede activar usando trifenilfosfina y tricloroacetonitrilo en un solvente adecuado, tal como CH_2Cl_2. Los cloruros ácidos formados de esta manera se combinan con la amina **7** en un solvente adecuado, tal como CH_2Cl_2 o CH_2Cl_2, y DMF en presencia de una base, preferentemente, piridina. Cuando R^2 es CF_3, la ciclización de la amida **9** en un compuesto

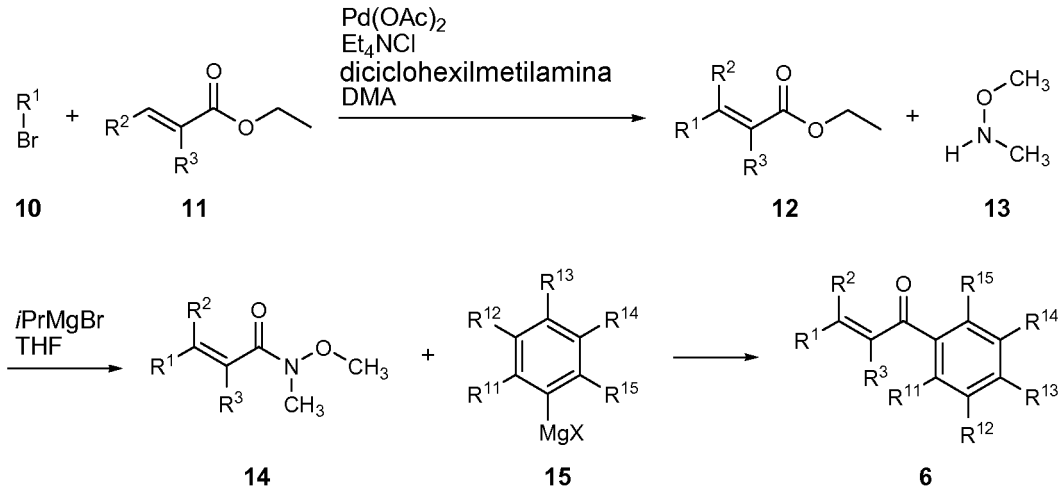
de la Fórmula (I) se produce, en general, durante el proceso de preparación de la amida **9**; por ejemplo, cuando una solución de EtOAc de la amida **9** se lava con $NaHCO_3$ acuoso saturado. Cuando la ciclización no se produce en estas condiciones, se puede realizar mediante la agitación de la amida **9** en presencia de una base débil, tal como piperidina, en un solvente adecuado, tal como EtOH, a una temperatura entre temperatura ambiente y de reflujo.

Esquema 2



Una síntesis alternativa a la α,β-cetona insaturada **6**, en donde R^1 es $-(CH_2)_m-$(fenilo sustituido con 0-3 R^b) y m = 0, se muestra en el Esquema 3. El bromuro de arilo **10** y el α,β-éster insaturado **11** se acoplan usando acetato de paladio (II), cloruro de tetrabutilamonio y diciclohexilamina en DMA a 110°C. El α,β-éster insaturado **12** se combina con *O,N*-dimetilhidroxil amina **13** en presencia de una base fuerte, tal como bromuro de iso propilmagnesio en un solvente aprótico, tal como THF. La α,β-amida insaturada **14** se combina con haluro de arilmagnesio **15** para obtener la α,β-cetona insaturada **6**. La identidad del haluro en el haluro de arilmagnesio depende de la disponibilidad del haluro de arilo que se usa para obtener el reactivo de Grignard; en general, el haluro es cloruro o bromuro.

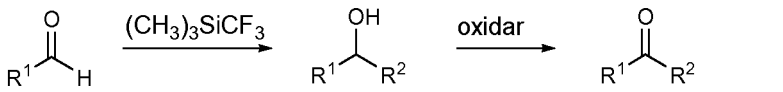
Esquema 3



Las α,α,α-trifluorocetonas no comerciales **2**, en donde R^2 = CF_3, se pueden obtener del aldehído **16**

correspondiente como se muestra en el Esquema 4. El aldehído **16** se hace reaccionar con trimetil-(trifluorometil)silano en presencia de una fuente de fluoruro, por ejemplo, fluoruro de cesio, usando un solvente adecuado, tal como dimetoxietano, a temperatura ambiente. También se pueden usar otras fuentes de fluoruro, tales como fluoruro ácido de potasio o difluorotrifenilsilicato de tetrabutilamonio, y otros solventes, tales como THF o acetonitrilo y metanol. El alcohol de trifluorometilo **17** se oxida, por ejemplo, con periodinano de Dess Martin, en un solvente adecuado, tal como CH_2Cl_2.

Esquema 4

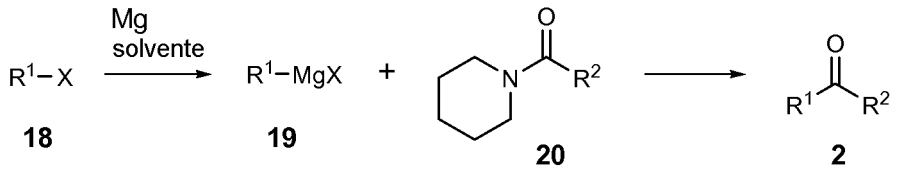


16 **17**: $R^2 = CF_3$ **2**: $R^2 = CF_3$

Las cetonas de la Fórmula **2** se pueden obtener de acuerdo con el Esquema 5. Por ejemplo, el haluro de arilo **18**, en donde X = bromo y el grupo arilo es una porción química adecuada para formar un reactivo de Grignard, se combina con metal de magnesio en presencia de un iniciador, tal como yodo, en un solvente adecuado, tal como THF. Se pueden usar otros haluros de alquilo que tienen una porción química adecuada para formar reactivos de Grignard, otros haluros, tales como cloro o yodo, otros solventes, tales como dietiléter o 1,4-dioxano, y otros iniciadores, tales como

1,2-dibromoeteno, según lo determinen las personas del oficio de nivel medio. El reactivo de Grignard **19** se combina con la amida **20** en un solvente adecuado, tal como THF, para obtener cetona **2**. Se pueden usar otros solventes, tales como 1,4-dioxano o dietiléter, según lo determinen las personas del oficio de nivel medio.

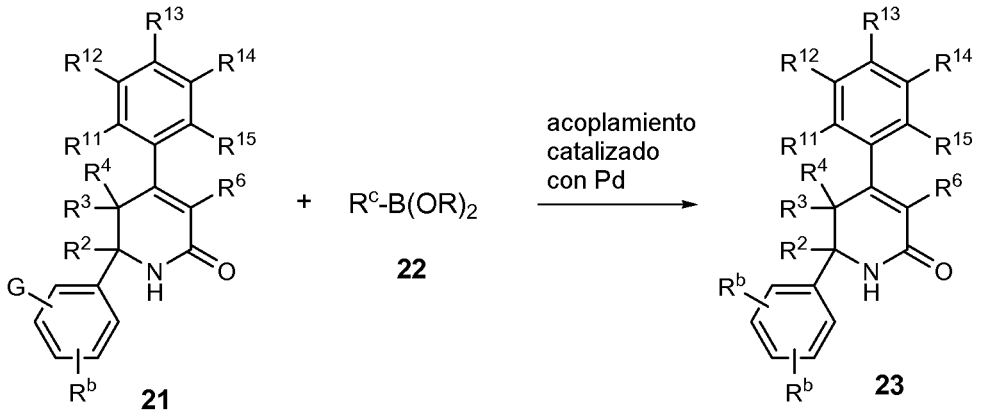
Esquema 5



Los compuestos de la Fórmula **23** que tienen $R^3 = R^4 =$ H, $R^1 = (CH_2)_m$-(fenilo sustituido con 0-3 R^b), en donde m = 0 y al menos un $R^b = -(CH_2)_n-(X)_t-(CH_2)_m-R^c$ en donde n = m = t = 0 o n = m = 0 y t = 1 cuando X = O o NH, y R^c es una porción química adecuada para participar en las reacciones de acoplamiento cruzado de paladio, se pueden obtener de acuerdo con Esquema 6. El compuesto **21** se calienta con ácido borónico **22**, en donde R = H, en presencia de un catalizador de paladio y una base usando un solvente adecuado, tal como 1,4-dioxano, tolueno, DMF con o sin agua. El ácido borónico **22** se puede sustituir con análogos de ácido borónico alternativos, tales como ésteres de boronato, trifluoroboratos y otros conocidos por las personas del oficio de nivel medio. Los catalizadores de paladio que se usan habitualmente incluyen, entre otros, $Pd(PPh_3)_4$ y $PdCl_2$(dppf). Se puede usar otro catalizador de

paladio conocido por las personas del oficio de nivel medio. Las bases que se usan habitualmente incluyen, entre otras, K_3PO_4 y K_2CO_3. También se pueden usar otras bases conocidas por las personas del oficio de nivel medio. Cuando n = m = 0 y t = 1 cuando X = O o NH, se pueden obtener biariléteres o biarilaminas, tales como **23**, de **21** cuando G = OH. De manera alternativa, también se pueden obtener aminas y éteres de biarilo de **21**, en donde G = ácido borónico o un equivalente, mediante el acoplamiento catalizado por metal con fenoles o aminas adecuadas.

Esquema 6

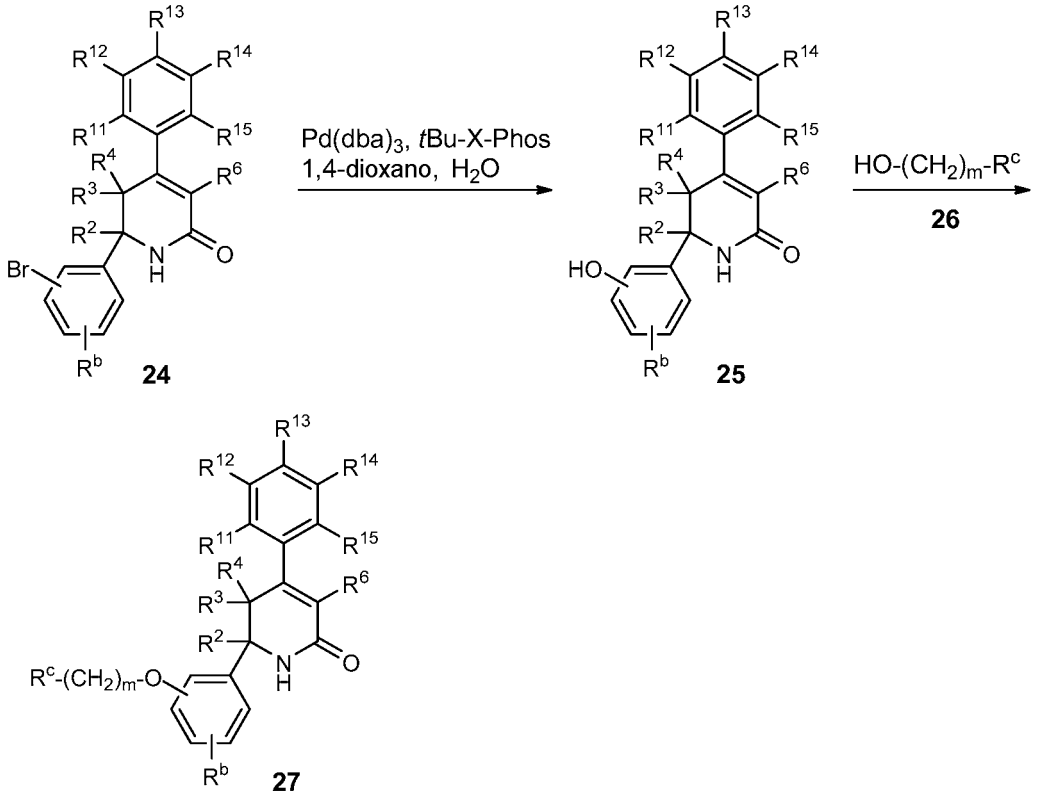


G = Cl, Br, I, OMs, OTs, OTf, OH, NH_2

Los compuestos de la Fórmula **27** que tienen $R^3 = R^4 =$ H, $R^1 = -(CH_2)_m-$(fenilo sustituido con 0-3 R^b) en donde m = 0, y al menos un $R^b = -(CH_2)_n-(X)_t-(CH_2)_m-R^c$ en donde n = 0, t = 1, m = 1 4 y X = O, se pueden obtener de acuerdo con el Esquema 7. El bromuro **24** se trata con tris(dibencilidenacetona)paladio (0) en presencia de bis(1,1-

dimetiletil)[2′,4′,6′-tris(1-metiletil)[1,1′-bifenil]-2-il]-fosfina (*t*-butil-Xphos) usando 1,4-dioxano y agua como solvente y KOH como base. El fenol **25** y el alcohol **26** se agitan en presencia de trifenilfosfina y DIAD en un solvente adecuado, tal como CH_2Cl_2.

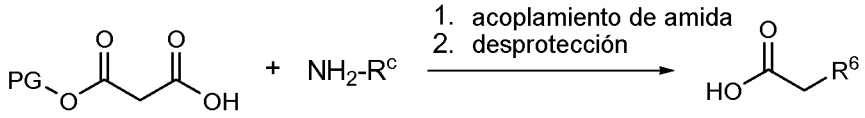
Esquema 7



El ácido carboxílico **8**, en donde R^6 = $CONHR^c$, se puede obtener de acuerdo con el Esquema 8. El monoéster de ácido malónico **28**, en donde PG = grupo bencilo, y la amina **29** se acoplan en condiciones estándares formadoras de enlaces de amida. Por ejemplo, el tratamiento de ácido carboxílico **28** con cloruro de oxalilo en CH_2Cl_2 y DMF proporciona el cloruro

ácido. Luego, el cloruro ácido se combina con la amina **29** en presencia de piridina en un solvente adecuado, tal como CH_2Cl_2. Se puede usar otra reacción formadora de enlaces de amida conocida por las personas del oficio de nivel medio. El grupo bencilo se retira usando una combinación de gas hidrógeno y 10% de paladio sobre carbón en un solvente adecuado, tal como metanol o metanol y EtOAc. Se pueden usar otras porciones PG y métodos para su eliminación conocidos por las personas del oficio de nivel medio.

Esquema 8



28 **29** **8**: $R^6 = CONHR^c$

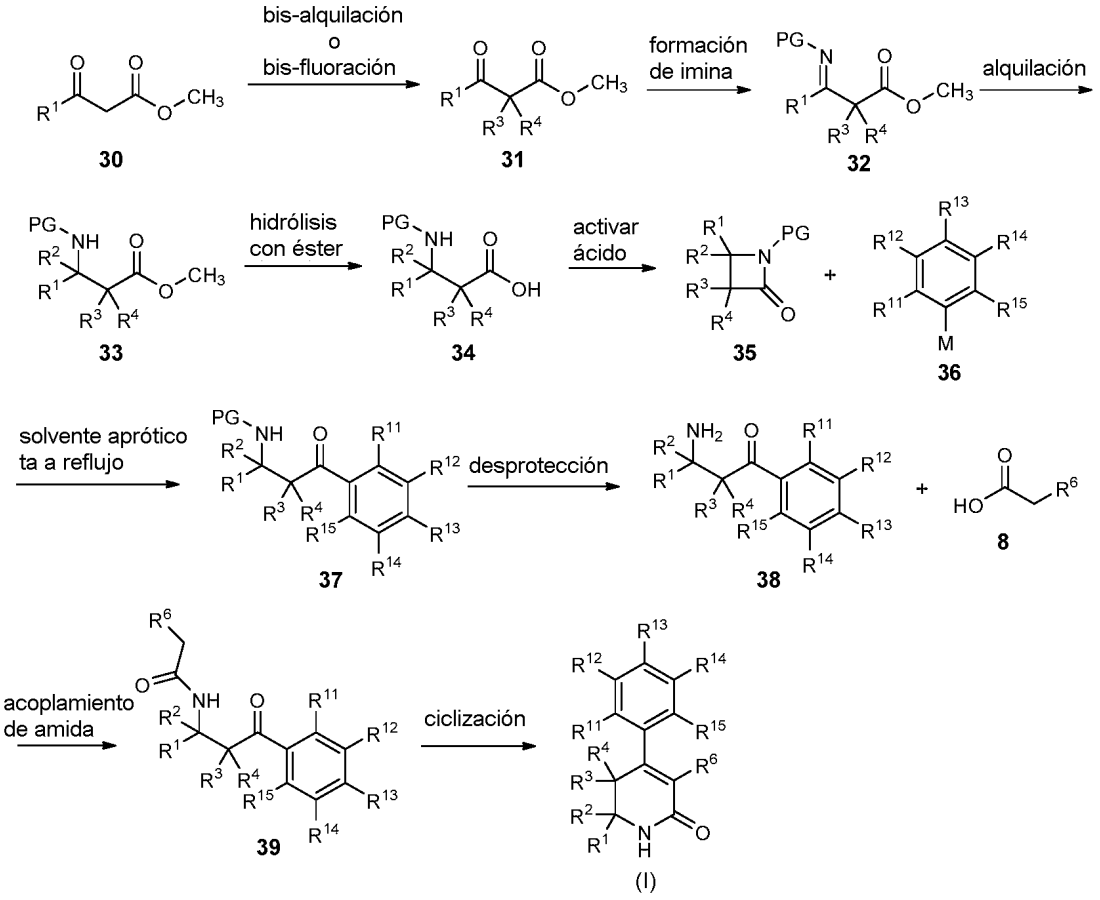
Los compuestos de la Fórmula (I), en donde R^3 y R^4, se combinan con el átomo de carbono al que están unidos para formar un carbociclo de 3-6 miembros, o $R^3 = R^4 = F$, se pueden obtener de acuerdo con el Esquema 9. Por ejemplo, para sintetizar los compuestos de la Fórmula (I) en donde R^3 y R^4 se combinan con el átomo de carbono al que están unidos para formar un anillo de 3 miembros (es decir, ciclopropilo), el β-cetoéster **30** se agita a temperatura ambiente con 1,2-dibromoetano en presencia de una base, por ejemplo K_2CO_3, en un solvente adecuado, tal como DMF, para obtener β-cetoéster de ciclopropilo **31**. El β-cetoéster de ciclopropilo **31** se agita con una amina adecuada, tal como bencilamina, en

presencia de un ácido de Lewis adecuado, tal como $TiCl_4$, en un solvente, tal como CH_2Cl_2, inicialmente a 0°C y luego calentándolo hasta alcanzar temperatura ambiente. Se pueden usar otras aminas, ácidos de Lewis, solventes y temperaturas, según lo determinen las personas del oficio de nivel medio. El uso de bencilamina proporciona la imina **32**, en donde PG = bencilo. La imina **32** se alquila, por ejemplo, con trimetil(trifluorometil)silano en presencia de una fluente de fluoruro, tal como fluoruro ácido de potasio y TFA, usando acetonitrilo y DMF. Se pueden usar otras fuentes de fluoruro, tales como difluorotrifenilsilicato de tetrabutilamonio o fluoruro de cesio, otros ácidos, tales como HOAc o HCl, y otros solventes, según lo determinen las personas del oficio de nivel medio. El uso de trimetil(trifluorometil)silano proporciona el aminoéster **33**, en donde $R^2 = CF_3$. La hidrólisis de éster del aminoéster **33** se realiza en presencia de yoduro de litio con piridina a reflujo para obtener el aminoácido **34**. Se pueden usar otras condiciones de hidrólisis conocidas por las personas del oficio de nivel medio. La ciclización del aminoácido **34** en β-lactama **35** se realiza mediante la activación del ácido carboxílico del aminoácido **34** con cloruro de oxalilo en un solvente adecuado, tal como CH_2Cl_2, que contiene DMF catalítica. La ciclización se produce de manera espontánea a temperatura ambiente para obtener β-lactama $_{35}$. Se pueden usar otros métodos para activar el ácido

carboxílico, según lo determinen las personas del oficio de nivel medio. La β-lactama 35 se arila con un reactivo organometálico. Los reactivos organometálicos pueden incluir, por ejemplo, reactivos de Grignard o reactivos de organolitio, formados de un anillo de fenilo sustituido de manera adecuada, que contiene un átomo de haluro capaz de reaccionar con magnesio elemental para formar un reactivo de Grignard o con un reactivo de alquil litio para formar un reactivo de fenil litio mediante transmetalación. Las condiciones exactas necesarias para formar estas especies organometálicas de fenilo deben determinarlas las personas del oficio de nivel medio. Se usa un solvente aprótico adecuado, por ejemplo, THF. Se pueden usar otros solventes adecuados, según lo determinen las personas del oficio de nivel medio. La reacción se realiza entre temperatura ambiente y de reflujo, según la identidad del reactivo organometálico que se use y el patrón de sustitución en β-lactama **35**. La β-aminocetona **37** formada de esta manera se desprotege con gas hidrógeno y 10% de paladio sobre carbón en un solvente adecuado, tal como metanol, que contiene 4.4% de ácido fórmico para obtener β-aminocetona **38**. Se pueden usar otras condiciones para eliminar el grupo bencilo, según lo determinen las personas del oficio de nivel medio. La β-aminocetona **38** se acila con ácido carboxílico **8** usando las condiciones descritas en el Esquema 2 para obtener β-

cetoamida **39**. La agitación de β-cetoamida **39** con una base, tal como etóxido de sodio, en un solvente adecuado, tal como etanol, a temperatura ambiente proporciona compuestos que tienen la Fórmula (I).

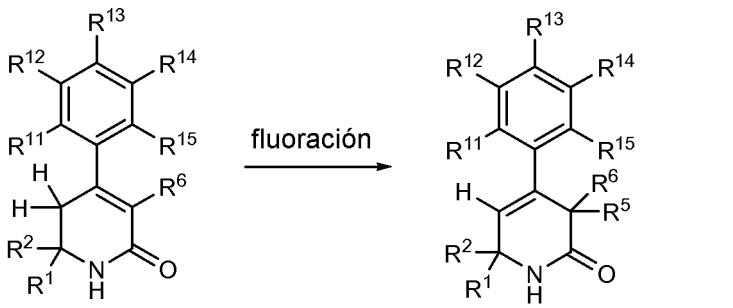
Esquema 9



Los compuestos de la Fórmula (I), en donde y es un enlace simple y R^5 = F, se pueden obtener de acuerdo con el Esquema 10. Esta síntesis se ejemplifica para un compuesto de la Fórmula (I) en donde R^6 = CN. Por ello, un compuesto de la Fórmula (I), en donde x es un enlace simple y R^6 = CN, se

calentó a 80°C en presencia de un reactivo de fluorinación, bis(tetrafluoroborato) de 1-fluoro-4-hidroxi-1,4-diazoniabiciclo[2,2,2]octano, en un solvente adecuado, tal como DMF, en presencia de una base, tal como Na_2CO_3, para obtener los compuestos de la Fórmula (I), en donde y es un enlace simple, R^5 = F y R^6 = CN. Se pueden usar otros reactivos de fluorinación, solventes y bases, según lo determinen las personas del oficio de nivel medio.

Esquema 10

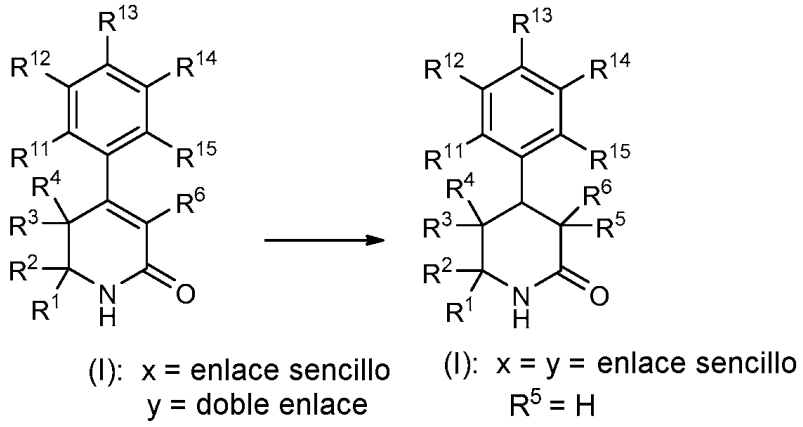


(I): x = enlace sencillo

(I): y = enlace sencillo
R^6 = F

Los compuestos de la Fórmula (I), en donde x e y son ambos enlaces simples y R^5 = H, se pueden obtener de acuerdo con el Esquema 11. La reducción de los compuestos de la Fórmula (I), en donde x es igual a un enlace simple e y es igual a un enlace doble, se realiza con un catalizador adecuado, tal como paladio sobre carbón, en una atmósfera de gas hidrógeno a una presión adecuada, tal como 50 psi, para la reducción del enlace doble y en un enlace simple. Los solventes adecuados incluyen, entre otros, metanol.

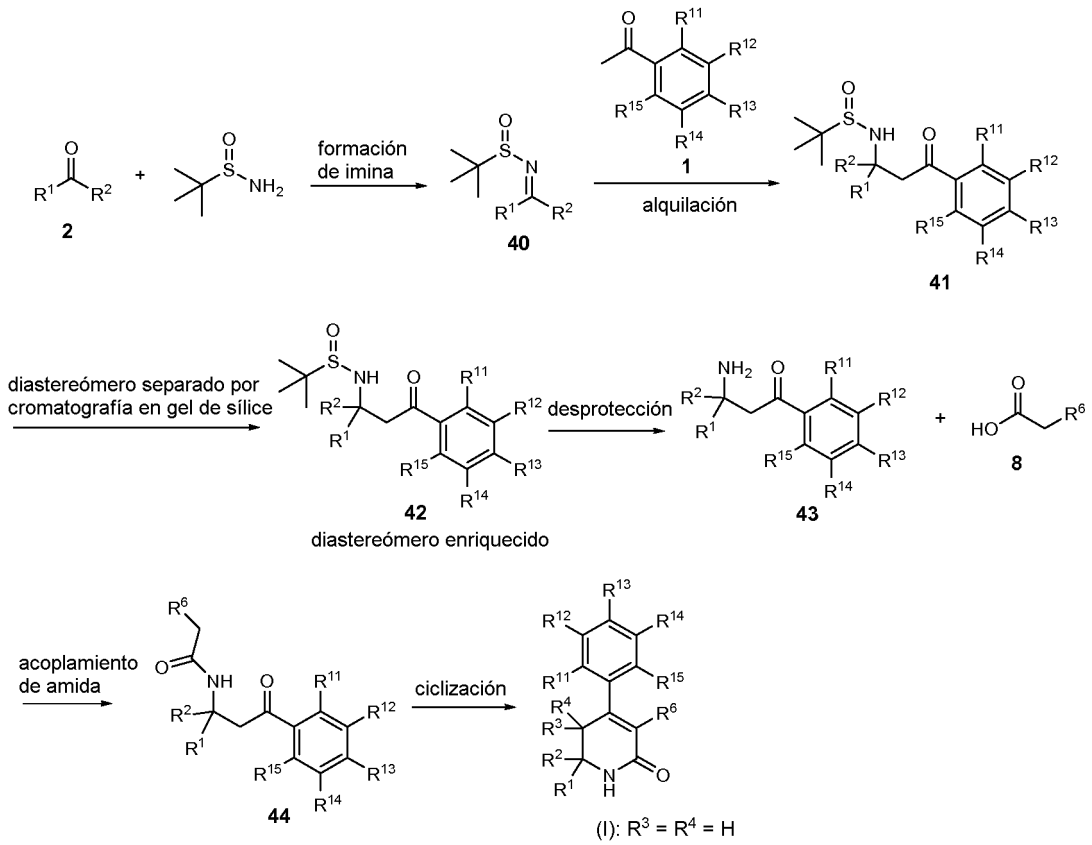
Esquema 11



Los compuestos de la Fórmula (II), un enantiómero simple, en donde R^3 = R^4 =H, se pueden obtener de acuerdo con el Esquema 12. La cetona **2** se agita con 2-metilpropan-2-sulfinamida en presencia de un ácido de Lewis adecuado, tal como $Ti(OEt)_4$, en un solvente, tal como THF, a temperatura de reflujo para obtener la imina **40**. Se pueden usar otros ácidos de Lewis, solventes y temperaturas, según lo determinen las personas del oficio de nivel medio. La imina **40** se alquila con cetona 1 en presencia de una base, tal como LiHMDS, KHMDS, NaHMDS o LDA, en un solvente aprótico, tal como THF o éter, a una temperatura que varía de -78°C a temperatura ambiente para obtener la β-aminocetona **41** como una mezcla de dos diastereómeros, que se pueden separar mediante cromatografía en gel de sílice para obtener el isómero **42** deseado. Se pueden usar otros

enolatos de metal (tal como enolato de titanio), solventes y temperaturas, según lo determinen las personas del oficio de nivel medio (T. P. Tang, J. A Ellman, *J. Org. Chem.* 1999, 64, 12-13, *J. Org. Chem.* 2002, 67, 7819-7832). Con preferencia, la *S*- o *R*-2-metilpropan-2-sulfinamida quiral se puede usar opcionalmente para generar cada uno de los enantiómeros ópticamente puros de imina **40** que pueden permitir la inducción quiral, a fin de preparar la cetona diastereoméricamente enriquecida **42**. En estos casos, la mezcla de producto se puede purificar aún más mediante cromatografía en gel de sílice para obtener los productos deseados con un exceso diaseteroménico de >97%. La β-aminocetona **42** formada de esta manera se desprotege usando HCl en un solvente adecuado, tal como MeOH, para obtener β-aminocetona **43**. Se pueden usar otras condiciones para eliminar el grupo *t*-butilsulfinilo, según lo determinen las personas del oficio de nivel medio. La β-aminocetona **43** se acila con ácido carboxílico **8** usando las condiciones descritas en el Esquema 2 para obtener β-cetoamida **44**. La agitación de β-cetoamida **44** con una base, tal como etóxido de sodio, en un solvente adecuado, tal como etanol, a temperatura ambiente proporciona compuestos que tienen la Fórmula (II).

Esquema 12

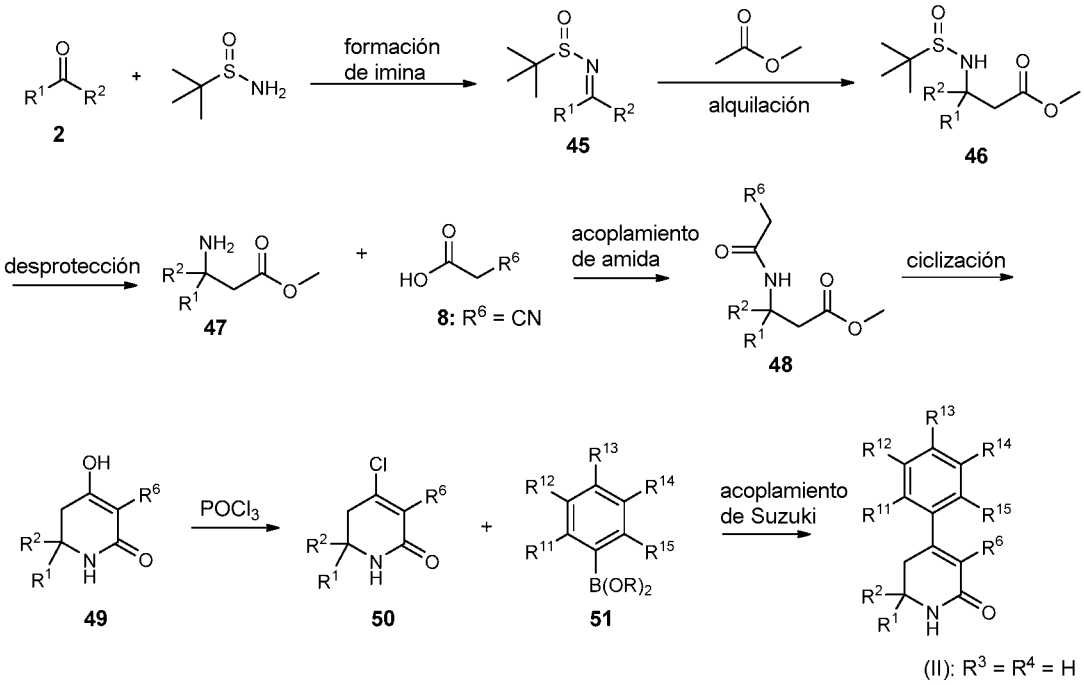


De manera alternativa, los compuestos de la Fórmula (II), en donde $R^3 = R^4 = H$, se pueden obtener de acuerdo con el Esquema 13. La cetona **2** se puede hacer reaccionar con 2-metilpropan-2-sulfinamida en presencia de un ácido de Lewis adecuado, tal como $Ti(OEt)_4$, en un solvente, tal como THF, a una temperatura que varíe de temperatura ambiente a reflujo para obtener la imina **45**. Se pueden usar otros ácidos de Lewis, solventes y temperaturas, según lo determinen las personas del oficio de nivel medio. La imina **45** se alquila con el enolato de

un éster en un solvente aprótico adecuado, tal como THF o éter inicialmente a -78°C y luego se calienta a 0°C o temperatura ambiente para obtener la β-aminocetona **46** protegida como una mezcla de dos diastereómeros, que se pueden separar mediante cromatografía en gel de sílice para obtener cada compuesto quiral individual. La generación del enolato del éster se logra mediante el tratamiento del éster, tal como acetato de metilo, con una base adecuada, tal como LHMDS, KHMDS, NaHMDS o LDA, en un solvente aprótico, tal como THF o éter, a una temperatura que varía de -78°C a temperatura ambiente. Se pueden usar otros enolatos de metal (tal como enolato de titanio), solventes y temperaturas, según lo determinen las personas del oficio de nivel medio (T. P. Tang, J. A Ellman, *J. Org. Chem.* 1999, 64, 12-13, *J. Org. Chem.* 2002, 67, 7819-7832). Con preferencia, la *S*- o *R*-2-metilpropan-2-sulfinamida quiral se puede usar opcionalmente para generar cada uno de los enantiómeros ópticamente puros de imina 45 que pueden permitir la inducción quiral, a fin de preparar el éster diastereoméricamente enriquecido **46**. En estos casos, la mezcla de producto se puede purificar aún más mediante cromatografía en gel de sílice para obtener los productos deseados con un exceso diastereomérico de >97%. El grupo *ter*-butilsulfinilo de **46** se retira mediante ácidos, tales

como HCl y TFA, en un solvente adecuado, tal como MeOH o dioxano, para generar el aminoéster **47**. Se pueden usar otras condiciones para eliminar el grupo *t*-butilsulfinilo, según lo determinen las personas del oficio de nivel medio. La β-aminocetona **47** se acila con ácido carboxílico **8** usando las condiciones descritas en el Esquema 2 para obtener β-cetoamida **48**. La agitación de β-cetoamida **48** con una base, tal como etóxido de sodio, en un solvente adecuado, tal como etanol, a una temperatura de temperatura ambiente a 80°C proporciona el enol cíclico **49**. También se pueden usar otras condiciones para realizar la ciclización, según lo determinen las personas del oficio de nivel medio. El compuesto **49**, cuando se trata con una cantidad estoiquiométrica de un agente de clorinación, tal como $POCl_3$, a temperatura elevada en un solvente inerte, tal como tolueno, se convierte en mono-cloruro **50**. Luego, el cloruro **50** se puede hacer reaccionar con varios reactivos borónicos mediante una reacción de acoplamiento cruzado tipo Suzuki para generar los compuestos de la Fórmula (II). Las elecciones de reactivos borónicos, catalizadores, ligandos, bases, solventes y temperaturas están documentados en la literatura y pueden ser seleccionadas de manera adecuada por las personas del oficio de nivel medio.

Esquema 13

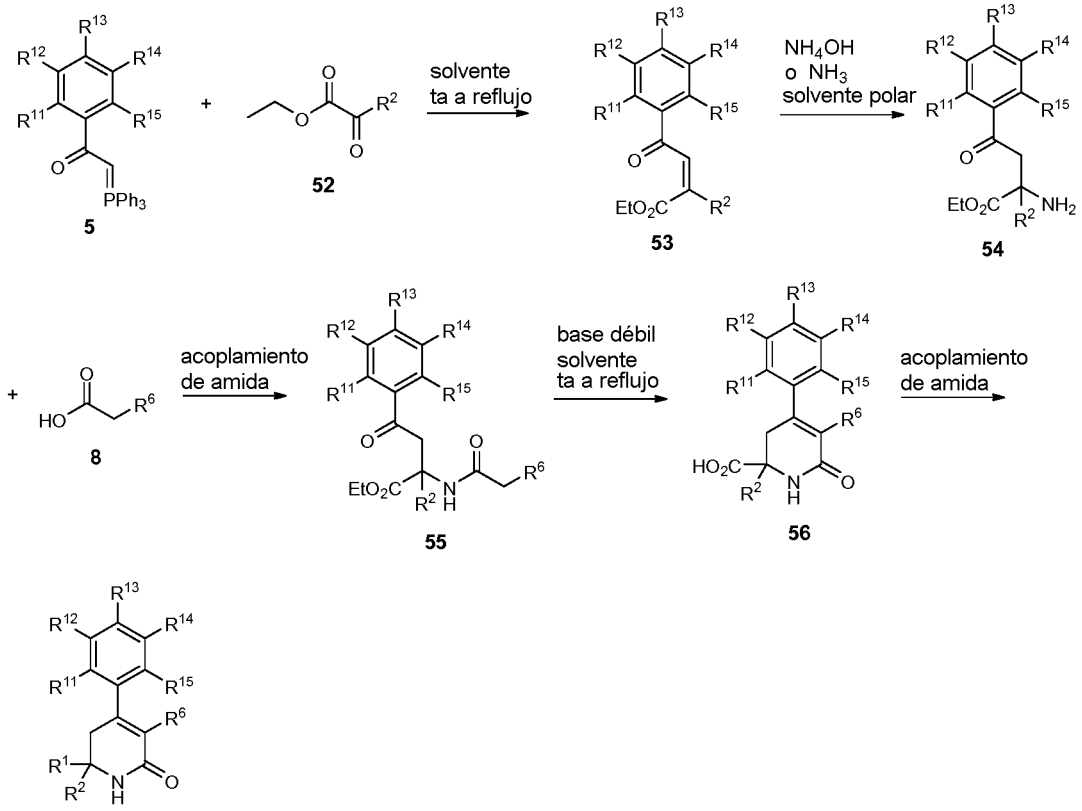


Los compuestos de la Fórmula (II), en donde R^3 = R^4 =H y R^1 = $CONHC_{4-18}$ alquilo o $CONH(CH_2)_{1-8}Ph$ se pueden obtener de acuerdo con el Esquema 14. El iluro de fósforo **5** se calienta, usando irradiación de microondas, a 150°C con α-cetona **52** en un solvente adecuado, tal como THF o DMSO, para obtener la α,β-cetona insaturada **53**. La α,β-cetona insaturada **53** se trata con NH_4OH acuoso concentrado en un solvente, tal como DMSO, en un recipiente sellado para obtener la amina **54**. De manera alternativa, el alqueno **53** se puede tratar con NH_3 en un solvente, tal como DMSO o DMSO y metanol en un recipiente sellado para obtener la amina **54**. La amina **54** se acopla con el ácido carboxílico **8** mediante varias reacciones formadoras de enlaces de amida. Por ejemplo, el ácido

carboxílico **8** se puede convertir en el cloruro ácido correspondiente usando cloruro de oxalilo en un solvente, tal como CH_2Cl_2 y DMF catalítica. De manera alternativa, el ácido carboxílico **8** se puede activar con 1-cloro-N,N,2-trimetilprop-en-1-amina en un solvente adecuado, tal como CH_2Cl_2. Los cloruros ácidos formados de esta manera se combinan con la amina **54** en un solvente adecuado, tal como CH_2Cl_2 o CH_2Cl_2 y DMF en presencia de una base, preferentemente, piridina. Se puede usar otra reacción formadora de enlaces de amida conocida por las personas del oficio de nivel medio. En general, la ciclización de la amida **55** y la posterior hidrólisis en el ácido carboxílico 56 se produce mediante la agitación de la amida **55** en presencia de una base débil, tal como piperidina, en un solvente adecuado, tal como EtOH, a una temperatura entre temperatura ambiente y de reflujo, o una base, tal como hidróxido de litio, en un solvente adecuado, tal como THF y agua, a temperatura ambiente. De manera alternativa, cuando R^6 es un nitrilo, la ciclización de la amida **55** se produce, en general, mediante la agitación de la amida **55** en presencia de una base, tal como hidróxido de litio, en un solvente adecuado, tal como THF y agua, a temperatura ambiente. Luego, la hidrólisis se realiza en condiciones ácidas con un ácido fuerte, tal como HCl, en un solvente adecuado, tal como ácido acético, a temperaturas entre temperatura ambiente y 50°C. El ácido

carboxílico 56 y una amina se acoplan usando condiciones estándares formadoras de enlaces de amida. Por ejemplo, el tratamiento de ácido carboxílico **56** y una amina con HOBt, EDC y DIEA, en presencia de piridina en un solvente adecuado, tal como DCM, a temperatura ambiente proporciona compuestos que tienen la Fórmula (II). Se puede usar otra reacción formadora de enlaces de amida conocida por las personas del oficio de nivel medio.

Esquema 14



5 **52** **53** **54** **8** **55** **56**

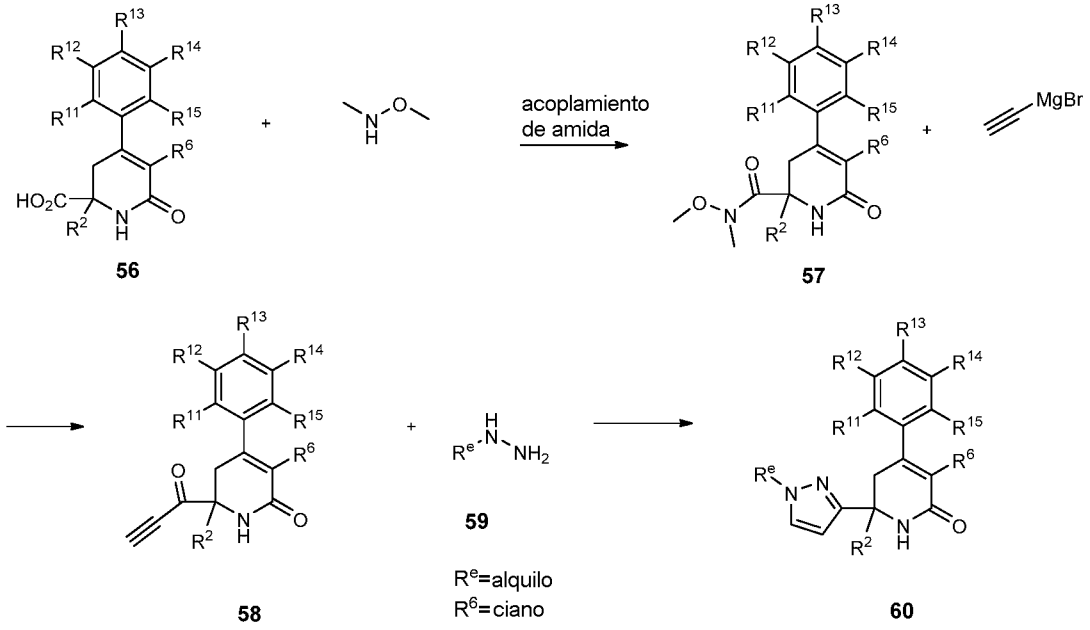
(II): R^1 = $CONHC_{4-18}$ alquilo, $CONH(CH_2)_{2-8}Ph$

$R^3 = R^4 = H$

Los compuestos de la Fórmula **60** que tienen R^e = alquilo y R^6 = ciano se pueden sintetizar mediante el

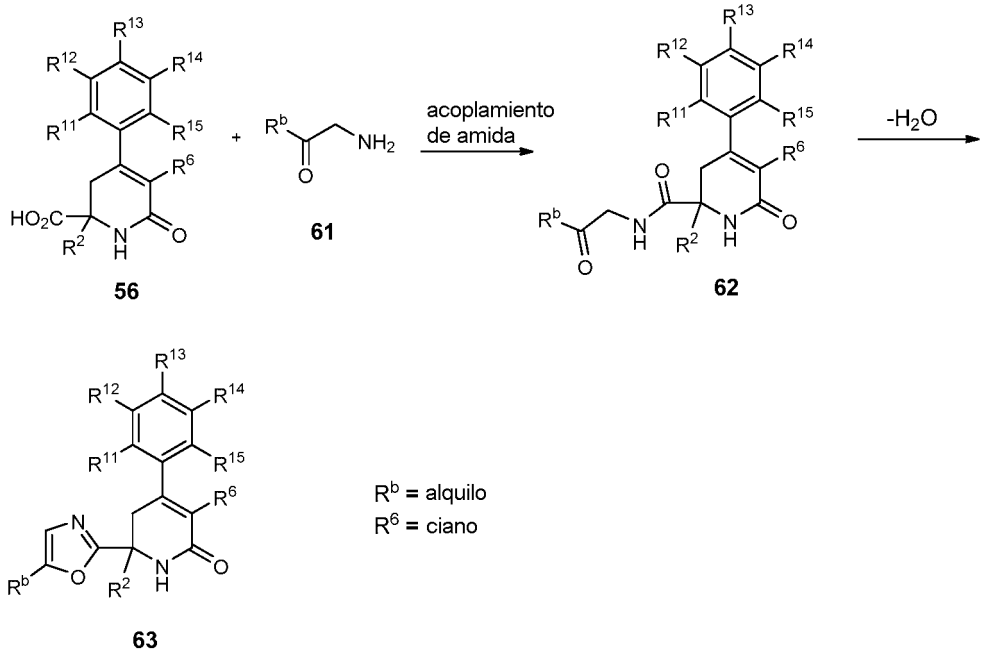
acoplamiento del ácido **56** con N,O-dimetilhidroxilamina usando las típicas reacciones formadoras de enlaces de amida. Por ejemplo, el ácido carboxílico **56** se acopla a N,O-dimetilhidroxilamina usando EDC en presencia de una base, preferentemente N-metilmorfolina, en un solvente adecuado, tal como CH_2Cl_2, para obtener la amida Weinreb **57**. También se pueden usar otras reacciones formadoras de amida conocidas por las personas del oficio de nivel medio. La amida Weinreb intermediaria **57** reacciona con bromuro de etinilmagnesio en un solvente aprótico, tal como THF, a 0-35°C para obtener el intermediario de acilacetiluro **58**. Los compuestos de la Fórmula **60** se obtienen cuando el intermediario de acilacetiluro **58** reacciona con la hidrazina **59** en presencia de una base, tal como TEA, en un solvente adecuado, tal como EtOH.

Esquema 15



Los compuestos de la Fórmula **63** que tienen R^b = alquilo y R^6 = ciano se pueden sintetizar, primero, mediante el acoplamiento del ácido **56** a la β-cetoamina **61** usando las típicas reacciones formadoras de enlaces de amida. Por ejemplo, el ácido carboxílico **56** se acopla a α-cetoamina **61** usando EDC y HOBt en presencia de una base, preferentemente DIEA, en un solvente adecuado, tal como CH_2Cl_2, para obtener β-cetoamida **62.** También se pueden usar otras reacciones formadoras de amida conocidas por las personas del oficio de nivel medio. Luego, el oxazol sustituido con 5-alquilo **63** se obtiene mediante la ciclización deshidratada de β-cetoamida **62** usando un agente de deshidratación, preferentemente $POCl_3$, en presencia de una base adecuada, tal como DIEA, en un solvente adecuado, tal como dicloroetano, a una temperatura de 80-120°C.

Esquema 16



IV. BIOLOGÍA

En los mamíferos, existen dos vías de síntesis de los triglicéridos: la vía de glicerol-3-fosfato y la vía de monoacilglicerol. La primera es fundamentalmente responsable del almacenamiento de energía en los tejidos periféricos, tales como tejidos adiposos, hepáticos y músculo esquelético; el segundo es esencial para la absorción de la grasa alimenticia, que se produce en el intestino delgado. Cuando se ingiere grasa alimenticia, la lipasa pancreática digiere los triglicéridos en ácidos grasos libres y 2-monoacilglicerol, que son absorbidos por los enterocitos epiteliales del intestino. Una vez que se encuentran dentro de los enterocitos, los ácidos grasos libres y el 2 monoacilglicerol se usan como bloques de construcción para volver a sintetizar los triglicéridos mediante dos etapas de acilación secuenciales: primero mediante MGAT y luego mediante reacciones enzimáticas DGAT. Luego, los triglicéridos se incorporan en los quilomicrones y se segregan en la linfa a fin de usarse como suministro energético para el cuerpo.

La monoacilglicerol aciltransferasa 2 (MGAT2) es una aciltransferasa fijada a la membrana que pertenece a la familia génica de diacilglicerol aciltransferasa 2 (DGAT2). Se expresa de manera selectiva y en gran medida en el intestino delgado. La eliminación genética de MGAT2 en los

ratones disminuyó la velocidad de absorción de los triglicéridos ingeridos por vía oral, lo cual indica que MGAT2 tiene una función importante en la vía intestinal de MGAT/DGAT [Yen, C.L. et al, *Nat. Med.*, 15(4):442-446 (2009); Okawa, M. et al., *Biochem. Biophys. Res. Commun.*, 390(3):377-381 (2009)]. A diferencia de los ratones de tipo silvestre que se volvieron obesos, los ratones con MGAT2 inactivado sometidos de manera crónica a una dieta alta en grasas resistieron el impacto de una alimentación alta en grasas y mostraron menos peso corporal, adiposidad y acumulación de grasas hepáticas. A diferencia de los ratones de tipo silvestre hiperinsulinémicos después de ser sometidos a una dieta alta en grasas, la eliminación de MGAT2 normalizó el nivel de insulina y disminuyó la glucosa en ayunas. En la prueba de tolerancia a la glucosa, también tuvieron una mejor fluctuación de la glucosa. Acorde con un perfil glucémico mejorado, los ratones con MGAT2 inactivado también exhibieron un mayor nivel de GLP1, una hormona intestinal incretina que tiene un gran impacto en el metabolismo de la glucosa [Yen, C.L. et al., *Nat. Med.*, 15(4):442-446 (2009)]. En conjunto, se espera que la inhibición de MGAT2 por medio de la intervención farmacológica proporcione el mismo beneficio que se muestra en los ratones inactivados, por ejemplo, resistencia al aumento de peso, o por el contrario, reducción de la masa corporal grasa. Además, la inhibición de MGAT2

mejoraría la sensibilidad a la insulina y el metabolismo de la glucosa, lo cual conduce a una menor incidencia de la diabetes tipo II o al tratamiento de una afección diabética.

Asimismo, se prefiere y resulta conveniente encontrar compuestos con características ventajosas y mejoradas en comparación con los agentes antidiabéticos conocidos, en una o más de las siguientes categorías que se proporcionan como ejemplo y no son taxativas: (a) propiedades farmacocinéticas, que incluyen la biodisponibilidad oral, la semivida y la depuración; (b) propiedades farmacéuticas; (c) requisitos de dosis; (d) factores que disminuyen las características de máximo a mínimo de la concentración del fármaco en sangre; (e) factores que aumentan la concentración del fármaco activo en el receptor; (f) factores que disminuyen la responsabilidad de interacciones farmacológicas clínicas; (g) factores que disminuyen los posibles efectos secundarios adversos, que incluyen la selectividad contra otras dianas biológicas; y (h) un índice terapéutico mejorado menos propenso a la hipoglucemia.

Como se usa en la presente, el término "paciente" abarca todas las especies de mamíferos.

Como se usa en la presente, el término "sujeto" se refiere a cualquier organismo humano o no humano que se podría beneficiar potencialmente del tratamiento con un inhibidor de MGAT2. Los sujetos de ejemplo incluyen seres

humanos de cualquier edad con factores de riesgo para enfermedades metabólicas. Los factores de riesgo habituales incluyen, entre otros, la edad, el género, el peso, los antecedentes familiares o signos de resistencia a la insulina, tales como acantosis pigmentaria, hipertensión, dislipidemia o síndrome del ovario poliquístico (PCOS, por sus siglas en inglés).

Como se usan en la presente, "tratar" o "tratamiento" abarcan el tratamiento de una enfermedad en un mamífero, particularmente, en un ser humano, e incluyen: (a) inhibir el estadio de enfermedad, es decir, detener su desarrollo; y/o (b) aliviar el estado de enfermedad, es decir, causar el retroceso del estadio de enfermedad.

Como se usan en la presente, "profilaxis" o "prevención" cubren el tratamiento preventivo del estadio subclínico de la enfermedad en un mamífero, en particular, un ser humano, cuyo fin es reducir la probabilidad de que se alcance el estadio clínico de la enfermedad. Se seleccionan pacientes para la terapia preventiva sobre la base de factores que se sabe aumentan el riesgo de sufrir un estado de enfermedad clínica en comparación con la población general. Las terapias "profilácticas" se pueden dividir en (a) prevención primaria y (b) prevención secundaria. La prevención primaria se define como el tratamiento en un sujeto que aún no presenta el estadio clínico de la

enfermedad, mientras que la prevención secundaria se define como la prevención de que se produzca, por segunda vez, un estadio clínico de la enfermedad o similar.

Como se usa en la presente, "reducción del riesgo" cubre terapias que disminuyen la incidencia del desarrollo de un estadio clínico de la enfermedad. Como tales, las terapias de prevención primaria y secundaria son ejemplos de reducción de riesgo.

La expresión "cantidad terapéuticamente eficaz" incluye una cantidad de un compuesto de la presente invención que es eficaz cuando se administra sola o en combinación para inhibir MGAT2 y/o para prevenir o tratar los trastornos enumerados en la presente. Cuando se aplica a una combinación, la expresión se refiere a cantidades combinadas de ingredientes activos que producen el efecto preventivo o terapéutico, ya sea que se administren de manera combinada, serial o simultánea.

A. MÉTODOS DE ENSAYO

Ensayo SPA de MGAT

La enzima MGAT2 se evaluó usando membranas aisladas de células Sf9 que expresan el cADN recombinante humano de MGAT2 con 2-monooleoilglicerol y [^{3}H]-oleoil-CoA como sustratos, como describen Seethala et al. [*Anal. Biochem.*, 383(2):144-150 (15 de diciembre de 2008)]. En síntesis, los ensayos se realizaron en placas de 384 cavidades en un

volumen total de 30 µl a 25°C. En cada ensayo, se incubaron 200 ng de membrana MGAT2 recombinante humana con 10 µM de 2-monooleoilglicerol y 15 µM de [^{3}H]-oleoil-CoA en 100 mM de fosfato de potasio (pH 7.4) durante 20 min con varias concentraciones de compuestos suministrados en DMSO. El ensayo finalizó con la adición de 20 µl de solución de detención (7.5 mg/ml de esferas de óxido de itrio y polilisina, 3.3 mg/ml de albúmina de suero bovino (BSA), fracción V, y 200 µM de cloruro de mercurio en 50 mM de HEPES, pH 7.4). La señal se midió 1 h después de inactivar la reacción con LEADSEEKER^{SM} durante 5 minutos. Para calcular el grado de inhibición, el nivel cero de actividad enzimática (blanco) se definió mediante el procedimiento de ensayo anterior usando membranas de células Sf9 no infectadas con baculovirus (no sometidas a tratamiento previo), y el nivel de 100% de actividad enzimática de MGAT2 se definió mediante el ensayo MGAT2 humano con el vehículo DMSO. Los IC_{50} de los inhibidores se determinaron mediante la ecuación logística de 4 parámetros en XL-fit.

Ensayo LCMS de MGAT

Las reacciones enzimáticas de MGAT se realizaron en placas de polipropileno de 96 cavidades CORNING® Falcon, en un volumen total de 60 µl de 50 mM de amortiguador de fosfato de potasio a pH 7.4, que contenían una concentración final de 100 µM de 2-oleoilglicerol, 15 µM de oleoil-coenzima A y

0.0013 µg/µl de MGAT-2 de ratón o humano, o 0.0026 µg/µl de membranas MGAT-2 recombinantes de rata expresadas en células Sf9. Las placas de ensayo se corrieron a través de un sistema robótico totalmente automatizado y se agitaron durante 5 segundos cada minuto durante un total de 10 minutos. Las reacciones se inactivaron con 120 µl de metanol enfriado con hielo, que contenía 1 µg/ml de 1,2-distearoil-*rac*-glicerol como estándar interno. Las placas se agitaron durante 2 minutos y se centrifugaron para retirar la precipitación de proteínas. Después de la centrifugación, las muestras se transfirieron a placas PRC compatibles con LC/MS. Para el análisis de LC/MS, se usó una bomba ThermoFisher Surveyor, que tenía una columna Waters Symmetry C8 de 50 x 2.1 mm, para la cromatografía de productos enzimáticos. El sistema de amortiguadores consistió en 0.1% de ácido fórmico en agua con una fase móvil que consistía en 0.1% de ácido fórmico en metanol. El ingrediente superficial fue 90-100% de fase móvil en 0.2 min con un tiempo de ejecución total de 2.3 min. Los primeros 0.5 minutos de cada inyección se desecharon para eliminar la presencia de amortiguador de fosfato en la reacción enzimática. La columna se corrió a 0.6 ml/min a una temperatura de 65°C. El análisis de espectrometría de masa de las muestras se realizó en un triple cuadrupolo ThermoFisher Quantum con APCI (+) como modo de ionización. Los datos se obtuvieron en modo SIM (monitoreo selectivo de iones) que

analiza dioleína = *m/z* 603.6 (PRODUCTO) y 1,2-distearoil-*rac*-glicerol (IS)= *m/z* 607.6. La relación entre dioleína y el estándar interno (relación del área pico) se usó para calcular los valores IC_{50}.

Los ejemplos descritos a continuación se evaluaron en los ensayos de MGAT2 *in vitro* que se indican más adelante y se descubrió que tienen actividad inhibidora de MGAT2. La siguiente Tabla 1 enumera valores IC_{50} de MGAT2 humano medidos para los siguientes ejemplos. "NT" indica "no evaluado".

Tabla 1

Ejemplo N.°	h-MGAT2 IC_{50} (nM)	
	Ensayo SPA	Ensayo LCMS
1	651	2049
2	85	5
2-1	35	8
2-2	1400	261
3	1804	NT
4	5871	NT
5	309	21
6	15	7
6-1	1435	NT
6-2	14	2
7	818	NT
8	NT	7
9	33330	121
10	2716	138
11	48	13

Ejemplo N.°	h-MGAT2 IC_{50} (nM)	
12	NT	374
13	3333	35
14	NT	2050
15-1	3306	12
15-2	33330	431
15-3	33330	756
15-4	33330	2049
16-1	25	7
16-2	8430	416
17	1931	NT
18	5762	NT
19	2905	NT
20	3456	NT
21	913	NT
22	801	NT
23	1292	NT
24	1731	NT
25	4569	NT
26	6428	NT
27	2519	NT
28	564	NT
29	7602	NT
30	774	NT
31	1510	NT
32	9956	NT
33	167	12
34	656	126
35	5199	13

Ejemplo N.°	h-MGAT2 IC_{50} (nM)	
36	396	57
37	263	15
38	2143	NT
39	401	20
40	2546	164
41	170	15
42	403	77
43	5387	60
44	1458	NT
45	569	NT
46	871	NT
47	756	NT
48	226	7
49	127	64
50	242	95
51	63	13
52	477	99
53	111	3
54	258	20
55	846	20
56	6550	NA
57	412	16
58	275	29
59	53	4
60	441	12
61	709	NT
62	156	24
63	116	28

Ejemplo N.°	h-MGAT2 IC_{50} (nM)	
64	761	280
65	96	3
66	731	265
67	1935	253
68	7523	1282
69	9230	983
70	3404	NA
71	2931	1917
72	3519	214
73	684	15
74	2476	697
75	873	209
76	5073	370
77	89	27
78	151	4
79	1856	45
80	310	5
81	55	4
82	133	2
83	89	1
84	115	2
85	1465	7
86	201	1
87	NT	1215
88	28	5
89	731	20
90	815	18
91	916	2

Ejemplo N.°	h-MGAT2 IC_{50} (nM)	
92	NT	136
93	37	30
94	32	4
95	95	43
96	NT	1431
97	NT	1199
98	154	69
99	NT	795
100	NT	1575
101	379	108
102	NT	1088
103	NT	645
104	NT	103
105	672	24
106	NT	552
107	NT	93
108	NT	189
109	NT	39
110	11	5
111	9	7
112	1297	204
113	158	8
114	NT	704
115	NT	40
116	48	4
117	22	18
118	32	4
119	94	21

Ejemplo N.°	h-MGAT2 IC_{50} (nM)	
120	58	6
121	231	20
122	14	1
123	743	5
124	4264	55
125	NT	282
126	1874	33
127	655	10
128	NT	328
129	NT	222
130	20	1
131	NT	1050
132	NT	163
133	1518	127
134	NT	168
135	NT	778
136	NT	328
137	NT	252
138	NT	5799
140	NT	356
141	NT	459
142	93	10
143	156	4
144	175	16
145	130	25
146	397	25
147	91	14
148	102	9

Ejemplo N.°	h-MGAT2 IC_{50} (nM)	
149	53	6
150	11	3
151	NT	5115
152	NT	252
153	NT	247
154	34	8
155	NT	484
156	NT	254
157	168	84
158	302	75
159	NT	16710
160	NT	5401
161	NT	1261
162	NT	214
163	1176	47
164	NT	162
165	60	8
166	237	102
167	8	2
168	NT	113
169	NT	421
170	NT	210
171	724	57
172	16	3
173	43	63
174	237	60
175	NT	264
176	NT	3

Ejemplo N.°	h-MGAT2 IC_{50} (nM)	
177	NT	399
178	47	78
179	24	2
180	36	30
181	NT	2049
182	NT	2049
183	NT	50
184	NT	76
185	NT	121
186	NT	229
187	NT	4
188	NT	1524
189	NT	1159
190	NT	155
191	NT	797
192	NT	433
193	NT	46
194	NT	6
195	NT	33
196	NT	826
197	NT	178
198	NT	16
199	NT	16
200	NT	37
201	NT	24
202	NT	89
203	NT	59
204	NT	41

Ejemplo N.º	h-MGAT2 IC_{50} (nM)	
205	NT	13
206	NT	78
207	NT	11
208	NT	30
209	NT	37
210	NT	2
211	NT	97
212	NT	416
213	NT	1096
214	NT	12
215	NT	11
216	NT	440
217	NT	118
218	NT	166
219	NT	172
220	NT	13
221	NT	152
222	NT	733
223	NT	112
224	NT	414
225	NT	889
226	NT	206
227	NT	63
228	NT	7
229	NT	25
230	NT	1532
231	NT	34
232	NT	6

Ejemplo N.º	h-MGAT2 IC_{50} (nM)	
233	NT	542
234	NT	40
235	NT	22
236	NT	489
237	NT	130
238	NT	7
239	NT	15
240	NT	7
242	NT	44
243	NT	14
244	NT	61
245	NT	46
246	NT	36
247	NT	51
248	NT	8
249	NT	185
250	NT	243
251	NT	3
252	NT	7
253	NT	411
254	NT	170
255	NT	702
256	NT	22
257	NT	421
258	NT	1147
259	NT	15
260	NT	56
261	NT	1222

Ejemplo N.º	h-MGAT2 IC_{50} (nM)	
262	NT	96
263	NT	103
264	NT	46
265	NT	40
266	NT	10
267	NT	796
268	NT	8
269	NT	171
270	NT	407
271	NT	12
272	NT	112
273	21	10
274	NT	1
275	NT	2
276	NT	2
277	NT	2
278	NT	2
279	NT	2
280	NT	2
281	NT	3
282	NT	3
283	NT	3
284	NT	4
285	NT	4
286	NT	4
287	NT	13
288	NT	19
289	NT	19

Ejemplo N.º	h-MGAT2 IC_{50} (nM)	
290	NT	56
291	NT	178
292	NT	304
293	NT	7
294	NT	87
295	NT	183
296	NT	2
297	NT	639
298	NT	2
299	NT	11
300	NT	11
301	NT	19
302	NT	105
303	NT	28
304	NT	6
305	NT	94
306	NT	3
307	NT	3
308	NT	61
309	NT	1
310	NT	4
311	NT	3
312	NT	21
313	NT	4
314	NT	109

Los compuestos de la presente invención tienen actividad como inhibidores de MGAT2 y, por lo tanto, se

pueden usar para el tratamiento de enfermedades asociadas a la actividad de MGAT2. Mediante la modulación de MGAT2, los compuestos de la presente invención se pueden usar preferentemente para modular, ya sea mejorar o disminuir, la producción/secreción de insulina y/u hormonas intestinales, tales como GLP1, GIP, CCK, PYY, PP, Amylin.

En consecuencia, los compuestos de la presente invención se pueden administrar a mamíferos, preferentemente seres humanos, para el tratamiento de varias afecciones y trastornos que incluyen, entre otros, tratar, prevenir o hacer más lenta la progresión de la diabetes y las afecciones relacionadas, complicaciones microvasculares asociadas a la diabetes, complicaciones macrovasculares asociadas a la diabetes, enfermedades cardiovasculares, síndrome metabólico y sus afecciones relacionadas, enfermedades inflamatorias y otros trastornos. En consecuencia, se cree que los compuestos de la presente invención se pueden usar para prevenir, inhibir o tratar diabetes, hiperglucemia, intolerancia a la glucosa, diabetes gestacional, resistencia a la insulina, hiperinsulinemia, retinopatía, neuropatía, nefropatía, cicatrización, ateroesclerosis y sus secuelas (síndrome coronario agudo, infarto de miocardio, angina de pecho, enfermedad vascular periférica, claudicación intermitente, isquemia de miocardio, apoplejía, insuficiencia cardíaca), síndrome metabólico, hipertensión, obesidad, dislipidemia,

hiperlipidemia, hipertrigliceridemia, hipercolesterolemia, bajo nivel de HDL, alto nivel de LDL, trastornos lipídicos, síndrome del ovario poliquístico (PCOS) y glaucoma.

El síndrome metabólico o el "síndrome del cromosoma X" se describe en Ford et al., *J. Am. Med. Assoc.*, 287:356-359 (2002) y Arbeeny et al., *Curr. Med. Chem. – Imm., Endoc. & Metab. Agents*, 1:1-24 (2001).

V. COMPOSICIONES, FORMULACIONES Y COMBINACIONES FARMACÉUTICAS

Los compuestos de la presente invención se pueden administrar para cualquiera de los usos descritos en la presente mediante cualquier medio adecuado, por ejemplo, por vía oral, tal como comprimidos, cápsulas (cada uno de los cuales incluye formulaciones de liberación sostenida o de liberación controlada), píldoras, polvos, gránulos, elixires, tinturas, suspensiones (que incluyen nanosuspensiones, microsuspensiones, dispersiones secadas por aspersión), jarabes y emulsiones; por vía sublingual; por vía bucal; por vía parenteral, tal como mediante inyección subcutánea, intravenosa, intramuscular o intrasternal, o técnicas de infusión (por ejemplo, como suspensiones o soluciones acuosas o no acuosas inyectables estériles); por vía nasal, que incluye la administración en las membranas nasales, tal como mediante spray para inhalar; por vía tópica, tal como en forma de crema o ungüento; o por vía rectal, tal como en

forma de supositorios. También se pueden administrar solos, pero en general, se administrarán con un portador farmacéutico seleccionado sobre la base de la ruta de administración elegida y de la práctica farmacéutica estándar.

La expresión "composición farmacéutica" significa una composición que comprende un compuesto de la invención con, al menos, un portador aceptable desde el punto de vista farmacéutico adicional. Un "portador aceptable desde el punto de vista farmacéutico" se refiere a medios generalmente aceptados por las personas del oficio de nivel medio para la administración de agentes activos desde el punto de vista biológico a animales, en particular, mamíferos, incluidos, entre otros, adyuvantes, excipientes o vehículos, tales como diluyentes, agentes conservantes, agentes de relleno, agentes reguladores del flujo, agentes desintegrantes, agentes humectantes, agentes emulgentes, agentes de suspensión, agentes endulzantes, agentes saborizantes, agentes perfumantes, agentes antibacterianos, agentes antifúngicos, agentes lubricantes y dispensantes, en función de la naturaleza del modo de administración y de las formas de administración de la dosis.

Los portadores aceptables desde el punto de vista farmacéutico se formulan de acuerdo con varios factores que se encuentran dentro del ámbito de las personas del oficio de

nivel medio. Estos incluyen, entre otros, el tipo y la naturaleza del agente activo que se formula; el sujeto al que se le administra la composición que contiene el agente; la vía de administración prevista de la composición; y las indicaciones terapéuticas. Los portadores aceptables desde el punto de vista farmacéutico incluyen medios líquidos acuosos y no acuosos, así como varias formas de dosificación sólidas y semisólidas. Los portadores pueden incluir varios ingredientes y aditivos diferentes, además del agente activo; estos ingredientes adicionales se incluyen en la formulación por varios motivos, por ejemplo, la estabilización del agente activo, los aglutinantes, etc., conocidos por las personas del oficio de nivel medio. Las descripciones de portadores adecuados aceptables desde el punto de vista farmacéutico y los factores involucrados en su selección se pueden encontrar en diversas fuentes de fácil acceso, tales como Allen, L. V. Jr. et al. *Remington: The Science and Practice of Pharmacy* (2 volúmenes), 22.a edición (2012), Pharmaceutical Press.

El régimen de dosificación de los compuestos de la presente invención variará, naturalmente, según ciertos factores conocidos, tales como las características farmacodinámicas del agente particular y su modo y vía de administración; la especie, la edad, el sexo, la salud, la afección médica y el peso del receptor; la naturaleza y el alcance de los síntomas; el tipo de tratamiento concurrente;

la frecuencia del tratamiento; la vía de administración, la función renal y hepática del paciente, y el efecto deseado.

A modo orientativo general, la dosis oral diaria de cada ingrediente activo, cuando se usa para los efectos indicados, variará de alrededor de 0.001 a alrededor de 5000 mg por día, preferentemente, de alrededor de 0.01 a alrededor de 1000 mg por día y, con máxima preferencia, de alrededor de 0.1 a alrededor de 250 mg por día. Las dosis intravenosas más preferidas variarán de alrededor de 0.001 a alrededor de 10 mg/kg/minuto durante una infusión constante. Los compuestos de la presente invención se pueden administrar en una sola dosis diaria, o la dosis diaria total se puede administrar en dosis divididas de dos, tres o cuatros veces por día.

En general, los compuestos se administran mezclados con diluyentes, excipientes o portadores farmacéuticos adecuados (conjuntamente denominados portadores farmacéuticos) que se seleccionan de manera adecuada con respecto a la forma de administración prevista, por ejemplo, comprimidos orales, cápsulas, elíxires y jarabes, de acuerdo con las prácticas farmacéuticas convencionales.

Las formas de dosificación (composiciones farmacéuticas) adecuadas para la administración pueden contener de alrededor de 1 miligramo a alrededor de 2000 miligramos de ingrediente activo por unidad de dosis. En general, en estas composiciones farmacéuticas el ingrediente

activo estará presente en una cantidad de alrededor de 0.1-95% en peso sobre la base del peso total de la composición.

Una cápsula típica para la administración oral contiene al menos uno de los compuestos de la presente invención (250 mg), lactosa (75 mg) y estearato de magnesio (15 mg). La mezcla se hace pasar a través de un tamiz de 60 mallas y se envasa en una cápsula de gelatina N.° 1.

Una preparación inyectable típica se produce mediante la colocación aséptica de al menos uno de los compuestos de la presente invención (250 mg) en un vial, la liofilización aséptica y el sellado. Para usarlos, el contenido del vial se mezcla con 2 ml de solución salina fisiológica, a fin de producir una preparación inyectable.

La presente invención incluye composiciones farmacéuticas que comprenden, como ingrediente activo, una cantidad terapéuticamente eficaz de al menos uno de los compuestos de la presente invención, solo o en combinación con un portador farmacéutico. Opcionalmente, los compuestos de la presente invención se pueden usar solos, en combinación con otros compuestos de la invención o en combinación con uno o más agentes terapéuticos, por ejemplo, un agente contra la diabetes u otro material activo desde el punto de vista farmacéutico.

Los compuestos de la presente invención se pueden usar en combinación con otros inhibidores de MGAT2 o uno o

más agentes terapéuticos adecuados adicionales útiles para el tratamiento de los trastornos antes indicados que incluyen los siguientes: agentes antidiabéticos, agentes antihiperglicémicos, agentes antihiperinsulinémicos, agentes antirretinopáticos, agentes antineuropáticos, agentes antinefropáticos, agentes antiateroescleréticos, agentes antiisquémicos, agentes antihipertensores, agentes contra la obesidad, agentes antidislipidémicos, agentes antihiperlipidémicos, agentes antihipertrigliceridémicos, agentes antihipercolesterolémicos, agentes contra la restenosis, agentes antipancreáticos, hipolipemiantes, anorexígenos, agentes que mejoran la memoria, agentes contra la demencia o agentes promotores del desarrollo cognitivo, supresores del apetito, tratamientos para la insuficiencia cardíaca, tratamientos para la arteriopatía periférica y agentes antiinflamatorios.

Si se desea, el compuesto de la presente invención se puede usar en combinación con uno o más de otros tipos de agentes contra la diabetes y/o uno o más de otros tipos de agentes terapéuticos que se pueden administrar por vía oral en la misma forma de dosificación, en una forma de dosificación oral diferente o mediante inyección. El otro tipo de agente contra la diabetes que se puede usar opcionalmente en combinación con el inhibidor de MGAT2 de la presente invención puede ser 1, 2, 3 o más agentes contra la

diabetes o agentes antihiperglucémicos que se pueden administrar por vía oral en la misma forma de dosificación, en una forma de dosificación oral diferente o mediante inyección para producir un beneficio farmacológico adicional.

Los agentes contra la diabetes que se usan en combinación con el compuesto de la presente invención incluyen, entre otros, secretagogos de insulina o sensibilizadores de insulina, otros inhibidores de MGAT2 u otros agentes contra la diabetes. Estos agentes incluyen, entre otros, inhibidores de dipeptidil peptidasa IV (DP4) (por ejemplo, sitagliptin, saxagliptin, alogliptin, vildagliptin y similares), biguanidas (por ejemplo, metformin, phenformin y similares), sulfonilureas (por ejemplo, glyburide, glimepiride, glipizide y similares), inhibidores de glucosidasa (por ejemplo, acarbose, miglitol y similares), agonistas de PPARγ, tales como tiazolidindionas (por ejemplo, rosiglitazone, pioglitazone y similares), agonistas duales de PPAR α/γ (por ejemplo, muraglitazar, tesaglitazar, aleglitazar y similares), activadores de glucocinasa (como se describen en Fyfe, M.C.T. et al., *Drugs of the Future,* 34(8):641-653 (2009) que se incorpora en la presente por referencia), moduladores del receptor de GRP40, moduladores del receptor de GPR^{119} (MBX-2952, PSN821, APD597 y similares), inhibidores de SGLT2 (dapagliflozin, canagliflozin, remagliflozin y similares), análogos de

amilina, tales como pramlintide y/o insulina. Las reseñas de terapias actuales y emergentes para el tratamiento de la diabetes se pueden encontrar en: Mohler, M.L. et al., *Medicinal Research Reviews*, 29(1):125-195 (2009), y Mizuno, C.S. et al., *Current Medicinal Chemistry*, 15:61-74 (2008).

Los compuestos de la presente invención también se pueden usar opcionalmente en combinación con agentes para el tratamiento de complicaciones de la diabetes. Estos agentes incluyen inhibidores de PKC y/o inhibidores de AGE.

Los compuestos de la presente invención también se pueden usar opcionalmente en combinación con uno o más agentes hipofágicos, tales como diethylpropion, phendimetrazine, phentermine, orlistat, sibutramine, lorcaserin, pramlintide, topiramate, antagonistas del receptor de MCHR[1], oxyntomodulin, naltrexone, péptido amilina, moduladores del receptor de NPY Y5, moduladores del receptor de NPY Y2, moduladores del receptor de NPY Y4, cetilistat, moduladores del receptor de 5HT2c y similares. El compuesto de la estructura I también se puede usar en combinación con un agonista del receptor de péptido 1 tipo glucagón (GLP-1 R), tal como exenatide, liraglutide, amida GPR-1(1-36), amida GLP-1(7-36), GLP-1(7-37) (como se describe en la patente estadounidense N.° 5,614,492 de Habener, cuya descripción se incorpora en la presente por referencia), que se puede administrar mediante inyección, por vía intranasal o

mediante dispositivos transdérmicos o bucales. Las reseñas de terapias actuales y emergentes para el tratamiento de la obesidad se pueden encontrar en: Melnikova, I. et al., *Nature Reviews Drug Discovery*, 5:369-370 (2006); Jones, D., *Nature Reviews: Drug Discovery*, 8:833-834 (2009); Obici, S., *Endocrinology*, 150(6):2512-2517 (2009); y Elangbam, C.S., *Vet. Pathol.*, 46(1):10-24 (2009).

Los compuestos de la presente invención también se puede usar opcionalmente en combinación con uno o más de otros tipos de agentes terapéuticos, tales como inhibidores de DGAT, fármacos reductores de LDL, tales como estatinas (inhibidores de HMG CoA reductasa) o inhibidores de la absorción del colesterol, modulatores de PCSK9 y fármacos que aumentan HDL, tales como inhibidores de CETP.

Los otros agentes terapéuticos anteriores, cuando se usan en combinación con los compuestos de la presente invención, se pueden emplear, por ejemplo, en las cantidades indicadas en el manual de referencia para médicos *Physicians' Desk Reference*, como en las patentes mencionadas anteriormente, o según lo determine una persona del oficio de nivel medio.

En particular, cuando se suministran como una sola unidad de dosis, es posible que se produzca una interacción química entre los ingredientes activos combinados. Por ello, cuando el compuesto de la presente invención y un segundo

agente terapéutico se combinan en una sola unidad de dosis, se formulan de manera tal que, si bien los ingredientes activos se combinan en una sola unidad de dosis, se minimiza (es decir, se reduce) el contacto físico entre los ingredientes activos. Por ejemplo, un ingrediente activo se puede recubrir de manera entérica. Mediante el recubrimiento entérico de los ingredientes activos, es posible no solo minimizar el contacto entre los ingredientes activos combinados, sino también controlar la liberación de uno de estos componentes en el tracto gastrointestinal, de manera que uno de estos componentes no se libere en el estómago sino en el intestino. Uno de los ingredientes activos también se puede recubrir con un material que afecte la liberación sostenida en el tracto gastrointestinal y, además, minimice el contacto físico entre los ingredientes activos combinados. Además, el componente de liberación sostenida también se puede recubrir de manera entérica, de manera que la liberación de este componente se produzca en el intestino. Otro enfoque involucraría la formulación de un producto combinado en el que un componente se recubre con un polímero de liberación sostenida y/o entérica, y el otro componente también se recubre con un polímero, tal como hidroxipropilmetilcelulosa (HPMC) de baja viscosidad u otros materiales adecuados conocidos en el estado de la técnica, a fin de separar aún más los componentes activos. El

recubrimiento polimérico sirve para formar una barrera adicional que evita a interacción con el otro componente.

Estas y otras formas de minimizar el contacto entre los componentes de los productos combinados de la presente invención, ya sea que se administren en una sola forma de dosificación o en formas separadas, pero al mismo tiempo y de la misma manera, serán evidentes para las personas del oficio de nivel medio una vez leída la presente descripción.

Los compuestos de la presente invención se pueden administrar solos o en combinación con uno o más agentes terapéuticos adicionales. "Administrado en combinación con" o "terapia de combinación" significa que el compuesto de la presente invención y uno o más agentes terapéuticos adicionales se administran de manera concurrente al mamífero que se trata. Cuando se administra en combinación, cada componente se puede administrar al mismo tiempo o de manera secuencial en cualquier orden en diferentes momentos. De este modo, cada componente se puede administrar por separado, pero lo suficientemente cerca en el tiempo para proporcionar el efecto terapéutico deseado.

Los compuestos de la presente invención también son útiles como compuestos estándares o de referencia, por ejemplo, como control o estándar de calidad, en pruebas o ensayos que involucran la enzima MGAT2. Estos compuestos se pueden proporcionar en un kit comercial, por ejemplo, para

usar en investigaciones farmacéuticas que involucran la actividad contra la diabetes o MAGT2. Por ejemplo, un compuesto de la presente invención se podría usar como referencia en un ensayo para comparar su actividad conocida con un compuesto con actividad desconocida. Esto le garantizaría al experimentador que el ensayo se llevó a cabo de manera adecuada y le proporcionaría una base para la comparación, en especial si el compuesto de prueba era un derivado del compuesto de referencia. Cuando se desarrollan nuevos ensayos o protocolos, los compuestos de acuerdo con la presente invención podrían usarse para evaluar su eficacia.

Los compuestos de la presente invención también se pueden usar en ensayos de diagnóstico que involucran MGAT2.

La presente invención también abarca un artículo de fabricación. Como se usa en la presente, un artículo de fabricación pretende incluir, entre otros, kits y envases. El artículo de fabricación de la presente invención comprende: (a) un primer recipiente; (b) una composición farmacéutica ubicada dentro del primer recipiente, en donde la composición comprende: un primer agente terapéutico que comprende: un compuesto de la presente invención o una sal de este aceptable desde el punto de vista farmacéutico; y (c) un prospecto que indica que la composición farmacéutica se puede usar para el tratamiento y/o la profilaxis de varias enfermedades o trastornos asociados a MGAT2 (como se definió

previamente). En otra modalidad, el prospecto indica que la composición farmacéutica se puede usar en combinación (como se definió previamente) con un segundo agente terapéutico para el tratamiento y/o la profilaxis de varias enfermedades o trastornos asociados a MGAT2. El artículo de fabricación también puede comprender: (d) un segundo recipiente, en donde los componentes (a) y (b) se ubican dentro del segundo recipiente y el componente (c) se ubica dentro o fuera del segundo recipiente. La expresión "que se ubica dentro del primer y segundo recipiente" significa que el recipiente respectivo contiene el ítem dentro de sus límites.

El primer recipiente es un receptáculo que se usa para contener una composición farmacéutica. Este recipiente puede servir para la fabricación, el almacenamiento, el envío y/o la venta individual/a granel. El primer recipiente pretende abarcar una botella, una jarra, un vial, un matraz, una jeringa, un tubo (por ejemplo, para una preparación en crema) o cualquier otro recipiente para fabricar, contener, almacenar o distribuir un producto farmacéutico.

El segundo recipiente se usa para contener el primer recipiente y, opcionalmente, el prospecto. Los ejemplos del segundo recipiente incluyen, entre otros, cajas (por ejemplo, de cartón o plástico), cajones, cartones, bolsos (por ejemplo, bolsas de papel o de plástico), bolsas y sacos. El prospecto se puede unir físicamente a la parte

exterior del primer recipiente mediante cinta adhesiva, pegamento, grapas u otro método de sujeción, o se puede hallar en el interior del segundo recipiente sin ningún tipo de sujeción física al primer recipiente. De manera alternativa, el prospecto se puede ubicar fuera del segundo recipiente. Cuando se ubica fuera del segundo recipiente, es aconsejable que se una físicamente con cinta adhesiva, pegamento, grapas u otro método de sujeción. De manera alternativa, puede estar adyacente o en contacto con el exterior del segundo recipiente sin sujeción física.

El prospecto es una etiqueta, un rótulo, un marcador, etc. que proporciona información relacionada con la composición farmacéutica que se encuentra en el primer recipiente. En general, la información provista es determinada por un ente regulador a cargo del área donde se vende el artículo de fabricación (por ejemplo, la FDA). Con preferencia, el prospecto proporciona específicamente indicaciones para las cuales la composición farmacéutica fue aprobada. El prospecto puede fabricarse de cualquier material que permita la lectura de la información contenida en él. Preferentemente, el prospecto es un material que se puede imprimir (por ejemplo, papel, plástico, cartón, lámina, papel o plástico adhesivos, etc.) sobre el cual se formó (por ejemplo, se imprimió o aplicó) la información deseada.

Otras características de la invención serán

evidentes al analizar la siguiente descripción de las modalidades ilustrativas que se proporcionan para ilustrar la invención y no pretenden limitarla.

VI. EJEMPLOS

Los siguientes ejemplos se ofrecen a modo ilustrativo, como alcance parcial y modalidades particulares de la invención, y no pretenden limitar el alcance de la invención. Las abreviaturas y los símbolos químicos tienen sus significados usuales y habituales, a menos que se indique lo contrario. A menos que se indique lo contrario, los compuestos descritos en la presente se prepararon, aislaron y caracterizaron usando los esquemas y otros métodos descritos en la presente o se pueden preparar usando estos esquemas y métodos.

HPLC/MS, HPLC PREPARATIVA/ANALÍTICA Y MÉTODOS DE SEPARACIÓN QUIRAL QUE SE USAN PARA LA CARACTERIZACIÓN O PURIFICACIÓN DE EJEMPLOS

La HPLC/MS analítica (a menos que se indique lo contrario) se realizó en cromatógrafos de líquidos Shimadzu SCL-10A y espectrómetros de masa Waters MICROMASS® ZQ (gas de desolvatación: nitrógeno; temp. de desolvatación: 250°C; temp. de la fuente iónica: 120°C; condiciones de electrospray positivas) usando los siguientes métodos:

Gradiente lineal de 0% a100% de solvente B durante 2 min, con 1 minuto de retención a 100% B, o

Gradiente lineal de 0% a100% de solvente B durante 4 min, con 1 minuto de retención a 100% B;

visualización de UV a 220 nm;

Columna: PHENOMENEX® Luna C18 (2) 30mm x 4,6 mm; 5µ de partícula (calentado a temp. 40°C);

velocidad de flujo: 1.0 ml/min (2 min de gradiente) o 0.8 ml/min (4 min de gradiente);

solvente A: 10% de ACN, 90% de agua, 0.1% de TFA; o 10% de MeOH, 90% de agua, 0.1% de TFA; y

solvente B: 90% de ACN, 10% de agua, 0.1% de TFA; o 90% de MeOH, 10% de agua, 0.1% de TFA.

La HPLC preparativa (a menos que se indique lo contrario) se realizó en un cromatógrafo de líquidos Shimadzu SCL-10A con un gradiente lineal de 20-100% de solvente B durante 10 a 30 min, con 2 a 5 min de retención con 100% de solvente B, según lo determinó una persona del oficio de nivel medio;

visualización de UV a 220 nm;

Columna: PHENOMENEX® Luna Axia 5µ C18 30 x 100 mm;

velocidad de flujo: 20 ml/min;

solvente A: 10% de ACN, 90% de agua, 0.1% de TFA; o 10% de MeOH, 90% de agua, 0.1% de TFA; y

solvente B: 90% de ACN, 10% de agua, 0.1% de TFA; o 90% de MeOH, 10% de agua, 0.,1% de TFA.

La cromatografía SFC preparativa quiral (a menos

que se indique lo contrario) se realizó en un cromatógrafo SFC Berger Multigram II usando uno de los siguientes métodos:

Método A de SFC preparativa quiral:

Columna: CHIRALCEL® OD-H, 30 x 250 mm ID, 5 µ

velocidad de flujo: 90 ml/min, 100 bar BP, 40°C

fase móvil: 15% de metanol/85% de CO_2

longitud de onda del detector: 254 nm

Volumen de inyección y solución de muestra: 0.5 mL de 4.65 g en 35 ml de metanol (133 mg/ml)

Método B de SFC preparativa quiral:

Instrumento: Berger SFC MGII (HPW-2501)

Columna: CHIRALPAK® IA 25 x 3 cm ID, 5 µm

velocidad de flujo: 10 ml/min

fase móvil: 85/15/0.1,CO_2/IPA/DEA, 150 bar

longitud de onda del detector: 225 nm (lambda máx.)

Preparación de las muestras y volumen de inyección: 300 µl de ~13 mg / 0.5 ml de IPA (~26 mg/ml)

Método C de SFC preparativa quiral:

Columna: CHIRALPAK® IA 25 x 3 cm ID, 5 µm

velocidad de flujo: 90 ml/min

fase móvil: 85/15/0.1,CO_2/MeOH/DEA, 150 bar

longitud de onda del detector: 270 nm (lambda máx.)

Prep. de muestra y volumen de inyección: 300 µl de ~90 mg / 2 ml de MeOH (~45 mg/ml)

Método D de SFC preparativa quiral:

velocidad de flujo: 40 ml/min, 100 bar, 35°C

fase móvil: 20% de metanol/80% de CO_2

longitud de onda del detector: 224 nm (lambda máx.)

Volumen de inyección: 300 µl

Preparación de las muestras:10 mg disueltos en 0.5 ml de MeCN (20 mg/ml); 17 mg disueltos en 0.5 ml de MeCN (34 mg/ml)

La cromatografía SFC analítica quiral (a menos que se indique lo contrario) se realizó en una SFC analítica Aurora o SFC analítica Berger usando uno de los siguientes métodos:

Método A de SFC analítica quiral:

Columna: CHIRALCEL® OD-H, 4.6 x 250mm ID, 5 µm

velocidad de flujo: 3.0 ml/min, 100 bar BP, 35°C.

fase móvil: 15% de metanol/85% de CO_2

longitud de onda del detector: 220 nm

Solución de muestra: 1 mg/ml en metanol (concentrado/reconstituido)

Volumen de inyección: 10 µl

Método B de SFC analítica quiral: Columna: CHIRALPAK® IA 250 x 4.6 mm ID, 5 µm

velocidad de flujo: 2.0 ml/min

fase móvil: 85/15/0.1, CO_2/IPA/DEA, 150 bar

longitud de onda del detector: 225 nm (lambda máx.)

Volumen de inyección: 10 µl

Método C de SFC analítica quiral:

Columna: CHIRALPAK® IA 250 x 4.6 mm ID, 5 µm

velocidad de flujo: 3.0 ml/min

fase móvil: 65/35/0.1, CO_2/MeOH/DEA, 150 bar

longitud de onda del detector: 270 nm (lambda máx.)

Volumen de inyección: 10 µl

Método D de SFC analítica quiral:

Columna: CHIRALCEL® OD, 250 x 4.6 mm ID, 10 µm

velocidad de flujo: 2.0 ml/min, 100 bar, 35°C

fase móvil: 20% de metanol/80% de CO_2

longitud de onda del detector: 223 nm

Volumen de inyección: 10 µl

RMN QUE SE USA EN LA CARACTERIZACIÓN DE LOS EJEMPLOS

Los espectros de RMN ^{1}H (a menos que se indique lo contrario) se obtuvieron con espectrómetos de transformación JEOL o Bruker FOURIER® que funcionan a 400 MHz o 500 MHz. En algunos casos, los experimentos ^{1}H-nOe se realizaron para la aclaración regioquímica con un espectrómetro de transformación Bruker FOURIER® a 400 MHz.

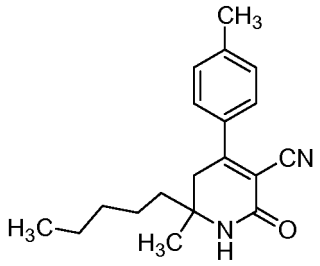
Los datos espectrales se informan como desplazamientos químicos (multiplicidad, cantidad de hidrógenos, constantes de acoplamiento en Hz) y se indican en ppm (unidades δ) con respecto a un estándar interno (tetrametilsilano = 0 ppm) para los espectros de ^{1}H RMN, o

hacen referencia al pico de solvente residual (2.49 ppm para CD_3SOCD_2H, 3.30 ppm para CD_2HOD, 1.94 para CHD_2CN, 7.26 ppm para $CHCl_3$, 5.32 ppm para $CDHCl_2$).

Se utilizaron instrumentos para microondas en las reacciones de calentamiento.

Iniciador BIOTAGE® 2.5, potencia máxima 400 W, rango de volumen de reacción 0.2 - 10 ml. Las reacciones se ejecutaron en recipientes sellados a presión fabricados especialmente para este instrumento.

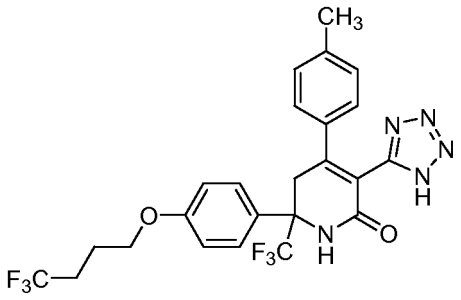
Ejemplo 1. 6-metil-2-oxo-6-fenil-4-p-tolil-1,2,5,6-tetrahidropiridin-3-carbonitrilo



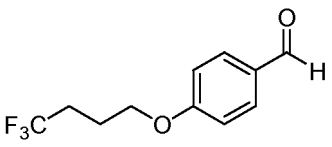
Una solución de heptan-2-ona (51 mg, 0.45 mmol), 1-p-toliletanona (60 mg, 0.45 mmol), etil-2-cianoacetato (51 mg, 0.45 mmol) y acetato de amonio (42 mg, 0.55 mmol) en anhidro DMF (0.6 ml) se calentó con agitación a 100°C durante 16 h. La reacción se diluyó con EtOAc y se lavó con agua. El solvente se retiró al vacío, y el producto se purificó mediante HPLC preparativa ($MeOH/H_2O$/TFA) para obtener el producto deseado (8 mg, 6%) como un sólido blanco. LCMS Anal. calc. para $C_{19}H_{24}N_2O$ 297.41, encontrado [M+H] 297.2. RMN 1H

(500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.87 Hz, 3 H), 1.24 - 1.40 (m, 9 H), 1.51 - 1.71 (m, 2 H) 2.42 (s, 3 H), 2.73 - 2.97 (m, 2 H), 6.09 (s, 1 H), 7.30 (d, *J* = 7.70 Hz, 2 H), 7.52 (d, *J* = 7.70 Hz, 2 H).

Ejemplo 2. 3-(1*H*-tetrazol-5-il)-4-p-tolil-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-5,6-dihidropiridin-2(1*H*)-ona



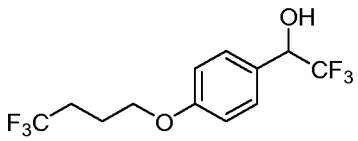
Intermediario 2A. 4-(4,4,4-trifluorobutoxi)benzaldehído



A una solución de 4-hidroxibenzaldehído (20 g, 164 mmol) y 4,4,4-trifluorobutan-1-ol (25 g, 195 mmol) en CH_2Cl_2 anhidro (500 ml) a 0°C en Ar, se agregó una solución de PPh_3 (51.5 g, 196 mmol) en CH_2Cl_2 (200 ml) durante 15 min, y luego se agregó por goteo DIAD (36.4 g, 180 mmol) en CH_2Cl_2 anhidro (150 ml). La mezcla se agitó a 0°C durante 0.5 h. La reacción se calentó a temperatura ambiente y se agitó durante 3 h más. El solvente se retiró al vacío, y el residuo se trituró con

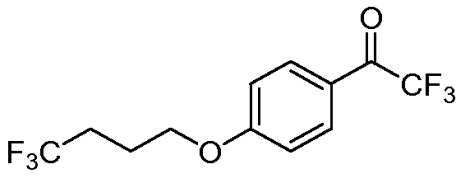
CH_2Cl_2 tres veces para retirar los sólidos insolubles. Los lavados de CH_2Cl_2 combinados se concentraron, y el residuo se purificó mediante cromatografía en gel de sílice (330 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el Intermediario 2A (27 g, 71%) como un aceite marrón claro. LCMS Anal. calc. para $C_{11}H_{11}F_3O_2$ 232.20. encontrado [M+H] 233.0.

Intermediario 2B. 2,2,2-trifluoro-1-(4-(4,4,4-trifluorobutoxi)fenil)etanol



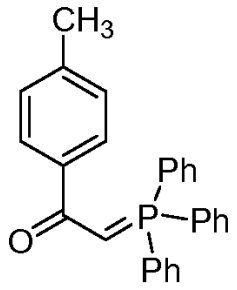
A la solución del Intermediario 2A (26.7 g, 114 mmol) y trimetil(trifluorometil)silano (16.9 g, 119 mmol) en DME anhidro (112 ml), se agregó CsF (500 mg, 3.29 mmol). La reacción se agitó a temperatura ambiente durante 16 h. A la mezcla se agregó HCl acuoso 4 N (114 ml), y la reacción se agitó a temperatura ambiente durante 2.5 h. La reacción se diluyó con EtOAc (300 ml) y se lavó con agua, $NaHCO_3$ acuoso saturado y NaCl acuoso saturado, se secó en $MgSO_4$ anhidro, se filtró y se concentró para obtener el Intermediario 2B (42.5 g, 122%) como un aceite. El producto crudo se usó sin purificación adicional. LCMS Anal. calc. para $C_{12}H_{12}F_6O_2$ 302.21, encontrado [M-H] 301.2.

Intermediario 2C. 2,2,2-trifluoro-1-(4-(4,4,4-trifluorobutoxi)fenil)etanona



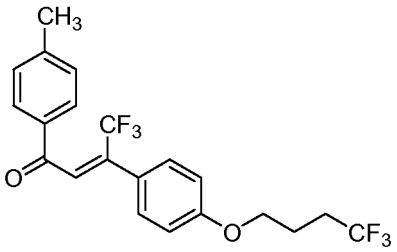
A una solución del Intermediario 2B (115 mmol) en CH_2Cl_2 anhidro (320 ml), se agregó periodinano de Dess-Martin (50.2 g, 118 mmol) en porciones a 0°C. La reacción se agitó a 0°C durante 0.5 h y luego a temperatura ambiente durante 3 h. A la reacción se agregaron 100 ml de Na_2CO_3 acuoso saturado y 250 ml de EtOAc. La reacción se agitó durante 2 h más. El material insoluble se retiró mediante filtración. Las capas se separaron. La capa orgánica se lavó con Na_2CO_3 acuoso saturado. Se retiraron los sólidos adicionales formados mientras se encontraba en reposo durante la noche. La solución orgánica se lavó con NaCl acuoso saturado, se secó en $MgSO_4$ anhidro, se filtró y se concentró para obtener un líquido marrón oscuro, que se purificó mediante cromatografía en gel de sílice (220 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el Intermediario 2C (26 g, 76%) como un aceite incoloro.

Intermediario 2D. *p*-tolilcarbonililuro de trifenilfosfonio



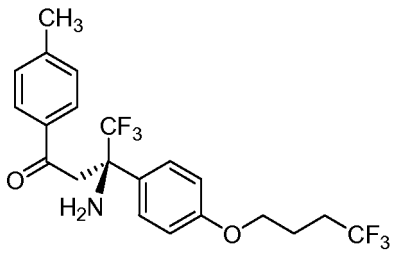
A una solución de PPh3 a reflujo (6.15 g, 23.47 mmol) en THF anhidro (220 ml) en argón, se agregó por goteo una solución de 2-bromo-1-*p*-toliletanona (5 g, 23.47 mmol) en THF (60 ml). La reacción se sometió a reflujo durante 2.5 h y luego se enfrió a temperatura ambiente. El precipitado se recolectó mediante filtración y se enjuagó con dietiléter. Los sólidos se suspendieron en 1:1 de MeOH y H_2O (500 ml), y luego se agregó NaOH acuoso 2 N (55 ml). La reacción se agitó a temperatura ambiente durante 16 h. Se retiró MeOH al vacío, y la solución acuosa se extrajo con $CHCl_3$. Los extractos orgánicos combinados se lavaron con NaCl acuoso saturado, se secaron en Na2SO4 anhidro, se filtraron y se concentraron para obtener el Intermediario 2D (9 g, 97%) como un sólido blanco. LCMS Anal. calc. para $C_{27}H_{23}OP$ 394.44, encontrado [M+H] 395.2.

Intermediario 2E. (Z)-4,4,4-trifluoro-1-*p*-tolil-3-(4-(4,4,4-trifluorobutoxi)fenil)but-2-en-1-ona

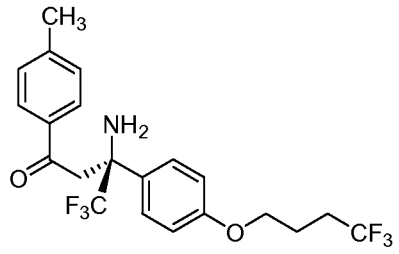


Se suspendieron el Intermediario 2D (5.13 g, 13 mmol) y el Intermediario 2C (3.90 g, 13 mmol) en DMSO (15 ml). La reacción se calentó a 160°C durante 1000 s en condiciones de microondas. La reacción se enfrió a temperatura ambiente y se diluyó con EtOAc (60 ml). La mezcla se lavó con agua y NaCl acuoso saturado, se secó en $MgSO_4$ anhidro, se filtró y se concentró. El producto crudo se purificó mediante cromatografía en gel de sílice (120 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el Intermediario 2E (5.9 g, 98%) como un aceite de color marrón claro.

Intermediario 2F, isómero 1. (*R*)-3-amino-4,4,4-trifluoro-1-*p*-tolil-3-(4-(4,4,4-trifluorobutoxi)fenil)-butan-1-ona



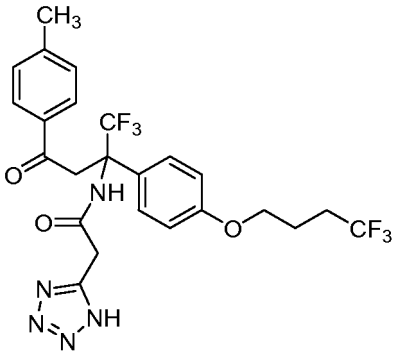
Intermediario 2F, isómero 2. (*S*)-3-amino-4,4,4-trifluoro-1-*p*-tolil-3-(4-(4,4,4-trifluorobutoxi)fenil)-butan-1-ona



A una solución del Intermediario 2E (2.1 g, 5.04 mmol) en DMSO (50 ml), se agregó NH4OH acuoso 15 N (25 ml). La mezcla se agitó en un recipiente sellado a presión durante 2 días. La reacción se diluyó con EtOAc (60 ml), se lavó con agua y NaCl acuoso saturado, se secó en MgSO4 anhidro, se filtró y se concentró. El residuo se purificó mediante cromatografía de columna en gel de sílice (eluida con EtOAc en hexanos) para obtener el Intermediario racémico 2F (2.2 g, 101%) como un sólido blanco. LCMS Anal. calc. para $C_{21}H_{21}F_6NO_2$ 433.39, encontrado [M+H] 434.2. La separación de los enantiómeros individuales del Intermediario 2F se realizó con el método A de SFC preparativa quiral: El Intermediario racémico 2F (2200 mg) proporcionó el Intermediario 2F, isómero 1 (817 mg) y el Intermediario 2F, isómero 2 (790 mg). La determinación de la pureza enantiomérica del

Intermediario 2F, isómero 1 y 2 se llevó a cabo usando el método A de SFC analítica. Intermediario 2F, isómero 1: RT = 2.2 min, 99% ee. Intermediario 2F, isómero 2: RT = 2.8 min, 99% ee. Los datos de cristales de rayos X que se recolectaron para la sal del ácido canforsulfónico del Intermediario 2F, isómero 1 mostraron que el centro tiene configuración *R*; por lo tanto, el centro quiral del Intermediario 2F, isómero 2 tiene configuración *S*.

Intermediario 2G. 2-(1*H*-tetrazol-5-il)-*N*-(1,1,1-trifluoro-4-oxo-4-*p*-tolil-2-(4-(4,4,4-trifluorobutoxi)-fenil)butan-2-il)acetamida



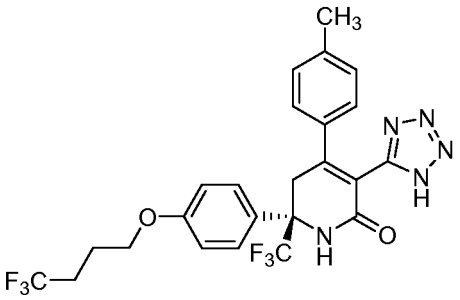
A una solución del Intermediario 2F (789 mg, 1.82 mmol) en THF anhidro (9 ml) a 0°C, se agregó DCC (1.13 g, 5.46 mmol). Se agregó por goteo ácido 2-tetrazolacético (700 mg, 5.46 mmol) como una suspensión en THF anhidro (8 ml). La reacción se agitó a 0°C durante 1 h y luego a temperatura ambiente durante la noche. La reacción se filtró, y los sólidos se enjuagaron con THF.

El filtrado se diluyó con EtOAc (40 ml), se lavó con Na_2CO_3 saturado y NaCl acuoso saturado, se secó en $MgSO_4$ anhidro, se filtró y se concentró para obtener el Intermediario 2G (1.5 g, 152%) como un sólido de color marrón rojizo. El Intermediario 2G se usó en la siguiente etapa sin purificación adicional. LCMS Anal. calc. para $C_{24}H_{23}F_6N_5O_3$ 543.46, encontrado [M+H] 543.9.

Ejemplo 2

A una solución del Intermediario 2G (1.5 g) en EtOH (11 ml) se agregó piperidina (0.33 ml). La reacción se calentó a 78°C durante 16 h en un vial sellado. La reacción se enfrió a temperatura ambiente, y el solvente se retiró al vacío. El residuo se purificó mediante HPLC preparativa ($MeOH/H_2O$/TFA). Las fracciones que contenían el producto se secaron al vacío, y el producto se volvió a disolver en MeOH y se concentró de nuevo. El producto oleoso de color marrón se volvió a disolver en CH_2Cl_2 (5 ml) y se concentró al vacío para obtener el Ejemplo 2 (552 mg, 57% en 2 etapas) como una espuma rojiza. LCMS Anal. calc. para $C_{24}H_{21}F_6N_5O_2$ 525.45, encontrado [M+H] 526.2. RMN 1H (500 MHz, CD3OD) δ 7.61 (d, *J* = 9.1 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.07 - 7.01 (m, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 4.10 (t, *J* = 6.1 Hz, 2H), 3.84 - 3.64 (m, 2H), 2.48 - 2.35 (m, 2H), 2.30 (s, 3H), 2.14 - 2.00 (m, 2H).

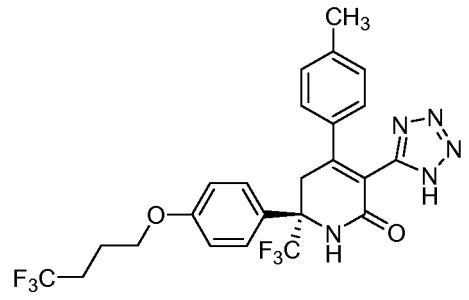
Ejemplo 2-1. (*S*)-3-(1*H*-tetrazol-5-il)-4-*p*-tolil-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-5,6-dihidropiridin-2(1*H*)-ona



La separación de los enantiómeros individuales del Ejemplo 2 se realizó con el método C de SFC preparativa quiral: El Ejemplo racémico 2 (89 mg) proporcionó el Ejemplo 2-1 (21 mg). La determinación de la pureza enantiomérica del Ejemplo 2-1 se realizó con el método C de SFC analítica. RT = 6.0 min, 99% ee.

El Ejemplo 2-1 se puede obtener de manera alternativa del Intermediario 2F, isómero 2 usando una secuencia similar a la que se usa para la conversión del Intermediario 2F en el Ejemplo 2.

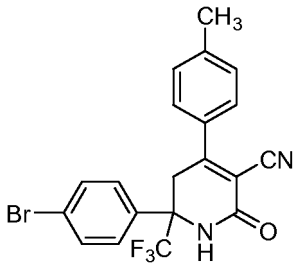
Ejemplo 2-2. (*R*)-3-(1*H*-tetrazol-5-il)-4-*p*-tolil-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-5,6-dihidropiridin-2(1*H*)-ona



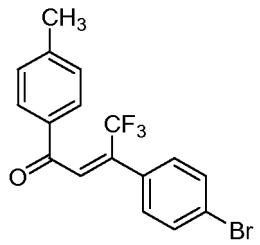
La separación de los enantiómeros individuales del Ejemplo 2 se realizó con el método C de SFC preparativa quiral: El Ejemplo racémico 2 (89 mg) proporcionó el Ejemplo 2-2 (22 mg). La determinación de la pureza enantiomérica del Ejemplo 2-2 se realizó con el método C de SFC analítica. RT = 15.1 min, 99% ee.

El Ejemplo 2-2 se puede obtener de manera alternativa del Intermediario 2F, isómero 1 usando una secuencia similar a la que se usa para la conversión del Intermediario 2F en el Ejemplo 2.

Ejemplo 3. 6-(4-bromofenil)-2-oxo-4-*p*-tolil-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carbonitrilo



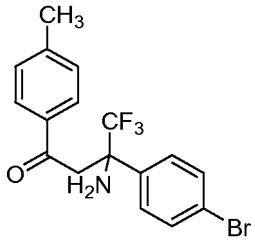
Intermediario 3A. (Z)-3-(4-bromofenil)-4,4,4-trifluoro-1-*p*-tolilbut-2-en-1-ona



El Intermediario 2D (1.84 g, 4.74 mmol) y 1-(4-bromofenil)-2,2,2-trifluoroetanona (1.2 g, 4.74 mmol) se

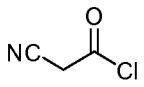
disolvieron en THF (8 ml) y se calentaron a 150°C durante 1000 s en condiciones de microondas. La reacción se enfrió a temperatura ambiente, y el solvente se retiró al vacío. El residuo se purificó mediante cromatografía en gel de sílice (24 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el Intermediario 3A (1.51 g, 86%) como un sólido marrón clalo. LCMS Anal. calc. para $C_{17}H_{12}BrF_3O$ 369.18, encontrado [M+H] 371.0.

Intermediario 3B. 3-amino-3-(4-bromofenil)-4,4,4-trifluoro-1-*p*-tolilbutan-1-ona



A una solución del Intermediario 3A (1.53 g, 4.14 mmol) en DMSO (23 ml), se agregó NH4OH acuoso 15 N (10 ml). El recipiente de reacción se selló, y la reacción se agitó a temperatura ambiente durante 16 h. Se agregaron más DMSO (3 ml) y NH_4OH acuoso 15 N (1 ml), y la reacción se agitó a temperatura ambiente durante 16 h. Se repitió la adición de DMSO (4 ml), y la reacción se agitó durante 16 h más. La solución se concentró al vacío y luego se liofilizó para obtener el Intermediario 3B (1.8 g, 100%) como un aceite marrón. LCMS Anal. calc. para $C_{17}H_{15}BrF_3NO$ 386.21, encontrado [M+H] 388.1.

Intermediario 3C. Cloruro de 2-cianoacetilo



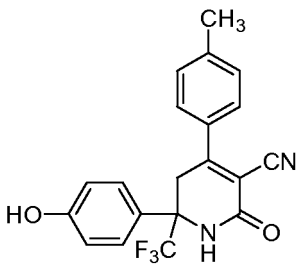
A una mezcla de ácido de 2-cianoacético (893 mg, 10.5 mmol) y DMF (16 µl) en CH_2Cl_2 anhidro (20 ml) a 0°C, se agregó por goteo una solución de cloruro de oxalilo 2 M (6 ml, 12 mmol) en CH_2Cl_2. La reacción se agitó a 0°C durante 20 min, luego se calentó a temperatura ambiente y se agitó durante 2 h. El solvente se retiró al vacío para obtener el Intermediario 3C, que se usó en la siguiente reacción sin purificación.

Ejemplo 3

A una solución del Intermediario 3B (1.6 g, 4.1 mmol) en CH_2Cl_2 anhidro (15 ml) a 0°C, se agregó una solución del Intermediario 3C (1.1 g, 10.5 mmol), piridina (0.85 ml) y DMAP (20 mg) en CH_2Cl_2 anhidro (5 ml). La reacción se agitó a 0°C durante 20 min y luego a temperatura ambiente durante 2.5 h. El solvente se retiró al vacío. El producto crudo se disolvió en EtOAc (30 ml), se lavó con Na_2CO_3 acuoso saturado y NaCl acuoso saturado, se secó en Na_2SO_4 anhidro, se filtró y se concentró para obtener un sólido marrón. El sólido se trituró con CH_2Cl_2/dietiléter para obtener el Ejemplo 3 (1.27 g) como un sólido blancuzco. El sobrenadante se evaporó, y el residuo se purificó mediante cromatografía en gel de sílice

(eluida con EtOAc en hexanos) para obtener un segundo lote del Ejemplo 3 (0.22 g). El rendimiento combinado fue de 1.49 g (80%). LCMS Anal. calc. para $C_{20}H_{14}BrF_3N_2O$ 435.24, encontrado [M+H] 437.0. RMN 1H (500 MHz, CDCl3) δ 2.42 (s, 3 H), 3.45 - 3.67 (m, 2 H), 7.30 (d, *J* = 7.70 Hz, 2 H), 7.39 (d, *J* = 8.25 Hz, 2 H), 7.45 (d, *J* = 7.70 Hz, 2 H), 7.60 (d, *J* = 8.80 Hz, 2 H).

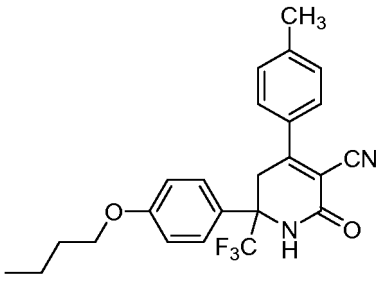
Ejemplo 4. 6-(4-hidroxifenil)-2-oxo-4-*p*-tolil-6-(trifluorometil)-1,2,5,6-tetrahidro-piridin-3-carbonitrilo



El Ejemplo 3 (1.49 g, 3.42 mmol), Pd_2dba_3 (78 mg, 0.086 mmol), KOH (403 mg, 7.2 mmol) y bis(1,1-dimetiletil)[2′,4′,6′-tris(1-metiletil)[1,1′-bifenil]-2-il]-fosfina (73 mg, 0.17 mmol) se colocaron en un vial para microondas. El vial se evacuó y se volvió a llenar con Ar. Se agregaron 1,4-dioxano (23 ml) y agua (13 ml) al vial, y la mezcla de reacción se calentó a 140°C durante 15 min en condiciones de microondas. La reacción se enfrió a temperatura ambiente, se neutralizó con HCl 1 N, se diluyó con agua y se extrajo con EtOAc. Los extractos orgánicos combinados se lavaron con agua y NaCl acuoso saturado, se

secaron en Na_2SO_4 anhidro, se filtraron y se concentraron. El residuo se purificó mediante cromatografía en gel de sílice para obtener el Ejemplo 4 (1.14 g, 85%) como un sólido marrón claro. LCMS Anal. calc. para $C_{20}H_{15}F_3N_2O_2$ 372.34, encontrado [M+H] 373.2. RMN 1H (500 MHz, DMSO-d_6) δ 2.30 (s, 3 H), 3.65 (q, *J* = 18.15 Hz, 2 H), 6.73 (d, *J* = 8.25 Hz, 2 H), 7.28 (d, *J* = 8.25 Hz, 2 H), 7.38 (d, *J* = 8.80 Hz, 2 H), 7.47 (d, *J* = 8.25 Hz, 2 H), 9.63 (s, 1 H), 9.70 (s, 1 H).

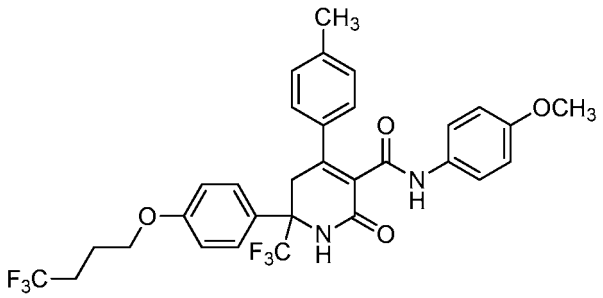
Ejemplo 5. 6-(4-butoxifenil)-2-oxo-4-*p*-tolil-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carbonitrilo



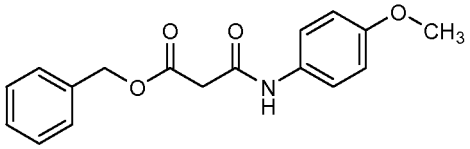
A una solución del Ejemplo 4 (20 mg, 0.054 mmol) y *n*-butanol (6 mg, 0.081 mmol) en CH_2Cl_2 anhidro (0.3 ml) en Ar, se agregaron secuencialmente trifenilfosfina (21 mg, 0.081 mmol) en CH_2Cl_2 (0.3 ml) y DEAD (14 mg, 0.081 mmol) en CH_2Cl_2 (0.3 ml). La mezcla de reacción se agitó a 0°C en argón durante 20 min y luego a temperatura ambiente durante 2 h. El solvente se evaporó al vacío, y el producto se purificó mediante HPLC preparativa (CH_3CN/H_2O/TFA) para obtener el Ejemplo 5 (5.6 mg, 24%). LCMS Anal. calc. para $C_{24}H_{23}F_3N_2O_2$ 428.45, encontrado [M+H] 429.3. RMN 1H (500 MHz, CDCl3) δ

0.98 (t, *J* = 7.42 Hz, 3 H), 1.41 - 1.56 (m, 2 H), 1.73 - 1.84 (m, 2 H), 2.41 (s, 3 H), 3.56 (q, *J* = 18.15 Hz, 2 H), 3.92-4.03 (m, 2 H), 6.94 (d, *J* = 8.25 Hz, 3 H), 7.29 (d, *J* = 8.25 Hz, 2 H), 7.37 (d, *J* = 8.80 Hz, 2 H), 7.45 (d, *J* = 7.70 Hz, 2 H).

Ejemplo 6. *N*-(4-metoxifenil)-2-oxo-4-*p*-tolil-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluoro-metil)-1,2,5,6-tetrahidropiridin-3-carboxamida



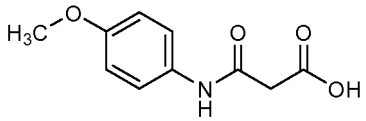
Intermediario 6A. 3-(4-(metilamino)fenilamino)-3-oxopropanoato de bencilo



A una solución de malonato de monobencilo (12.2 g, 63.1 mmol) y DMF (90 µl) en CH_2Cl_2 anhidro (100 ml) a 0°C, se agregó cloruro de oxalilo 2 M (35 ml, 70 mmol) en CH_2Cl_2. La reacción se agitó a 0°C durante 30 min y luego a temperatura ambiente durante 2.5 h. El solvente se retiró al vacío para obtener cloruro de ácido recién preparado. Esto se disolvió en CH_2Cl_2 anhidro (50 ml) y se agregó por goteo a una solución

de 4-metoxianilina (7.76 g, 63 mmol) en CH_2Cl_2 anhidro (50 ml) a 0°C; luego se agregó piridina (5.35 ml, 66.2 mmol). La reacción se agitó a 0°C durante 0.5 h y luego a temperatura ambiente durante la noche. La reacción se lavó con agua y NaCl acuoso saturado, se secó en $MgSO_4$ anhidro, se filtró y se concentró. El residuo se trituró con EtOAc/CH_2Cl_2 para obtener el primer lote del Intermediario 6A como un sólido marrón claro (6.95 g). El sobrenadante se evaporó, y el residuo se purificó mediante cromatografía en gel de sílice (eluida con EtOAc en hexanos) para obtener un segundo lote del Intermediario 6A como un sólido marrón claro (7.4 g). El rendimiento combinado fue de 14.4 g (76%). LCMS Anal. calc. para $C_{17}H_{18}N_2O_3$ 298.34, encontrado [M+H] 300.2.

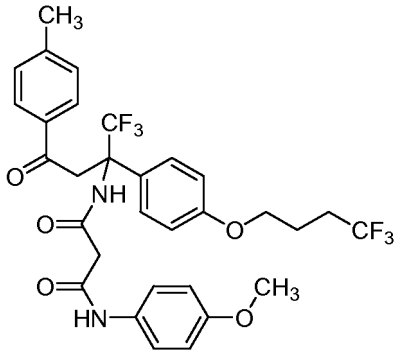
Intermediario 6B. Ácido 3-(4-metoxifenilamino)-3-oxopropanoico



A una solución del Intermediario 6A (14.4 g, 4.8 mmol) en 10:1 de EtOAc/MeOH (220 ml), se agregó 10% de Pd/C (250 mg). La mezcla de reacción se agitó vigorosamente en una atmósfera de hidrógeno (40 psi) durante 2 h. Se agregó, en forma adicional, 10% de Pd/C (250 mg), y la reacción se agitó en hidrógeno a 50 psi durante 1 h más. Se agregó, en forma adicional, 10% de Pd/C (500 mg), y la reacción se agitó en hidrógeno a 50 psi) durante 1 h más. La reacción se filtró a

través de una almohadilla de Celite®, y el filtrado se concentró al vacío para obtener el Intermediario 6B (11.1 g, 96%) como un sólido blancuzco. LCMS Anal. calc. para $C_{10}H_{11}NO_4$ 209.20, encontrado [M+H] 210.1.

Intermediario 6C. *N*^{1}-(4-metoxifenil)-N^3-(1,1,1-trifluoro-4-oxo-4-*p*-tolil-2-(4-(4,4,4-trifluoro-butoxi)fenil)-butan-2-il)malonamida



A trifenilfosfina (8.42 g, 32.1 mmol) en CH_2Cl_2 anhidro (70 ml), se agregó el Intermediario 6B (2.24 g, 10.7 mmol) en CH_2Cl_2 anhidro (30 ml) y luego tricloroacetonitrilo (1.86 g, 12.8 mmol). La mezcla se agitó a temperatura ambiente durante 3 h. El cloruro ácido recién preparado se agregó a una solución del Intermediario 2F (1.13 g, 2.61 mmol) en CH_2Cl_2 anhidro (20 ml), y luego se agregó piridina (1.04 ml, 1.02 g, 12.85 mmol). La reacción se agitó a temperatura ambiente en argón durante la noche. La reacción se enfrió a 0°C, y se agregó MeOH (40 ml). La reacción se agitó a 0°C durante 10 min y luego a temperatura ambiente durante 30 min. El solvente se retiró al vacío, y el producto

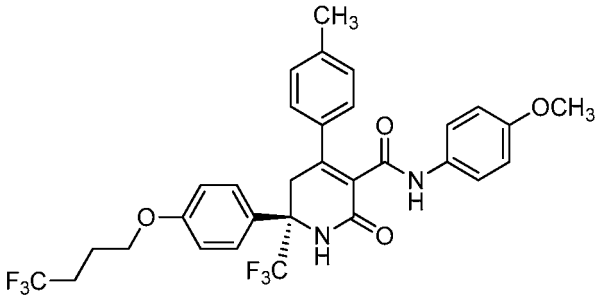
crudo se purificó mediante cromatografía en gel de sílice (120 g de gel de sílice, eluido con EtOAc en hexanos). El producto y el óxido de trifenilfosfina se coeluyeron. Las fracciones que contenían a ambos se combinaron y se evaporaron hasta secarse. Los sólidos se trituraron con hexanos/EtOAc para retirar la mayor parte del óxido de trifenilfosfina. El producto se volvió a purificar mediante cromatografía en gel de sílice (40 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el Intermediario 6C (1.03 g, 63%) como un aceite marrón. LCMS Anal. calc. para $C_{31}H_{30}F_6N_2O_5$ 624.57, encontrado [M+H] 625.3.

Ejemplo 6

A una solución del Intermediario 6C (1.03 g, 1.65 mmol) en MeOH (10 ml), se agregó piperidina (100 µl, 1.01 mmol). La reacción se agitó a 75°C durnate 1 h. El solvente se retiró al vacío, y el producto crudo se purificó mediante cromatografía en gel de sílice (120 g de gel de sílice, eluido con EtOAc en hexanos). Las fracciones mezcladas de la primera columna se volvieron a purificar mediante cromatografía en gel de sílice (40 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el Ejemplo 6 (546 mg, 55%) como un sólido blancuzco. LCMS Anal. calc. para $C_{31}H_{28}F_6N_2O_4$ 606.56, encontrado [M+H] 607.3. RMN 1H (500 MHz, CD_3OD) δ 1.97-2.08 (m, 2 H), 2.30 (s, 3 H), 2.32-2.44 (m, 2 H), 3.45-3.67 (m, 2 H), 3.72 (s, 3 H), 4.06 (t, *J* = 6.05 Hz, 2 H),

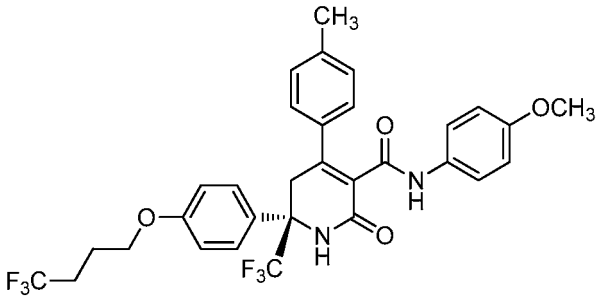
6.77 (d, *J* = 9.35 Hz, 2 H), 6.97 (d, *J* = 8.80 Hz, 2 H), 7.13-7.24 (m, 4 H), 7.28 (d, *J* = 8.25 Hz, 2 H), 7.52 (d, *J* = 8.80 Hz, 2 H).

Ejemplo 6-1. (*R*)-*N*-(4-metoxifenil)-2-oxo-4-*p*-tolil-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluoro-metil)-1,2,5,6-tetrahidropiridin-3-carboxamida



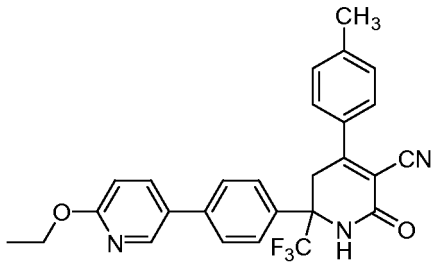
El Ejemplo 6-1 se preparó usando un procedimiento análogo al Ejemplo 6 reemplazando el Intermediario 2F por el Intermediario 2F, isómero 1.

Ejemplo 6-2. (*S*)-*N*-(4-metoxifenil)-2-oxo-4-*p*-tolil-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluoro-metil)-1,2,5,6-tetrahidropiridin-3-carboxamida



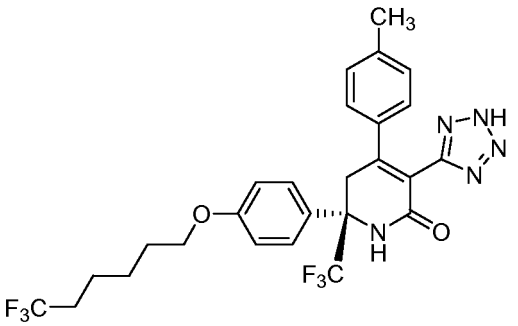
El Ejemplo 6-2 se preparó usando un procedimiento análogo al Ejemplo 6 reemplazando el Intermediario 2F por el Intermediario 2F, isómero 2.

Ejemplo 7. 6-(4-(6-etoxipiridin-3-il)fenil)-2-oxo-4-*p*-tolil-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carbonitrilo

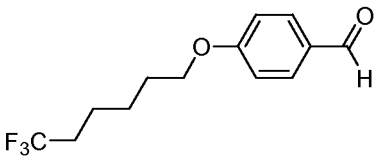


A una solución del Ejemplo 3 (20 mg, 0.046 mmol), ácido 6-etoxipiridin-3-ilborónico (11 mg, 0.07 mmol) y tetrakis(trifenilfosfina)paladio(0) (5 mg, 10 mol%) en DMF (0.6 ml) rociada con Ar, se agregó K_2CO_3 acuoso 2 N (46 µl, 0.096 mmol). El recipiente se selló, y la reacción se calentó a 80°C durante 22 h. La reacción se enfrió a temperatura ambiente, y el producto se purificó dos veces mediante HPLC preparativa (CH_3CN/H_2O/TFA y CH_3OH/H_2O/TFA en forma secuencial) para obtener el Ejemplo 7 (10 mg, 45%) como un sólido marrón claro. LCMS Anal. calc. para $C_{27}H_{22}F_3N_3O_2$ 477.48, encontrado [M+H] 478.3. RMN 1H (500 MHz, CD_3OD) δ 1.40 (t, *J* = 6.87 Hz, 3 H), 2.40 (s, 3 H), 3.71 - 3.88 (m, 2 H), 4.37 (q, *J* = 7.15 Hz, 2 H), 6.94 (d, *J* = 8.25 Hz, 1 H), 7.33 (d, *J* = 7.70 Hz, 2 H), 7.54 (d, *J* = 8.25 Hz, 2 H), 7.66 - 7.78 (m, 4 H), 8.05 (dd, *J* = 8.80. 2.20 Hz, 1 H), 8.42 (d, *J* = 2.20 Hz, 1 H).

Ejemplo 8. (*S*)-3-(2*H*-tetrazol-5-il)-4-*p*-tolil-6-(4-(6,6,6-trifluorohexiloxi)fenil)-6-(trifluorometil)-5,6-dihidropiridin-2(1*H*)-ona



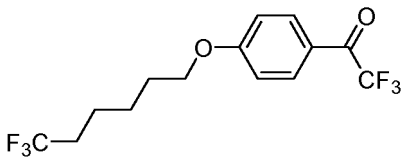
Intermediario 8A. 4-(6,6,6-trifluorohexiloxi)benzaldehído



A una suspensión de 4-hidroxibenzaldehído (488 mg, 4 mmol) y 6-bromo-1,1,1-trifluorohexano (657 mg, 3 mmol) en MeCN (10 ml), se agregó K_2CO_3 (829 mg, 6.00 mmol). La mezcla resultante se sometió a reflujo durante la noche. El material insoluble se filtró y se enjuagó con MeCN. El filtrado combinado se concentró para obtener un sólido blanco. Este sólido blanco se dividió en EtOAc y una solución de NaOH 1 N. La capa orgánica se separó, se lavó con NH4Cl saturado, se secó en $MgSO_4$, se filtró y se concentró para obtener el Intermediario 8A como un líquido transparente. LCMS Anal. calc. para $C_{13}H_{15}F_3O_2$ 260.10. encontrado [M+H] 261.0.

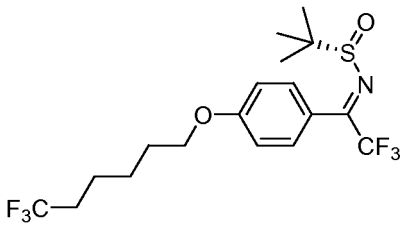
Intermediario 8B. 2,2,2-trifluoro-1-(4-(6,6,6-

trifluorohexiloxi)fenil)etanona



El Intermediario 8B se preparó usando un procedimiento análogo al Intermediario 2C, excepto que el Intermediario 2A se reemplazó por el Intermediario 8A. RMN 1H (500 MHz, $CDCl_3$) δ 8.06 - 8.02 (m, 2 H), 6.99 - 6.97 (m, 1 H), 4.08 (t, *J* = 6.2 Hz, 2 H), 2.19 - 2.06 (m, 2 H), 1.92 - 1.82 (m, 2 H), 1.71 - 1.55 (m, 4 H).

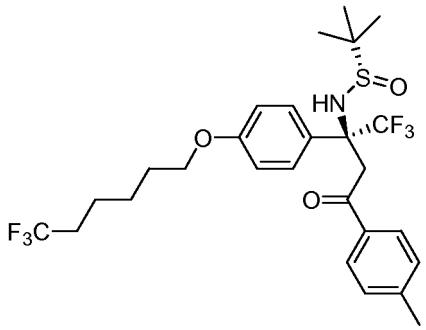
Intermediario 8C. (S,*E*)-2-metil-*N*-(2,2,2-trifluoro-1-(4-(6,6,6-trifluorohexiloxi)fenil)etiliden)propan-2-sulfinamida



A una solución del Intermediario 8B (717 mg, 2.184 mmol) y (*S*)-2-metilpropan-2-sulfinamida (529 mg, 4.37 mmol) en THF (10 ml), se agregó tetraetoxititanio (1993 mg, 8.74 mmol) en THF (20 ml). La mezcla resultante se sometió a reflujo durante 5 h. La TLC (20% de EtOAc en hexano) indicó que la cetona de inicio se había consumido por completo. El solvente se evaporó para obtener un aceite amarillo. Este aceite amarillo se disolvió en EtOAc y luego se lavó con

NaHCO3 saturado (25 ml); se formó una gran cantidad de precipitación blanca, que se retiró mediante filtración por medio de una almohadilla de Celite®. La precipitación blanca se enjuagó con EtOAc. La solución de EtOAc combinada se lavó nuevamente con NaHCO3 saturado, se secó ($MgSO_4$) y se concentró. El producto crudo se purificó mediante cromatografía en gel de sílice (40 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el Intermediario 8C (620 mg, 66%).

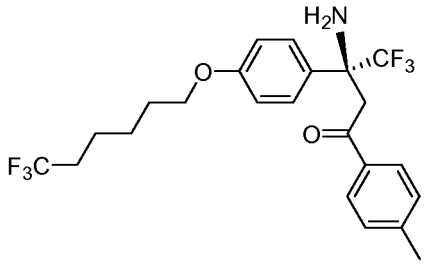
Intermediario 8D. (*S*)-2-metil-*N*-((*S*)-1,1,1-trifluoro-4-oxo-4-*p*-tolil-2-(4-(6,6,6-trifluorohexiloxi)fenil)butan-2-il)propan-2-sulfinamida



Una solución de 1-(*p*-tolil)etanona (609 mg, 4.31 mmol) en THF (10 ml) se enfrió a -78°C, y a esta solución se agregó bis(trimetilsilil)amida de litio (4.31 ml, 4.31 mmol). La mezcla resultante se agitó a -78°C durante 20 min, y luego se agregó por goteo el Intermediario 8C (620 mg, 1.437 mmol) en THF (3 ml). La mezcla resultante se agitó a -78°C durante 1.5 h y luego a 0°C durante 1.5 h. La reacción se inactivó con NH4Cl y se concentró. El producto crudo se purificó

mediante cromatografía en gel de sílice (80 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el Intermediario 8D (482 mg, 59%) como el diastereómero de elución más lenta en una columna de gel de sílice. LCMS Anal. calc. para $C_{27}H_{33}F_6NO_3S$ 565.21, encontrado [M+H] 566.0.

Intermediario 8E. (*S*)-3-amino-4,4,4-trifluoro-1-p-tolil-3-(4-(6,6,6-trifluorohexiloxi)fenil)butan-1-ona



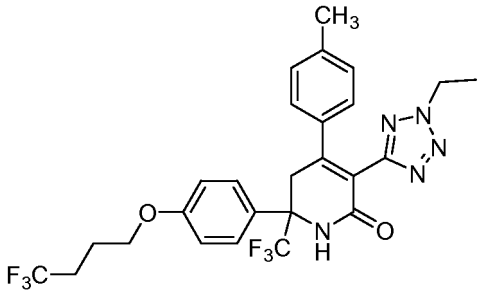
A una solución del Intermediario 8D (482 mg, 0.852 mmol) en MeOH (4 ml), se agregó HCl 4 M (1 ml, 4.00 mmol) en dioxano. La mezcla resultante se agitó a temperatura ambiente durante 2 h y luego se concentró. El residuo se absorbió en EtOAc, se lavó con $NaHCO_3$ saturado y salmuera, se secó ($MgSO_4$), se filtró y se concentró para obtener el Intermediario (386 mg, 58%) como un aceite incoloro, que se usó para la reacción posterior sin purificación adicional. LCMS Anal. calc. para $C_{23}H_{25}F_6NO_2$ 461.18, encontrado [M+H] 461.9.

Ejemplo 8

A una solución del Intermediario 8E (140 mg, 0.303 mmol) y ácido 2-(2*H*-tetrazol-5-il)acético (117 mg, 0.910 mmol) en THF (3 ml) a 0°C, se agregó DCC (188 mg, 0.910

mmol). La mezcla resultante se agitó durante la noche. El solvente se evaporó, y la mezcla cruda se absorbió en EtOAc. La solución orgánica se lavó con $NaHCO_3$ saturado, HCl 1 N y salmuera, se secó ($MgSO_4$), se filtró y se concentró para obtener un aceite marrón. Este aceite se disolvió en EtOH (3 ml), y se agregó piperidina (300 µl, 3.03 mmol). La mezcla resultante se agitó a 80°C durante la noche. La mezcla de reacción se diluyó con MeOH y se purificó mediante HPLC preparativa (MeCN/H_2O/TFA) para obtener el Ejemplo 8 (86 mg, 51%) como un sólido. LCMS Anal. calc. para $C_{26}H_{25}F_6N_5O_2$ 553.19, encontrado [M+H] 554.0. RMN 1H (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.8 Hz, 2 H), 7.19 (d, *J* = 8.0 Hz, 3 H), 7.02 - 6.93 (m, 4 H), 3.99 (t, *J* = 6.3 Hz, 2 H), 3.68 - 3.56 (m, 2 H), 2.39 (s, 3 H), 2.19 - 2.07 (m, 2 H), 1.89 - 1.79 (m, 2 H), 1.71 - 1.63 (m, 2 H), 1.62 - 1.53 (m, 2 H).

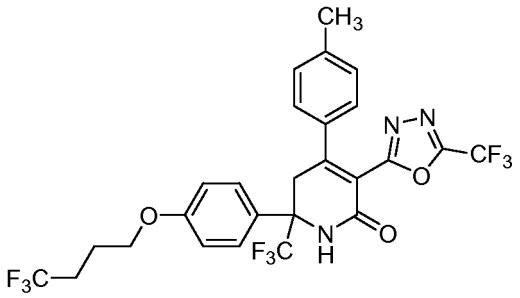
Ejemplo 9. 3-(2-etil-2*H*-tetrazol-5-il)-4-*p*-tolil-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-5,6-dihidropiridin-2(1*H*)-ona



Al Ejemplo 2 (30 mg, 0.057 mmol) en CH_2Cl_2 anhidro (0.6 ml), se agregaron yodoetano (9 mg, 0.057 mmol) y

trietilamina (24 µl, 0.17 mmol). La reacción se calentó a 120°C durante 10 min en condiciones de microondas. El solvente se evaporó al vacío, y el residuo se purificó mediante HPLC preparativa (CH_3CN/H_2O/TFA) para obtener el Ejemplo 9 (2.3 mg, 7%) como un sólido marrón claro. LCMS Anal. calc. para $C_{26}H_{25}F_6N_5O_2$ 553.50. encontrado [M+H] 554.3. RMN 1H (500 MHz, $CDCl_3$) δ 1.51 (t, *J* = 7.42 Hz, 2 H), 1.98 - 2.13 (m, 2 H), 2.21 - 2.39 (m, 5 H), 3.51 (d, *J* = 17.60 Hz, 1 H), 3.72 (d, *J* = 17.60 Hz, 1 H), 4.04 (t, *J* = 6.05 Hz, 2 H), 4.56 (q, *J* = 7.52 Hz, 2 H) 6.87 (d, *J* = 8.25 Hz, 2 H), 6.95 (d, *J* = 8.80 Hz, 2 H), 7.02 (d, *J* = 8.25 Hz, 2 H), 7.46 (d, *J* = 8.80 Hz, 2 H), 7.93 (s, 1 H).

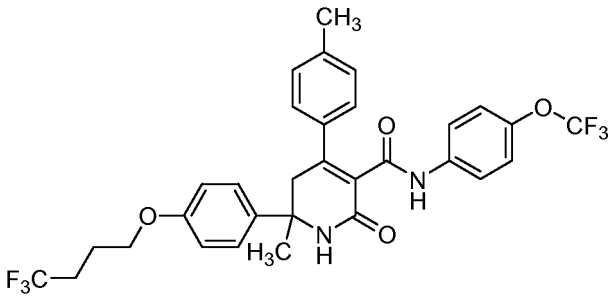
Ejemplo 10. 4-*p*-tolil-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-3-(5-(trifluorometil)-1,3,4-oxadiazol-2-il)-5,6-dihidropiridin-2(1*H*)-ona



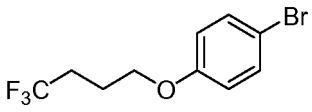
Al Ejemplo 2 (29 mg, 0.055 mmol) en CH_2Cl_2 anhidro (0.3 ml), se agregó por goteo una solución de anhídrido trifluoroacético (23.2 mg, 0.11 mmol) en CH_2Cl_2 anhidro (0.2 ml). La mezcla se agitó a temperatura ambiente durante 4 h y

luego se concentró. El residuo se purificó mediante HPLC preparativa para obtener el Ejemplo 10 (19 mg, 58%) como un sólido blanco. LCMS Anal. calc. para $C_{26}H_{20}F_9N_3O_3$ 593.44, encontrado [M+H] 594.2. RMN 1H (500 MHz, CD_3OD) δ 1.97 - 2.11 (m, 2 H), 2.31 (s, 3 H), 2.34 - 2.44 (m, 2 H), 3.64 - 3.88 (m, 2 H), 4.08 (t, *J* = 6.05 Hz, 2 H), 6.98 (d, *J* = 8.25 Hz, 2 H), 7.03 (d, *J* = 8.80 Hz, 2 H), 7.16 (d, *J* = 8.25 Hz, 2 H), 7.57 (d, *J* = 8.80 Hz, 2 H).

Ejemplo 11. 6-metil-2-oxo-4-*p*-tolil-6-(4-(4,4,4-trifluorobutoxi)fenil)-*N*-(4-(trifluorometoxi)-fenil)-1,2,5,6-tetrahidropiridin-3-carboxamida



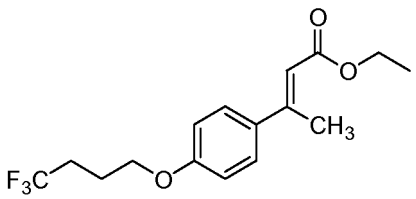
Intermediario 11A. 1-bromo-4-(4,4,4-trifluorobutoxi)benceno



A una solución de 4-bromofenol (2.2 g, 12.7 mmol) y 4-bromo-1,1,1-trifluorobutano (2.4 g, 12.7 mmol) en DMF anhidro (15 ml), se agregó K_2CO_3 (3.5 g, 25.4 mmol). La mezcla se agitó a temperatura ambiente durante la noche. La mezcla

se diluyó con EtOAc (120 ml), y los sólidos se retiraron mediante filtración. El filtrado se lavó con agua y NaCl acuoso saturado, se secó en $MgSO_4$ anhidro, se filtró y se concentró. El residuo se purificó mediante cromatografía en gel de sílice (40 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el Intermediario 11A (3.05 g, 85%) como un aceite incoloro.

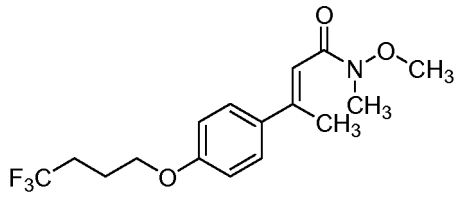
Intermediario 11B. 3-(4-(4,4,4-trifluorobutoxi)fenil)but-2-enoato de (*E*)-etilo



El Intermediario 11A (2.81 g, 9.93 mmol), but-2-enoato de (*E*)-etilo (1.25 g, 10.9 mmol), acetato de paladio (II) (0.11 g, 0.5 mmol), cloruro de tetraetilamonio (1.65 g, 9.9 mmol), *N*-ciclohexil-*N*-metilciclohexanamina (2.91 g, 14.9 mmol) y dimetilacetamida (30 ml) se colocaron en un vial secado al horno y se rociaron con argón durante 5 min. El vial se selló, y la reacción se calentó a 110°C durante 6 h. La reacción se enfrió a temperatura ambiente, se diluyó con EtOAc (75 ml), se lavó con agua y NaCl acuoso saturado, se secó en $MgSO_4$ anhidro, se filtró y se concentró. El residuo se purificó mediante cromatografía en gel de sílice eluida con EtOAc en hexanos para obtener el Intermediario 11B (1.81

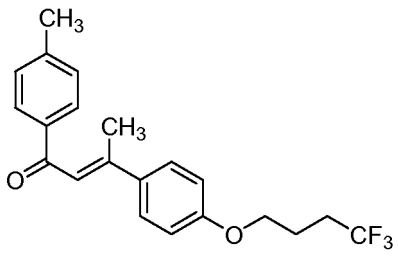
g, 49%) como un aceite incoloro. LCMS Anal. calc. para $C_{16}H_{19}F_3O_3$ 316.32, encontrado [M+H] 317.2.

Intermediario 11C. (*E*)-*N*-metoxi-*N*-metil-3-(4-(4,4,4-trifluorobutoxi)fenil)but-2-enamida



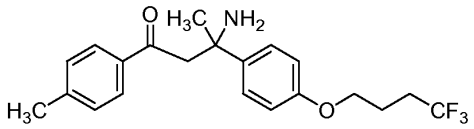
Una solución del Intermediario 11B (2.67 g, 8.44 mmol) y clorhidrato de *N,O*-dimetilhidroxilamina (1.65 g, 16.9 mmol) en THF anhidro (35 ml) se enfrió a -61°C ($CHCl_3$/hielo seco) en una atmósfera de Ar. A esta solución se agregó lentamente cloruro de isopropilmagnesio 0.5 M (16.9 ml, 33.8 mmol) en THF mediante una jeringa. La reacción se agitó a -61°C durante 1.5 h, se calentó a -20°C (NaCl acuoso saturado/hielo) y se agitó durante 40 min; luego se calentó a 0°C y se agitó durante 20 min. La reacción se vertió en 10 ml de NH_4Cl acuoso saturado y 12 ml de agua, y luego se extrajo con EtOAc. La capa orgánica se lavó con NaCl acuoso saturado, se secó en $MgSO_4$ anhidro, se filtró y se concentró. El residuo se purificó mediante cromatografía en gel de sílice que se eluyó con EtOAc en hexanos para obtener el Intermediario 11C (1.62 g, 58%) como un aceite marrón claro. LCMS Anal. calc. para $C_{16}H_{20}F_3NO_3$ 331.33, encontrado [M+H] 332.2.

Intermediario 11D. (E)-1-*p*-tolil-3-(4-(4,4,4-trifluorobutoxi)fenil)but-2-en-1-ona



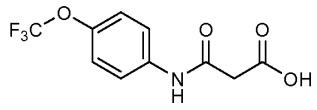
A una solución del Intermediario 11C (1.62 g, 4.89 mmol) en THF anhidro (25 ml) a -78°C, se agregó por goteo bromuro de p-tolilmagnesio 0.5 M en éter (25 ml, 12.5 mmol). La reacción se agitó a -78°C durante 40 min y luego se calentó gradualmente a temperatura ambiente. La reacción se vertió en 1:1 de NH_4Cl acuoso saturado y agua (60 ml). La mezcla se extrajo con EtOAc. La capa orgánica se lavó con NaCl acuoso saturado, se secó en $MgSO_4$, se filtró y se concentró. El residuo se purificó mediante cromatografía en gel de sílice (eluida con EtOAc en hexanos) para obtener el Intermediario 11D (1.34 g, 76%) como un sólido marrón claro. LCMS Anal. calc. para $C_{21}H_{21}F_3O_2$ 362.39, encontrado [M+H] 363.2. RMN 1H (500 MHz, $CDCl_3$) δ 2.01 - 2.11 (m, 2 H), 2.29 - 2.37 (m, 2 H), 2.42 (s, 3 H), 2.58 (s, 3 H), 4.07 (t, *J* = 6.05 Hz, 2 H), 6.92 (d, *J* = 8.80 Hz, 2 H), 7.14 (s, 1 H), 7.23 - 7.34 (m, *J* = 8.25 Hz, 2 H), 7.55 (d, *J* = 8.80 Hz, 2 H), 7.90 (d, *J* = 8.25 Hz, 2 H).

Intermediario 11E. 3-amino-1-*p*-tolil-3-(4-(4,4,4-trifluorobutoxi)fenil)butan-1-ona



Se hizo burbujear amoníaco en una solución del Intermediario 11D (1.34 mg, 0.64 mmol) en EtOH (20 ml) y DMSO (12 ml) durante 10 min a 0°C. La reacción se agitó a temperatura ambiente durante la noche en un recipiente sellado a presión. La HPLC analítica mostró que la reacción había progresado solo ca. 10%. La mezcla se enfrió a -15°C, y luego se hizo burbujear amoníaco durante 7 min. El recipiente se selló, y la reacción se agitó a temperatura ambiente durante la noche. La HPLC analítica mostró que la reacción estaba ca. 25-30% completa. La mezcla se diluyó con EtOAc (75 ml), se lavó con agua y NaCl acuoso saturado, se secó en $MgSO_4$ anhidro, se filtró y se concentró al vacío. El residuo se purificó mediante cromatografía en gel de sílice para obtener el Intermediario 11E (281 mg, 20%) como un aceite marrón claro. LCMS Anal. calc. para $C_{21}H_{24}F_3NO_2$ 379.42, encontrado [M+H] 380.3.

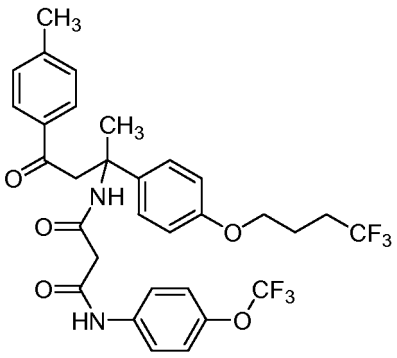
Intermediario 11F. Ácido 3-oxo-3-(4-(trifluorometoxi)fenilamino)propanoico



Mediante la aplicación secuencial de los

procedimientos de los Intermediarios 6A y 6B, 4-trifluorometoxianilina (2.3 g, 13 mmol) se convirtió en el Intermediario 11F (2.8 g, 11 mmol), que se aisló como un sólido blanco. LCMS Anal. calc. para $C_{10}H_8F_3NO_4$ 263.17, encontrado [M+H] 264.1.

Intermediario 11G. *N*^{1}-(4-oxo-4-*p*-tolil-2-(4-(4,4,4-trifluorobutoxi)fenil)butan-2-il)-*N*^{3}-(4-(trifluorometoxi)-fenil)malonamida



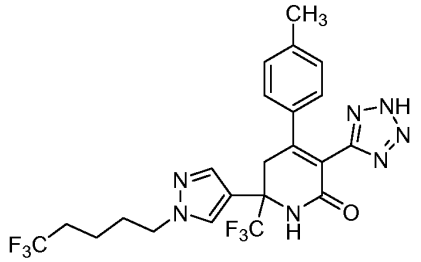
A una solución del Intermediario 11F (41.6 mg, 0.158 mmol) en CH_2Cl_2 anhidro (0.6 ml), se agregó PPh_3 (124 mg, 0.474 mmol) y luego, por goteo, se agregó tricloroacetonitrilo (27.4 mg, 0.19 mmol). La reacción se agitó a temperatura ambiente durante 3 h. Al cloruro ácido recién preparado, se agregó una solución del Intermediario 11E (20 mg, 0.053 mmol) en CH_2Cl_2 anhidro (0.3 ml) y luego piridina (19 µl, 0.237 mmol). La mezcla se agitó a temperatura ambiente durante la noche. El solvente se retiró al vacío. El producto se purificó mediante HPLC preparativa (MeOH/H_2O/TFA) para obtener el Intermediario 11G (11 mg, 33%)

como un sólido marrón. LCMS Anal. calc. para $C_{31}H_{30}F_6N_2O_5$ 624.57, encontrado [M+H] 625.4.

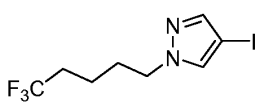
Ejemplo 11

A una solución del Intermediario 11G (11 mg, 0.018 mmol) en MeOH (0.8 ml), se agregó piperidina (15 µl). La reacción se agitó a 75°C durante 1,5 h. El producto se aisló mediante HPLC preparativa (CH_3CN/H_2O/TFA) para obtener el Ejemplo 11 (5.2 mg, 44%) como un sólido marrón. LCMS Anal. calc. para $C_{31}H_{28}F_6N_2O_4$ 606.56, encontrado [M+H] 607.4. RMN 1H (500 MHz, CD_3OD) δ 1.68 (s, 3 H), 1.95 - 2.07 (m, 2 H), 2.27 (s, 3 H), 2.30 - 2.41 (m, 2 H), 3.11 - 3.26 (m, 2 H), 4.03 (t, *J* = 6.05 Hz, 2 H), 6.91 (d, *J* = 8.80 Hz, 2 H), 7.08 - 7.18 (m, 4 H), 7.22 (d, *J* = 8.25 Hz, 2 H), 7.38 (d, *J* = 8.80 Hz, 2 H), 7.45 (d, *J* = 8.80 Hz, 2 H).

Ejemplo 12. 3-(2*H*-tetrazol-5-il)-4-*p*-tolil-6-(trifluorometil)-6-(1-(5,5,5-trifluoropentil)-1*H*-pirazol-4-il)-5,6-dihidropiridin-2(1*H*)-ona

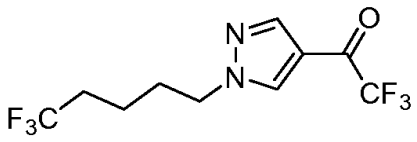


Intermediario 12A. 4-yodo-1-(5,5,5-trifluoropentil)-1*H*-pirazol



A una solución agitada de 4-yodo-1*H*-pirazol (337 mg, 1.737 mmol) en DMF (10 ml), se agregó hidruro de sodio (104 mg, 2.61 mmol). Después de 30 min, se agregó 5-bromo-1,1,1-trifluoropentano (427 mg, 2.085 mmol). La reacción se agitó a temperatura ambiente durante 2 h. Se agregaron 3:1 de hexano:éter y agua. La capa orgánica se lavó con H_2O, se secó en $MgSO_4$, se filtró y se concentró al vacío. El producto crudo se purificó mediante cromatografía en gel de sílice (24 g de gel de sílice, eluido con 0-60% de EtOAc en hexanos) para obtener el producto deseado (460 mg, 83%) como un aceite transparente. LCMS Anal. calc. para $C_8H_{10}F_3IN_2$ 318.0. encontrado [M+H] 319.0. RMN 1H (400 MHz, $CDCl_3$) δ 7.49 (s, 1 H), 7.40 (s, 1 H), 4.12 (t, *J* = 6.9 Hz, 2 H), 2.00 - 2.15 (m, 2 H), 1.85 - 1.96 (m, 2 H), 1.47 - 1.61 (m, 2 H).

Intermediario 12B. 2,2,2-trifluoro-1-(1-(5,5,5-trifluoropentil)-1*H*-pirazol-4-il)etanona



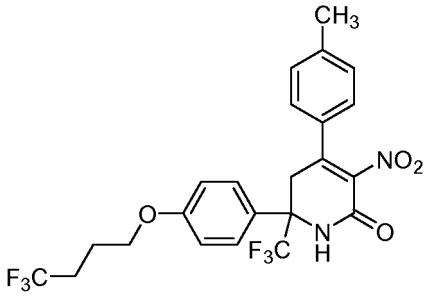
A una solución agitada del Intermediario 12A (460 mg, 1.446 mmol) en tetrahidrofurano (5 ml) a 0°C, se agregó rápidamente cloruro de isopropilmagnesio (0.795 ml, 1.591 mmol). Después de 30 min, se agregaron 0.25 eq.

más de *i*PrMgCl y, después de 30 min, la mezcla se enfrió a -78°C. Se agregó rápidamente 2,2,2-trifluoro-1-(piperidin-1-il)etanona (288 mg, 1.591 mmol), y la reacción se calentó a temperatura ambiente y se agitó durante 3 h. La reacción se inactivó con NH_4Cl acuoso saturado y se diluyó con EtOAc. La capa orgánica se lavó con NH_4Cl acuoso saturado, se secó en $MgSO_4$, se filtró y se concentró al vacío. El producto crudo se purificó mediante cromatografía en gel de sílice (40 g de gel de sílice, eluido con 0-100% de EtOAc en hexanos) para obtener el producto deseado (265 mg, 64%) como un aceite transparente. RMN 1H (500 MHz, $CDCl_3$) δ 8.08 (s, 2 H), 4.22 (t, *J* = 7.0 Hz, 2 H), 2.07 - 2.20 (m, 2 H), 1.98 - 2.05 (m, 2 H), 1.55 - 1.65 (m, 2 H).

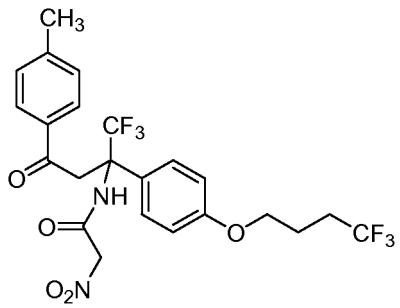
Ejemplo 12

El Ejemplo 12 se preparó usando un procedimiento análogo al Ejemplo 2, reemplazando el Intermediario 2C por el Intermediario 12B. LCMS Anal. calc. para $C_{22}H_{21}F_6N_7O$ 513.2, encontrado [M+H] 514.3. RMN 1H (500 MHz, $CDCl_3$) δ 7.75 (s, 1 H), 7.63 (s, 1 H), 7.54 - 7.59 (m, 1 H), 7.06 (d, *J* = 8.0 Hz, 2 H), 6.88 (d, *J* = 8.0 Hz, 2 H), 4.16 (t, *J* = 7.0 Hz, 2 H), 3.58 (d, *J* = 18.2 Hz, 1 H), 3.39 (d, *J* = 17.9 Hz, 1 H), 2.28 (s, 3 H), 2.02 - 2.17 (m, 2 H), 1.93 (quin, *J* = 7.4 Hz, 2 H), 1.46 - 1.55 (m, 2 H).

Ejemplo 13. 3-nitro-4-*p*-tolil-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-5,6-dihidropiridin-2(1*H*)-ona



Intermediario 13A. 2-nitro-*N*-(1,1,1-trifluoro-4-oxo-4-*p*-tolil-2-(4-(4,4,4-trifluorobutoxi)fenil)butan-2-il)-acetamida



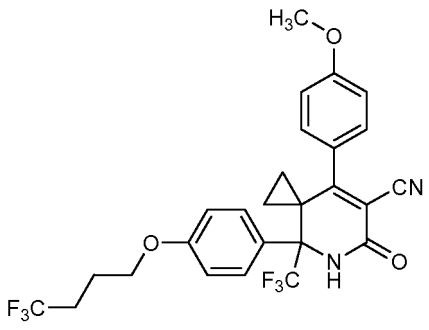
A una solución del Intermediario 2F (130 mg, 0.3 mmol) en THF anhidro (1 ml) a 0°C, se agregó por goteo DCC (204 mg, 0.99 mmol) y luego una solución de ácido 2-nitroacético (104 mg, 0.99 mmol) en THF anhidro (0.5 ml). La reacción se agitó a 0°C durante 1 h y luego a temperatura ambiente durante la noche. La reacción se calentó a 70°C durante 4 h. La reacción se enfrió a temperatura ambiente y se diluyó con EtOAc (3 ml). El sólidos se filtraron, y el filtrado se concentró al vacío. El residuo se purificó

mediante cromatografía en gel de sílice (eluida con EtOAc en hexanos) para obtener el Intermediario 13A (129 mg, 83%) como un aceite marrón. LCMS Anal. calc. para $C_{23}H_{22}F_6N_2O_5$ 520.42, encontrado [M+H] 521.1.

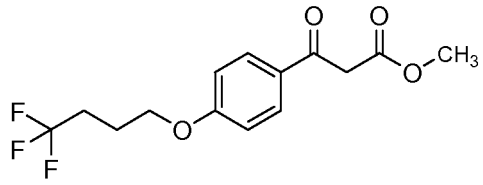
Ejemplo 13

A una solución del Intermediario 13A (126 mg, 0.24 mmol) en MeOH (2 ml), se agregó piperidina (35 µl). La mezcla de reacción se calentó a 75°C durante 1.5 h. El producto se aisló mediante HPLC preparativa (MeOH/H_2O/TFA) para obtener el Ejemplo 13 (21 mg, 17%) como un sólido blancuzco. LCMS Anal. calc. para $C_{23}H_{20}F_3N_2O_4$ 502.41, encontrado [M+H] 503.1. RMN 1H (500 MHz, CD_3OD) δ 1.98 - 2.08 (m, 2 H), 2.28 - 2.45 (m, 5 H), 3.58 (d, *J* = 17.60 Hz, 1 H), 3.76 (d, *J* = 17.60 Hz, 1 H), 4.08 (t, *J* = 6.05 Hz, 2 H), 7.02 (d, *J* = 8.80 Hz, 2 H), 7.12 - 7.19 (m, 2 H), 7.22 - 7.30 (m, 2 H), 7.53 (d, *J* = 8.80 Hz, 2 H).

Ejemplo 14. 8-(4-metoxifenil)-6-oxo-4-(4-(4,4,4-trifluorobutoxi)fenil)-4-(trifluoro-metil)-5-azaspiro[2.5]oct-7-en-7-carbonitrilo

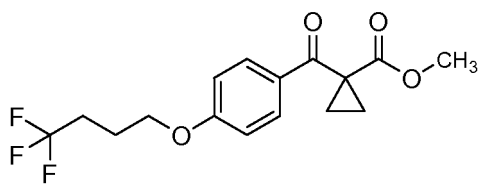


Intermediario 14A. 3-oxo-3-(4-(4,4,4-trifluorobutoxi)fenil)propanoato de metilo



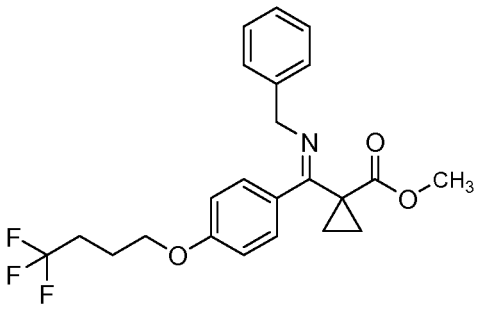
A una solución de 3-(4-hidroxifenil)-3-oxopropanoato de metilo (7.8 g, 40.2 mmol) y 4,4,4-trifluorobutan-1-ol (5.15 g, 40.2 mmol) en CH_2Cl_2 (201 ml) a 0°C, se agregó trifenilfosfina (12.6 g, 48.2 mmol). La mezcla se agitó durante unos pocos minutos, y luego se agregó DIAD (9.37 ml, 48.2 mmol). La reacción se agitó a 0°C durante 30 min, luego se calentó a temperatura ambiente y se agitó durante 3 días. La reacción se cargó directamente en una columna de gel de sílice de 300 g eluida con EtOAc en hexanos. Las fracciones que contenían el producto se combinaron y se concentraron para obtener el Intermediario 14A (9.9 g, 80%) como un sólido incoloro. RMN 1H (500 MHz, $CDCl_3$) δ 2.03 - 2.13 (m, 2 H), 2.26 - 2.39 (m, 2 H), 3.75 (s, 3 H), 3.96 (s, 2 H), 4.09 (t, *J* = 6.05 Hz, 2 H), 6.92 - 6.96 (m, 2 H), 7.86 - 7.97 (m, 2 H).

Intermediario 14B. 1-(4-(4,4,4-trifluorobutoxi)benzoil)ciclopropancarboxilato de metilo



A una solución del Intermediario 14A (6.0 g, 19.7 mmol) en DMF (197 ml), se agregó K_2CO_3 (8.18 g, 59.2 mmol) y luego 1,2-dibromoetano (2.6 ml, 30 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 días. La reacción se redujo en volumen al vacío, luego se diluyó con EtOAc, se lavó con una solución 1:1 de NaCl acuoso saturado y agua, se secó en MgSO4 anhidro, se filtró y se concentró. El producto se aisló mediante cromatografía en gel de sílice (220 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el Intermediario 14B (4.2 g, 61%) como un aceite incoloro. RMN 1H (500 MHz, $CDCl_3$) δ 1.45 - 1.49 (m, 2 H), 1.56 - 1.61 (m, 2 H), 2.03 - 2.14 (m, 2 H), 2.26 - 2.39 (m, 2 H), 3.60 (s, 3 H), 4.09 (t, *J* = 6.05 Hz, 2 H), 6.90 - 6.94 (m, 2 H), 7.86 - 7.93 (m, 2 H).

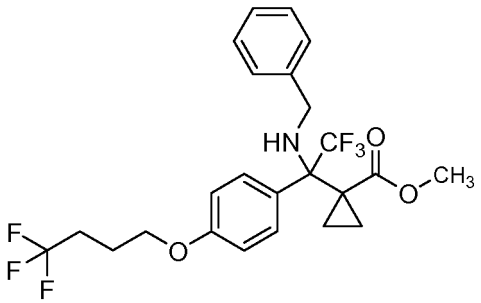
Intermediario 14C. 1-((bencilimino)(4-(4,4,4-trifluorobutoxi)fenil)metil)ciclopropancarboxilato de metilo



A una solución del Intermediario 14B (4.2 g, 13 mmol) y bencilamina (5.5 ml, 50 mmol) en dietiléter (63 ml) a 0°C, se agregó $TiCl_4$ 1.0 M en CH_2Cl_2 (7.6 ml, 7.5 mmol). La reacción se agitó a 0°C durante unos pocos minutos, luego se

calentó a temperatura ambiente y se agitó durante 16 h. Se agregó Celite® a la reacción, y los sólidos se retiraron mediante filtración por medio de una almohadilla de Celite®. El filtrado se concentró y se purificó mediante cromatografía en gel de sílice (120 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el Intermediario 14C (4.6 g, 83%) como un aceite incoloro. RMN 1H (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.8 Hz, 2*H*), 7.42 - 7.38 (m, 2*H*), 7.34 (t, *J* = 7.7 Hz, 2*H*), 7.27 - 7.24 (m, 1*H*), 6.87 (d, *J* = 8.8 Hz, 2*H*), 4.90 (s, 2*H*), 4.04 (t, *J* = 6.0 Hz, 2*H*), 3.69 (s, 3H), 2.39 - 2.26 (m, 2*H*), 2.11 - 2.02 (m, 2*H*), 1.78 - 1.72 (m, 2*H*), 1.11 (d, *J* = 3.3 Hz, 2*H*).

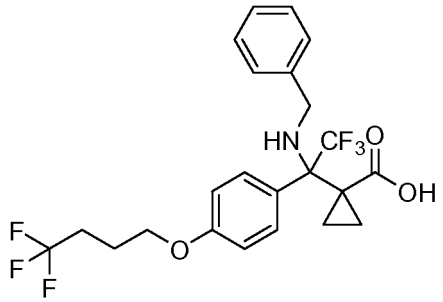
Intermediario 14D. 1-(1-(bencilamino)-2,2,2-trifluoro-1-(4-(4,4,4-trifluorobutoxi)fenil)etil)-ciclopropancarboxilato de metilo



A una solución del Intermediario 14C (4.6 g, 11 mmol) en acetonitrilo (22 ml) y DMF (2.6 ml, 33 mmol) a 0°C, se agregó TFA puro (1.1 ml, 13.7 mmol) y luego fluoruro ácido de potasio (0.64 g, 8.2 mmol). La reacción se agitó durante ca. 5 min, luego se agregó trimetil(trifluorometil)silano

(2.4 ml, 16.4 mmol), y la reacción se calentó a temperatura ambiente y se agitó durante 16 h. Se agregó $NaHCO_3$ acuoso saturado a la reacción, y la mezcla se extrajo con EtOAc. Los extractos orgánicos combinados se lavaron con NaCl acuoso saturado, se secaron en Na_2SO_4, se filtraron y se concentraron. El residuo se purificó mediante cromatografía en gel de sílice (220 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el Intermediario 14D (1.8 g, 31%) como un aceite. LCMS Anal. calc. para $C_{24}H_{25}F_6NO_3$ 489.45, encontrado [M+H] 490.1.

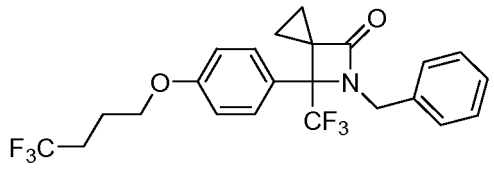
Intermediario 14E. Ácido 1-(1-(bencilamino)-2,2,2-trifluoro-1-(4-(4,4,4-trifluorobutoxi)fenil)etil)-ciclopropancarboxílico



A una solución del Intermediario 14D (558 mg, 1.140 mmol) en piridina (5.7 ml), se agregó yoduro de litio (1.53 g, 11.4 mmol). La reacción se calentó a reflujo durante la noche. La reacción se enfrió a temperatura ambiente y se diluyó con agua y EtOAc. La capa acuosa se acidificó con HCl 1 N, y las capas se separaron. La capa orgánica se lavó con NaCl acuoso saturado, se secó en $MgSO_4$, se filtró y se concentró para

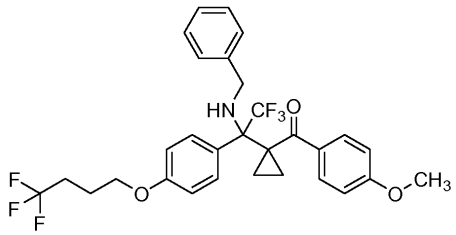
obtener el Intermediario 14E (506 mg, 84%), que se usó en la siguiente etapa sin purificación adicional. LCMS Anal. calc. para $C_{23}H_{23}F_6NO_3$ 475.42, encontrado [M+H] 476.2.

Intermediario 14F. 5-bencil-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-5-azaspiro[2.3]-hexan-4-ona



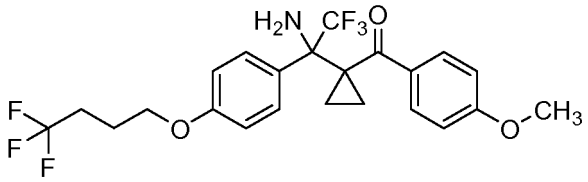
A una solución del Intermediario 14E (506 mg, 1,1 mmol) en CH_2Cl_2 (11 ml), se agregó cloruro de oxalilo (0.12 ml, 2.2 mmol) y luego varias gotas de DMF. La reacción se agitó a temperatura ambiente durante 16 h. El solvente se retiró al vacío, y el residuo se purificó mediante cromatografía en gel de sílice (24 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el Intermediario 14F (389 mg, 72%) como un aceite amarillo. LCMS Anal. calc. para $C_{23}H_{21}F_6NO_2$ 457.41, encontrado [M+H] 458.2.

Intermediario 14G. (1-(1-(bencilamino)-2,2,2-trifluoro-1-(4-(4,4,4-trifluorobutoxi)fenil)etil)-ciclopropil)-(4-metoxifenil)metanona



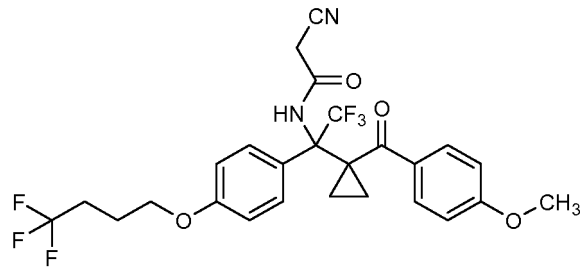
Las virutas de magnesio (130 mg, 5.4 mmol) se suspendieron en THF anhidro (13 ml). Se agregó 4-bromoanisol (1 g, 670 µl, 5.4 mmol) y luego unas pocas gotas de 1,2-dibromoetano. La mezcla de reacción se agitó a temperatura ambiente durante 1.5 h, después de lo cual se disolvió la mayor parte del magnesio. La reacción se calentó a 50°C durante 30 min y luego se enfrió a temperatura ambiente. La concentración final del reactivo de Grignard fue de 0.4 M, suponiendo la conversión completa. A una solucion fría (-40°C) del Intermediario 14F (200 mg, 0.44 mmol) en THF (4.4 ml), se agregó el reactivo de Grignard recién preparado. La reacción se calentó de -40°C a temperatura ambiente y luego se calentó a reflujo durante la noche. La reacción se enfrió a temperatura ambiente y se inactivó con NH_4Cl acuoso saturado. Las capas se separaron, y la capa acuosa se extrajo con EtOAc. Los extractos orgánicos combinados se lavaron con NaCl acuoso saturado, se secaron en $MgSO_4$, se filtraron y se concentraron. El producto se aisló mediante HPLC preparativa ($MeOH/H_2O$/TFA). Las fracciones que contenían el producto se combinaron, y su volumen se redujo al vacío. La solución acuosa resultante se volvió básica con $NaHCO_3$ acuoso saturado y se extrajo con EtOAc. Los extractos orgánicos combinados se lavaron con NaCl acuoso saturado, se secaron en Na_2SO_4, se filtraron y se concentraron para obtener el Intermediario 14G (6.1 mg, 2.5%). LCMS Anal. calc. para $C_{30}H_{29}F_6NO_3$ 565.55, encontrado [M+H] 566.3.

Intermediario 14H. (1-(1-amino-2,2,2-trifluoro-1-(4-(4,4,4-trifluorobutoxi)fenil)etil)ciclopropil)(4-metoxi-fenil)metanona



A una solución del Intermediario 14G (6 mg, 10.6 µmol) en MeOH (1 ml) que contenía 4.4% de ácido fórmico, se agregó 10% de paladio sobre carbón (2 mg, 2 µmol). La reacción se agitó a temperatura ambiente durante la noche. La reacción se filtró a través de Celite®. El filtrado se volvió básico con $NaHCO_3$ acuoso saturado y luego se evaporó para retirar MeOH. El residuo acuoso se diluyó con NaCl acuoso saturado y se extrajo con EtOAc. Los extractos orgánicos combinados se lavaron con NaCl acuoso saturado, se secaron en Na_2SO_4, se filtraron y se concentraron para obtener el Intermediario 14H (4 mg, 71%) como un vidrio de color tostado. LCMS Anal. calc. para $C_{23}H_{23}F_6NO_3$ 475.42, encontrado [M+H] 476.2.

Intermediario 14I. 2-ciano-*N*-(2,2,2-trifluoro-1-(1-(4-metoxibenzoil)ciclopropil)-1-(4-(4,4,4-trifluorobutoxi)-fenil)etil)acetamida



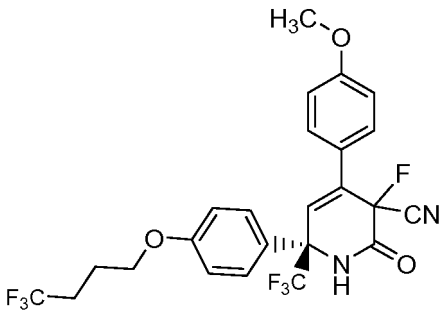
A una solución de ácido 2-cianoacético (320 mg, 3.8 mmol) en CH_2Cl_2 (9.1 ml), se agregó cloruro de oxalilo (523 mg, 360 µl, 4.1 mmol) y luego unas pocas gotas de DMF. La reacción se agitó a temperatura ambiente durante 1 h. La concentración final de cloruro de 2-cianoacetilo fue de 0.4 M, suponiendo una conversión completa. A una solución del Intermediario 14H (4 mg, 8.4 µmol) y piridina (2.0 µl, 0.025 mmol) en CH_2Cl_2 (100 µl) a 0°C, se agregó el cloruro de 2-cianoacetilo 0.4 M recién preparado en CH_2Cl_2 (0.032 ml, 0.013 mmol). La reacción se calentó a temperatura ambiente y se agitó durante 16 h. La reacción se inactivó con una gota de MeOH, se diluyó con EtOAc y se lavó con 1:1 de NaCl acuoso saturado y agua, se secó en $MgSO_4$, se filtró y se concentró para obtener el Intermediario 14I (7 mg, 153%), que se usó en la siguiente etapa sin purificación adicional. LCMS Anal. calc. para $C_{26}H_{24}F_6N_2O_4$ 542.47, encontrado [M+H] 543.3.

Ejemplo 14

A una solución del Intermediario 14I (7 mg, 0.013 mmol) en EtOH (2 ml), se agregó 25% p/p de metóxido de sodio (0.015 ml, 0.065 mmol). La reacción se agitó a temperatura ambiente durante 1.5 h. La reacción se acidificó con algunas gotas de HCl acuoso 1 N y luego se concentró. El producto se aisló mediante HPLC preparativa (MeOH/H_2OTFA). La fracción que contenía el producto se redujo en volumen al vacío, se volvió básica con $NaHCO_3$ acuoso saturado y se extrajo con EtOAc. Los extractos orgánicos combinados se lavaron con NaCl acuoso

saturado, se secaron en $MgSO_4$, se filtraron y se concentraron para obtener el Ejemplo 14 (2.9 mg, 42%). LCMS Anal. calc. para $C_{26}H_{22}F_6N_2O_3$ 524.46, encontrado [M+H] 525.2. RMN 1H (500 MHz, CD_3OD) δ 0.65 (t, *J* = 8.80 Hz, 2 H), 1.18 - 1.25 (m, 2 H), 1.99 - 2.08 (m, 2 H), 2.31 - 2.43 (m, 2 H), 3.85 (s, 3 H), 4.09 (t, *J* = 6.05 Hz, 2 H), 7.03 (d, *J* = 8.80 Hz, 2 H), 7.06 (br. s., 2 H), 7.23 (br. s., 2 H), 7.58 (d, *J* = 9.35 Hz, 2 H).

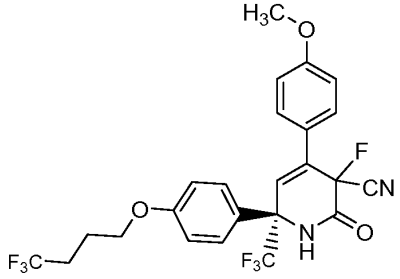
Ejemplo 15-1 y Ejemplo 15-2. 3-fluoro-4-(4-metoxifenil)-2-oxo-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,3,6-tetrahidropiridin-3-carbonitrilo



A una solución del Ejemplo 77 (70 mg, 0.140 mmol) en DMF (1.4 ml), se agregó Na_2CO_3 (30 mg, 0.28 mmol) y luego 1-fluoro-4-hidroxi-1,4-diazoniabiciclo[2,2,2]octan-bis-(tetrafluoroborato) (196 mg, 0.28 mmol). La reacción se calentó a 80°C durante la noche. La reacción se enfrió a temperatura ambiente y se diluyó con EtOAc y agua. Las capas se separaron, y la capa acuosa se extrajo con EtOAc. Las capas orgánicas combinadas se lavaron con NaCl acuoso saturado, se secaron en $MgSO_4$, se filtraron y se concentraron al vacío. El residuo se purificó mediante HPLC preparativa (MeOH/H_2OTFA) para obtener el

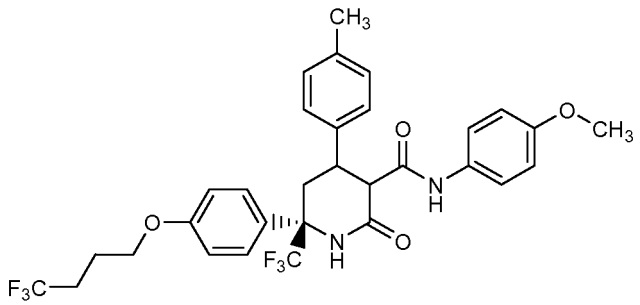
producto (44 mg, 61%) como una mezcla de dos diastereoisómeros. Los dos diastereoisómeros se separaron mediante el método B de SFC preparativa quiral para obtener el Ejemplo 15-1 (14.6 mg, 20%) y el Ejemplo 15-2 (17.2 mg, 23%). Datos para el Ejemplo 15-1: LCMS Anal. calc. para $C_{24}H_{19}F_7N_2O_3$ 516.41, encontrado [M+H] 517.2. RMN 1H (500 MHz, CD_3OD) δ 2.00 - 2.08 (m, 2 H), 2.32 - 2.44 (m, 2 H), 3.85 (s, 3 H), 4.10 (t, *J* = 6.05 Hz, 2 H), 6.92 (d, *J* = 1.10 Hz, 1 H), 7.02 (d, *J* = 8.80 Hz, 2 H), 7.07 (d, *J* = 9.35 Hz, 2 H), 7.50 (d, *J* = 8.25 Hz, 2 H), 7.57 (d, *J* = 8.80 Hz, 2 H). Método B de HPLC analítica quiral: RT = 3.23 min, 99% ee. Datos para el Ejemplo 15-2: LCMS Anal. calc. para $C_{24}H_{19}F_7N_2O_3$ 516.41, encontrado [M+H] 517.2. RMN 1H (500 MHz, CD_3OD) δ 2.00 - 2.08 (m, 2 H), 2.32 - 2.44 (m, 2 H), 3.85 (s, 3 H), 4.10 (t, *J* = 6.05 Hz, 2 H), 6.92 (d, *J* = 1.10 Hz, 1 H), 7.02 (d, *J* = 8.80 Hz, 2 H), 7.07 (d, *J* = 9.35 Hz, 2 H), 7.50 (d, *J* = 8.25 Hz, 2 H), 7.57 (d, *J* = 8.80 Hz, 2 H). Método B de HPLC analítica quiral: RT = 4.84 min, 99% ee.

Ejemplo 15-3 y Ejemplo 15-4. 3-fluoro-4-(4-metoxifenil)-2-oxo-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,3,6-tetrahidropiridin-3-carbonitrilo



Mediante la aplicación del método descrito para el Ejemplo 15-1 y el Ejemplo 15-2, se obtuvieron el Ejemplo 15-3 (4.6 mg, 43%) y el Ejemplo 15-4 (4.6 mg, 43%) del isómero *R* del Ejemplo 65 (10 mg, 0.02 mmol). Datos para el Ejemplo 15-3: LCMS Anal. calc. para $C_{24}H_{19}F_7N_2O_3$ 516.41, encontrado [M+H] 517.1. RMN 1H (500 MHz, CD_3OD) δ 2.00 - 2.08 (m, 2 H) 2.31 - 2.44 (m, 2 H) 3.85 (s, 3 H) 4.10 (t, *J* = 6.05 Hz, 2 H) 6.92 (d, *J* = 1.65 Hz, 1 H) 7.02 (d, *J* = 8.80 Hz, 2 H) 7.07 (d, *J* = 8.80 Hz, 2 H) 7.50 (d, *J* = 8.25 Hz, 2 H) 7.57 (d, *J* = 8.80 Hz, 2 H). Método B de HPLC analítica quiral: RT = 5.13 min, 99% ee. Datos para el Ejemplo 15-4: LCMS Anal. calc. para $C_{24}H_{19}F_7N_2O_3$ 516.41, encontrado [M+H] 517.1. RMN 1H (500 MHz, CD_3OD) δ 1.99 - 2.07 (m, 2 H) 2.30 - 2.43 (m, 2 H) 3.84 (s, 3 H) 4.09 (t, *J* = 6.05 Hz, 2 H) 6.78 (s, 1 H) 7.02 (d, *J* = 8.80 Hz, 2 H) 7.05 (d, *J* = 9.35 Hz, 2 H) 7.54 (dd, *J* = 8.25, 4.95 Hz, 4 H). Método B de HPLC analítica quiral: RT = 5.13 min, 99% ee.

Ejemplo 16-1 y Ejemplo 16-2. *N*-(4-metoxifenil)-2-oxo-4-*p*-tolil-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)piperidin-3-carboxamida

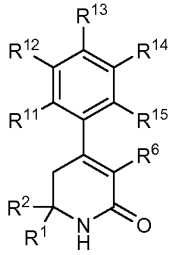


A una solución de Ejemplo 6-2 (90 mg, 0.15 mol) en MeOH (2 ml), se agregó 10% de paladio sobre carbón (5 mg). La mezcla se agitó en hidrógeno (50) durante la noche. Se agregó paladio sobre carbón adicional (5 mg), y la reacción se agitó en hidrógeno (50 psi) durante 1 h más. El catalizador se retiró mediante filtración a través de una almohadilla de Celite®, y la solución se concentró al vacío. Los productos se separaron parcialmente mediante HPLC preparativa (CH_3CN/H_2O/TFA). Las fracciones que contenían los dos productos se combinaron y se separaron mediante el método C de HPLC quiral para obtener el Ejemplo 16-1 y el Ejemplo 16-2. Datos para el Ejemplo 16-1: LCMS Anal. calc. para $C_{31}H_{30}F_6N_2O_4$ 608.57, encontrado [M+H] 609.2. RMN 1H (400 MHz, CD_3OD) δ 1.97 - 2.14 (m, 2 H), 2.25 (s, 3 H), 2.32 - 2.46 (m, 2 H), 2.54 - 2.69 (m, 2 H), 3.17 (td, *J* = 11.82, 3.85 Hz, 1 H), 3.60 (d, *J* = 11.54 Hz, 1 H), 3.71 (s, 3 H), 4.10 (t, *J* = 6.05 Hz, 2 H), 6.76 (d, *J* = 8.79 Hz, 2 H), 6.99 - 7.12 (m, 6 H), 7.13 - 7.23 (m, 2 H), 7.55 (d, *J* = 8.79 Hz, 2 H). Método D de HPLC analítica quiral, RT = 6.75 min, 99% ee. Datos para el Ejemplo 16-2: LCMS Anal. calc. para $C_{31}H_{30}F_6N_2O_4$ 608.57, encontrado [M+H] 609.2. RMN 1H (400 MHz, CD_3OD) δ 7.52 (d, *J* = 8.8 Hz, 2*H*), 7.25 - 7.20 (m, 2*H*), 7.19 - 7.15 (m, 2*H*), 7.14 - 7.10 (m, 2*H*), 7.02 - 6.97 (m, 2*H*), 6.81 - 6.75 (m, 2*H*), 4.07 (t, *J* = 6.0 Hz, 2*H*), 3.94 - 3.84 (m, 1*H*), 3.73 (s, 3H), 3.60 (d, *J* = 12.1 Hz, 1*H*), 2.90 (dd, *J* = 14.8, 3.3 Hz, 1*H*),

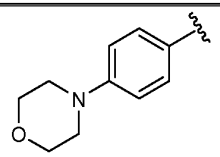
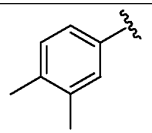
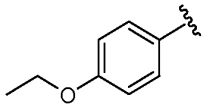
2.45 - 2.32 (m, 2*H*), 2.31 (dd, 1*H*, superposiciones con pico en δ 2.27), 2.27 (s, 3H), 2.08 - 1.98 (m, 2*H*). Método D de HPLC preparativa quiral: RT = 10.9 min, 99% ee.

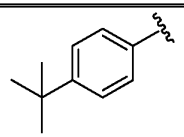
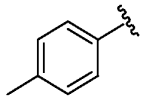
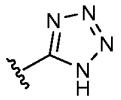
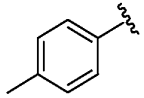
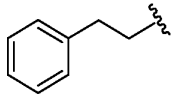
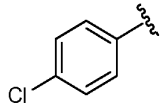
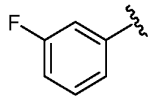
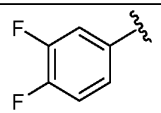
Los ejemplos 17-101 expresados mediante la Fórmula (IIa), a menos que se indiquen en la tabla, pueden ser realizados por una persona del oficio del nivel medio mediante la aplicación adecuada de los procedimientos descritos para los Ejemplos 1-16. R^{11} a R^{15} son hidrógeno, a menos que se indique en la tabla.

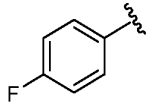
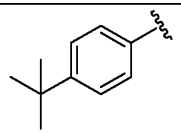
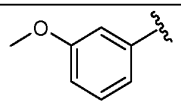
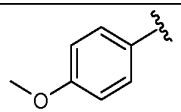
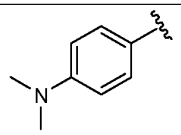
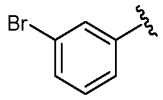
Tabla 2

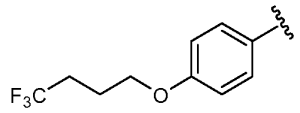
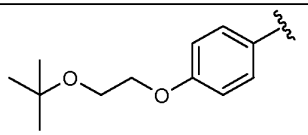
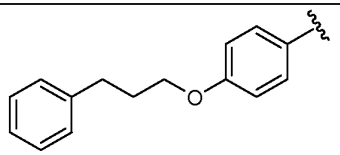


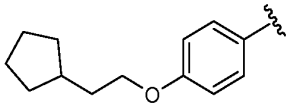
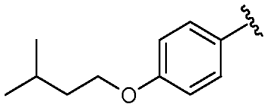
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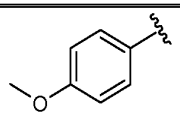
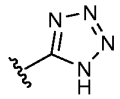
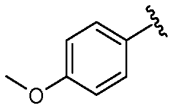
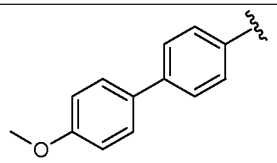
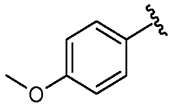
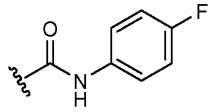
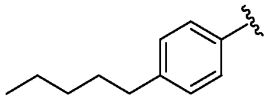
Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
17 Rac		CH_3	CN	R^{13} = morfolina	459.2*	
18 Rac		CH_3	CN	$R^{12} = CH_3$ $R^{13} = CH_3$	345.1*	
19 Rac		CH_3	CN	$R^{13} = OCH_2CH_3$	377.2*	

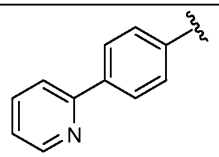
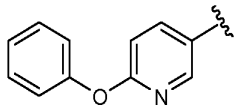
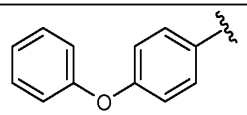
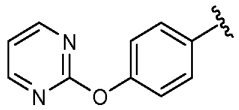
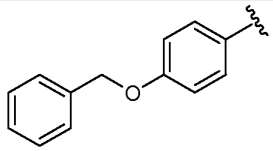
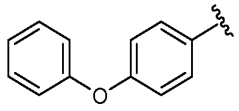
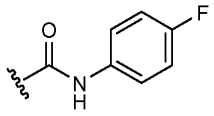
Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
20 Rac		CH_3	CN	R^{13} = *t*-Bu	401.2*	
21 Rac		CH_3		$R^{13} = CH_3$	360.2	
22 Rac		CF_3	CN	$R^{13} = CH_3$	371.2	
23 Rac		CH_3	CN	$R^{13} = CH_3$	331.3	
24 Rac		CF_3	CN	$R^{13} = CH_3$	391.1	
25 Rac		CF_3	CN	$R^{13} = CH_3$	375.2	
26 Rac		CF_3	CN	$R^{13} = CH_3$	393.2	

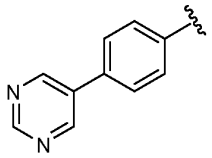
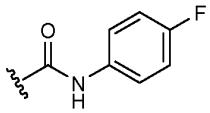
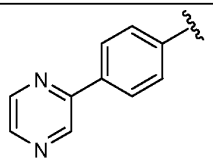
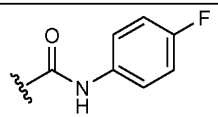
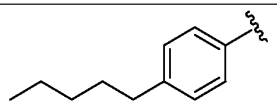
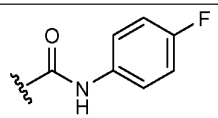
Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
27 Rac		CF_3	CN	$R^{13} = CH_3$	375.2	
28 Rac		CF_3	CN	$R^{13} = CH_3$	413.3	
29 Rac		CF_3	CN	$R^{12} = CH_3$	387.2	
30 Rac		CF_3	CN	$R^{13} = CH_3$	387.2	
31 Rac		CF_3	CN	$R^{13} = CH_3$	400.2	
32 Rac		CF_3	CN	$R^{13} = CH_3$	435.2	

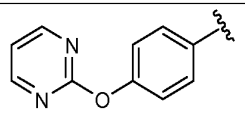
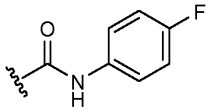
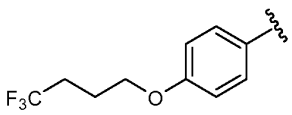
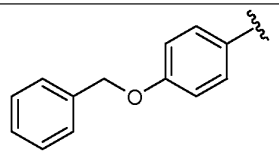
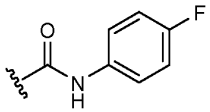
Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
33 Rac		CF_3	CN	$R^{13} = CH_3$	483.3	2.03 - 2.12 (m, 2 H) 2.25 - 2.36 (m, 2 H) 2.42 (s, 3 H) 3.51 - 3.68 (m, 2 H) 4.04 (t, *J* = 5.50 Hz, 2 H) 6.94 (d, *J* = 8.80 Hz, 2 H) 7.31 (d, *J* = 7.70 Hz, 2 H) 7.40 (d, *J* = 8.80 Hz, 2 H) 7.47 (d, *J* = 7.70 Hz, 2 H) 7.64 (br. s., 1 H).
34 Rac		CF_3	CN	$R^{13} = CH_3$	471.4 [M-H]-	
35 Rac		CF_3	CN	$R^{13} = CH_3$	491.3	2.06 - 2.18 (m, 2 H) 2.41 (s, 3 H) 2.81 (t, *J* = 7.70 Hz, 2 H) 3.45 - 3.68 (m, 2 H) 3.97 (t, *J* = 6.32 Hz, 2 H) 6.55 (s, 1 H) 6.93 (d, *J* = 8.80 Hz, 2 H) 7.21 (d, *J* = 7.15 Hz, 3 H)

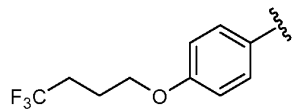
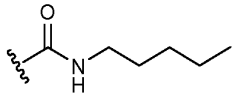
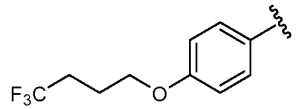
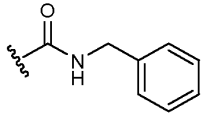
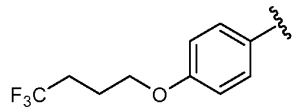
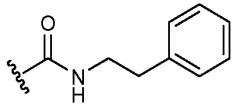
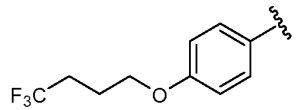
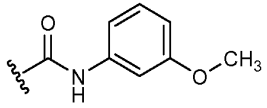
Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						7.25 - 7.31 (m, 4 H) 7.37 (d, *J* = 8.25 Hz, 2 H) 7.45 (d, *J* = 8.25 Hz, 2 H).
36 Rac		CF_3	CN	$R^{13} = CH_3$	469.3	1.16 (dd, *J* = 12.10, 8.25 Hz, 2 H) 1.54 (dd, *J* = 7.42, 4.67 Hz, 2 H) 1.60 - 1.70 (m, 2 H) 1.81 (q, *J* = 6.60 Hz, 4 H) 1.96 (m, *J* = 7.70 Hz, 1 H) 2.41 (s, 3 H) 3.45 - 3.64 (m, 2 H) 3.98 (t, *J* = 6.60 Hz, 2 H) 6.50 (s, 1 H) 6.94 (d, *J* = 9.35 Hz, 2 H) 7.23 - 7.32 (m, 2 H) 7.37 (d, *J* = 8.80 Hz, 2 H) 7.44 (d, *J* = 8.25 Hz, 2 H).
37 Rac		CF_3	CN	$R^{13} = CH_3$	443.3	

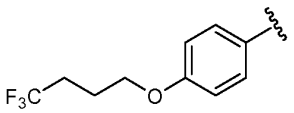
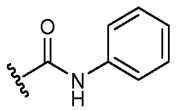
Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
38 Rac		CF_3		$R^{13} = CH_3$	430.1	
39 Isómero S		CF_3	CN	$R^{13} = CH_3$	387.2	
40 Rac		CF_3	CN	$R^{13} = CH_3$	463.2	
41 Rac		CF_3		$R^{13} = CH_3$	499.2	
42 Rac		CF_3	CN	$R^{13} = CH_3$	427.4	0.85 - 0.96 (m, 3 H) 1.33 (d, *J* = 2.75 Hz, 4 H) 1.47 - 1.69 (m, 4 H) 2.41 (s, 3 H) 2.56 - 2.67 (m, 2 H) 3.45 - 3.66 (m, 2 H) 6.46 (br. s., 1 H) 7.20 - 7.31 (m, 4 H) 7.37 (d, *J* = 7.15 Hz, 2 H) 7.45 (d, *J* =

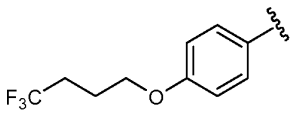
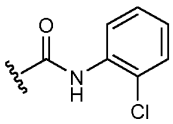
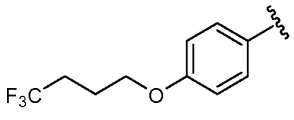
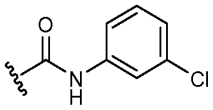
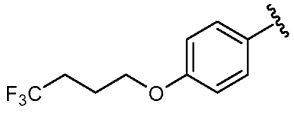
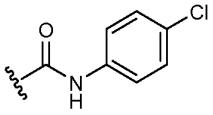
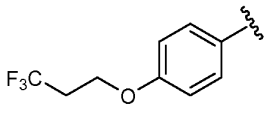
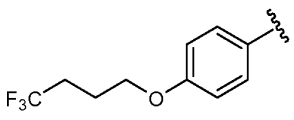
Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						6.60 Hz, 2 H).
43 Rac		CF_3	CN	$R^{13} = CH_3$	434.3	
44 Rac		CF_3	CN	$R^{13} = CH_3$	450.3	
45 Rac		CF_3	CN	$R^{13} = CH_3$	449.3	
46 Rac		CF_3	CN	$R^{13} = CH_3$	451.3	
47 Rac		CF_3	CN	$R^{13} = CH_3$	463.3	
48 Rac		CF_3		$R^{13} = CH_3$	561.4	2.36 (s, 3 H) 3.40 - 3.59 (m, 2 H) 6.82 (s, 1 H) 6.93 (t, *J* = 8.79 Hz, 2 H) 7.01 - 7.13 (m,

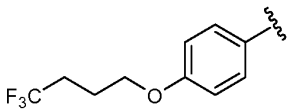
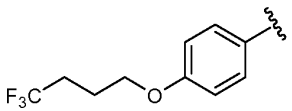
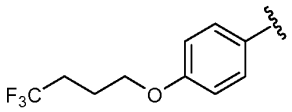
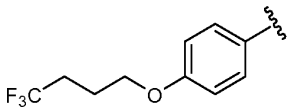
Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						5 H) 7.15 - 7.20 (m, 3 H) 7.34 - 7.45 (m, 4 H) 7.48 (d, *J* = 8.79 Hz, 2 H) 9.86 (s, 1 H).
49 Rac		CF_3		$R^{13} = CH_3$	547.4	2.30 (s, 3 H) 3.57 - 3.81 (m, 2 H) 6.96 (t, *J* = 8.79 Hz, 2 H) 7.17 (d, *J* = 7.70 Hz, 2 H) 7.27 - 7.38 (m, 4 H) 7.83 (m, 4 H) 9.11 (s, 2 H) 9.16 (s, 1 H).
50 Rac		CF_3		$R^{13} = CH_3$	547.4	
51 Rac		CF_3		$R^{13} = CH_3$	539.5	0.90 (t, *J* = 6.87 Hz, 3 H) 1.28 - 1.40 (m, 4 H) 1.58 - 1.71 (m, 2 H) 2.35 (s, 3 H) 2.55 - 2.71 (m, 2 H) 3.30 - 3.60 (m, 2 H) 6.63 (s, 1 H) 6.92 (t, *J* = 8.52 Hz, 2 H)

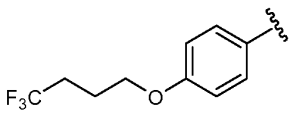
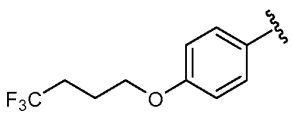
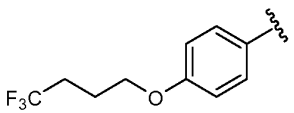
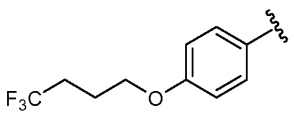
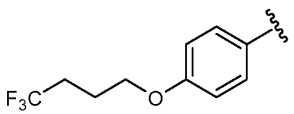
Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						7.05 - 7.12 (m, 2 H) 7.14 - 7.20 (m, 2 H) 7.22 - 7.31 (m, 2 H) 7.37 - 7.49 (m, 4 H) 9.94 (s, 1 H).
52 Rac		CF_3		$R^{13} = CH_3$	563.4	
53 Isómero S		CF_3	CN	$R^{13} = CH_3$	483.2	1.93 - 2.09 (m, 2 H) 2.27 - 2.38 (m, 2 H) 2.40 (s, 3 H) 3.62 - 3.78 (m, 2 H) 4.06 (t, *J* = 6.05 Hz, 2 H) 7.00 (d, *J* = 8.80 Hz, 2 H) 7.33 (d, *J* = 7.70 Hz, 2 H) 7.44 - 7.58 (m, 4 H).
54 Rac		CF_3		$R^{13} = CH_3$	575.3	

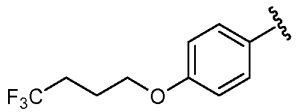
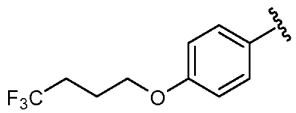
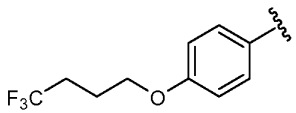
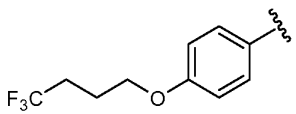
Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
55 Rac		CF_3		$R^{13} = CH_3$	571.4	
56 Rac		CF_3		$R^{13} = CH_3$	591.3	
57 Rac		CF_3		$R^{13} = CH_3$	605.4	2.02 (dd, *J* = 9.90, 6.05 Hz, 2 H) 2.28 - 2.40 (m, 5 H) 2.45 - 2.58 (m, 2 H) 3.12 - 3.35 (m, 2 H) 3.37 - 3.60 (m, 2 H) 4.05 (t, *J* = 6.05 Hz, 2 H) 6.91 - 7.01 (m, 4 H) 7.09 - 7.20 (m, 5 H) 7.21 - 7.26 (m, 2 H) 7.50 (d, *J* = 8.80 Hz, 2 H).
58 Rac		CF_3		$R^{13} = CH_3$	607.3	1.96 - 2.07 (m, 2 H) 2.26 - 2.32 (m, 3 H) 2.32 - 2.42 (m, 2 H) 3.45 - 3.67 (m, 2 H) 4.06 (t, *J* = 6.05 Hz, 2 H)

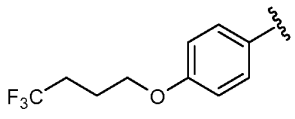
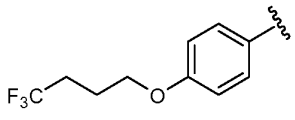
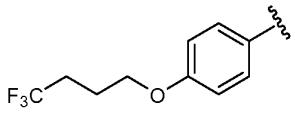
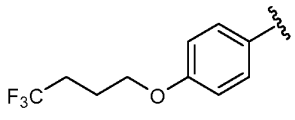
Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						6.61 (dd, *J* = 8.25, 2.20 Hz, 1 H) 6.83 (d, *J* = 8.25 Hz, 1 H) 6.98 (d, *J* = 8.80 Hz, 2 H) 7.03 (s, 1 H) 7.09 (t, *J* = 8.25 Hz, 1 H) 7.16 (d, *J* = 8.25 Hz, 2 H) 7.28 (d, *J* = 8.25 Hz, 2 H) 7.52 (d, *J* = 8.80 Hz, 2 H).
59 Rac		CF_3		$R^{13} = CH_3$	577.3	1.95 - 2.08 (m, 2 H) 2.28 (s, 3 H) 2.32 - 2.42 (m, 2 H) 3.42 - 3.70 (m, 2 H) 4.05 (t, *J* = 6.05 Hz, 2 H) 6.97 (d, *J* = 8.80 Hz, 2 H) 7.00 - 7.06 (m, 1 H) 7.15 (d, *J* = 8.25 Hz, 2 H) 7.20 (t, *J* = 7.97 Hz, 2 H) 7.30 (dd, *J* = 16.77, 7.97 Hz, 4 H) 7.52 (d, *J* = 8.80 Hz, 2 H).

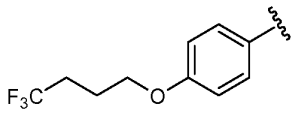
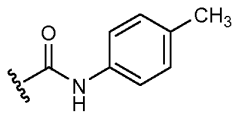
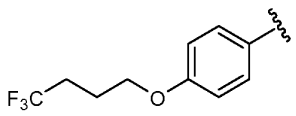
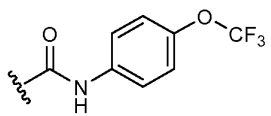
Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
60 Rac		CF_3		$R^{13} = CH_3$	611.3	
61 Rac		CF_3		$R^{13} = CH_3$	611.3	
62 Rac		CF_3		$R^{13} = CH_3$	611.3	
63 Rac		CF_3	CN	$R^{13} = CH_3$	469.1	2.40 (s, 3 H) 2.63 - 2.75 (m, 2 H) 3.65 - 3.77 (m, 2 H) 4.24 (t, *J* = 6.05 Hz, 2 H) 7.01 (d, *J* = 9.35 Hz, 2 H) 7.33 (d, *J* = 7.70 Hz, 2 H) 7.50 (d, *J* = 8.25 Hz, 2 H) 7.54 (d, *J* = 8.80 Hz, 2 H).
64 Rac		CF_3	CN	$R^{12} = OCH_3$	499.2	

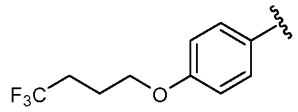
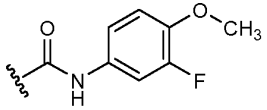
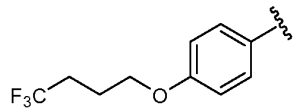
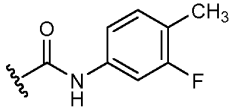
Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
65 Rac		CF_3	CN	$R^{13} = OCH_3$	499.2	1.95 - 2.07 (m, 2 H) 2.29 - 2.43 (m, 2 H) 3.88 (s, 3 H) 3.92 (d, *J* = 16.51 Hz, 1 H) 4.06 (t, *J* = 6.05 Hz, 2 H) 4.55 (d, *J* = 16.23 Hz, 1 H) 6.96 (d, *J* = 9.08 Hz, 2 H) 7.01 (d, *J* = 8.80 Hz, 2 H) 7.52 (d, *J* = 9.08 Hz, 2 H) 7.97 (d, *J* = 9.08 Hz, 2 H)
66 Rac		CF_3	CN	$R^{13} = CN$	494.2	
67 Rac		CF_3	CN	$R^{11} = F$	487.2	
68 Rac		CF_3	CN	$R^{12} = Cl$	503.2	

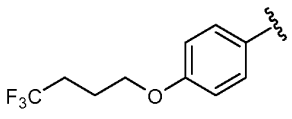
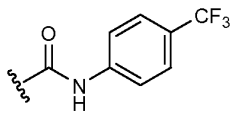
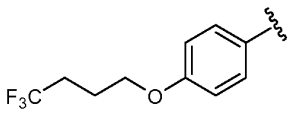
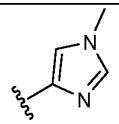
Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
69 Rac		CF_3	CN	R^{12} = CN	494.2	
70 Rac		CF_3	H	R^{13} = CH_3	458.2	
71 Rac		CF_3	CN	all H	469.2	
72 Rac		CF_3	CN	R^{13} = Cl	503.1	
73 Rac		CF_3	CN	R^{12} and R^{13} 	519.2	8.15 (d, *J* = 1.7 Hz, 1H), 8.01 - 7.95 (m, 2H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.65 - 7.55 (m, 5H), 7.05 - 7.00 (m, 2H), 4.07 (t, *J* = 6.1 Hz, 2H), 3.85 (ABq, *J* = 18.1 Hz, 2H), 2.42 - 2.29 (m, 2H), 2.06 - 1.98

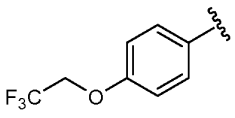
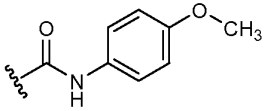
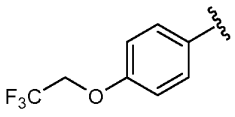
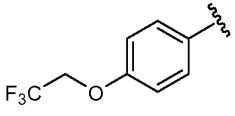
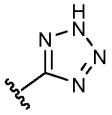
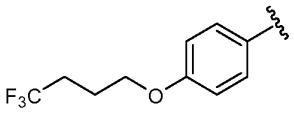
Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						(m, 2H)
74 Rac		CF_3	CN	R^{13} = F	487.2	
75 Rac		CF_3	CN	R^{13} = CF_3	537.2	
76 Rac		CF_3	CN	R^{12} = CH_3	483.2	
77 Isómero S		CF_3	CN	R^{13} = OCH_3	499.2	1.97 - 2.06 (m, 2 H) 2.27 - 2.42 (m, 2 H) 3.66 (d, *J* = 17.90 Hz, 1 H) 3.75 (d, *J* = 17.90 Hz, 1 H) 3.87 (s, 3 H) 4.06 (t, *J* = 6.05 Hz, 2 H) 6.96 - 7.02 (m, 2 H) 7.03 - 7.08 (m, 2 H) 7.52 (d, *J* = 8.80 Hz, 2 H) 7.61 - 7.68 (m, 2 H)

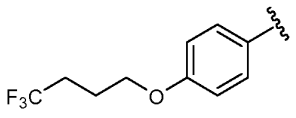
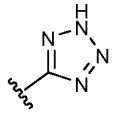
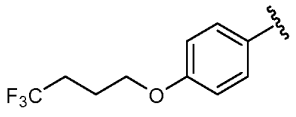
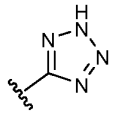
Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
78 Rac		CF_3	CN	$R^{13} = OCHF_2$	535.1	7.69 - 7.63 (m, 2H), 7.54 (d, *J* = 9.1 Hz, 2H), 7.31 - 7.25 (m, 2H), 7.01 (m, 2H), 6.96 (t, *J* = 73.5 Hz, 1 H), 4.07 (t, *J* = 6.1 Hz, 2H), 3.78 - 3.67 (m, 2H), 2.44 - 2.30 (m, 2H), 2.07 - 1.97 (m, 2H)
79 Rac		CF_3	CN	$R^{13} = OCF_3$	553.1	
80 Rac		CF_3	CN	$R^{13} = OCH_2CH_3$	513.2	
81 Rac		CF_3	CN	$R_{11} = F$ $R^{13} = OCH_3$	517.2	7.51 (d, *J* = 9.1 Hz, 2H), 7.36 (t, *J* = 8.8 Hz, 1H), 7.04 - 6.97 (m, 2H), 6.91 - 6.83 (m, 2H), 4.08 (t, *J* = 6.1 Hz, 2H), 3.87 (s, 3H), 3.65 (s, 2H), 2.46 - 2.29 (m, 2H), 2.08 -

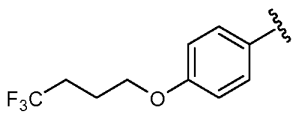
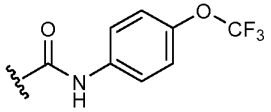
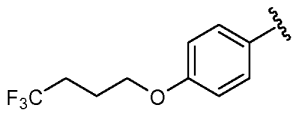
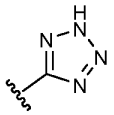
Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						1.98 (m, 2H)
82 Rac		CF_3		$R^{13} = CH_3$	591.2	7.52 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 7.7 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.98 (d, *J* = 7.7 Hz, 2H), 4.06 (t, *J* = 6.0 Hz, 2H), 3.64 (d, *J* = 17.0 Hz, 1H), 3.48 (d, *J* = 17.0 Hz, 1H), 2.39 - 2.32 (m, 2H), 2.29 (s, 3H), 2.24 (s, 3H), 2.06 - 1.98 (m, 2H).
83 Rac		CF_3		$R^{13} = CH_3$	661.2	7.53 (d, *J* = 8.8 Hz, 2H), 7.46 - 7.41 (m, 2H), 7.31 - 7.24 (m, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.17 (d, *J* = 7.7 Hz, 2H), 7.01 - 6.96 (m, 2H), 4.07 (t, *J* = 6.0 Hz, 2H),

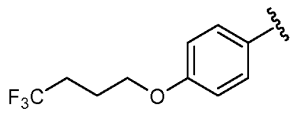
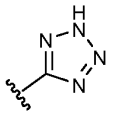
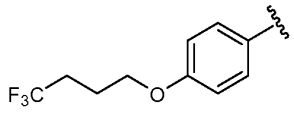
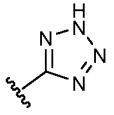
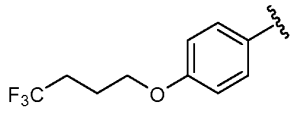
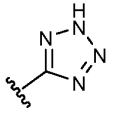
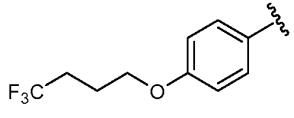
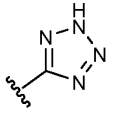
Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						3.65 (d, *J* = 17.0 Hz, 1H), 3.50 (d, *J* = 17.0 Hz, 1H), 2.43 - 2.33 (m, 2H), 2.30 (s, 3H), 2.07 - 1.99 (m, 2H).
84 Rac		CF_3		$R^{13} = CH_3$	625.2	7.52 (d, *J* = 8.8 Hz, 2H), 7.30 - 7.24 (m, 3H), 7.17 (d, *J* = 7.7 Hz, 2H), 7.01 - 6.90 (m, 4H), 4.06 (t, *J* = 6.0 Hz, 2H), 3.82 - 3.77 (s, 3H), 3.64 (d, *J* = 17.0 Hz, 1H), 3.49 (d, *J* = 17.0 Hz, 1H), 2.42 - 2.33 (m, 2H), 2.30 (s, 3H), 2.08 - 1.96 (m, 2H).
85 Rac		CF_3		$R^{13} = CH_3$	609.2	7.56 - 7.50 (ab cuarteto, *J* = 9.3 Hz, 2H), 7.30 - 7.20 (m, 3H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.05 (t, *J* = 8.2 Hz, 1H), 7.01 - 6.95 (m, *J* = 8.8 Hz, 2H),

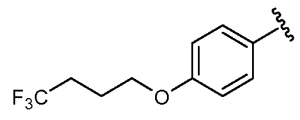
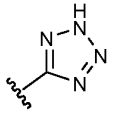
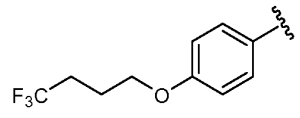
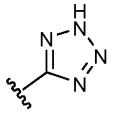
Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						6.91 (dd, *J* = 8.2, 1.6 Hz, 1H), 4.07 (t, *J* = 6.0 Hz, 2H), 3.64 (d, *J* = 17.6 Hz, 1H), 3.49 (d, *J* = 17.0 Hz, 1H), 2.43 - 2.32 (m, 2H), 2.30 (s, 3H), 2.16 (s, 3H), 2.08 - 1.97 (m, 2H).
86 Rac		CF_3		$R^{13} = CH_3$	645.2	7.58 - 7.48 (m, 6H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.00 - 6.95 (m, 2H), 4.06 (t, *J* = 6.0 Hz, 2H), 3.65 (d, *J* = 17.6 Hz, 1H), 3.50 (d, *J* = 17.0 Hz, 1H), 2.43 - 2.31 (m, 2H), 2.28 (s, 3H), 2.09 - 1.95 (m, 2H).
87 Rac S-isomer		CF_3		$R^{13} = CH_3$	538.2	

Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
88 Rac		CF_3		$R^{13} = CH_3$	579.2	2.31 (s, 3 H) 3.45 - 3.69 (m, 2 H) 3.70 - 3.76 (s, 3 H) 4.56 (q, J = 8.25 Hz, 2 H) 6.78 (d, J = 9.35 Hz, 2 H) 7.07 (d, J = 9.35 Hz, 2 H) 7.13 - 7.22 (m, 4 H) 7.29 (d, J = 8.25 Hz, 2 H) 7.59 (d, J = 8.80 Hz, 2 H).
89 Rac		CF_3	CN	$R^{13} = CH_3$	455.1	
90 Rac		CF_3		$R^{13} = CH_3$	498.1	2.28 (s, 3 H) 3.63 - 3.82 (m, 2 H) 4.58 (q, J = 8.61 Hz, 2 H) 6.88 (d, J = 8.25 Hz, 2 H) 7.10 (dd, J = 12.65, 8.80 Hz, 4 H) 7.65 (d, J = 8.80 Hz, 2 H).
91 Isómero S		CF_3	CN	$R_{11} = F$ $R^{13} = OCH_3$	517.2	7.51 (d, *J* = 9.1 Hz, 2H), 7.36 (t, *J* = 8.8 Hz, 1H), 7.03 - 6.99 (m, 2H), 6.90 - 6.84 (m,

Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						2H), 5.49 (s, 1H), 4.08 (t, *J* = 6.1 Hz, 2H), 3.87 (s, 3H), 3.65 (s, 2H), 2.46 - 2.28 (m, 2H), 2.10 - 1.97 (m, 2H)
92 Rac		CF_3		$R^{13} = OCH_2CH_3$	556.3	1.34 (t, J = 6.87 Hz, 3 H) 1.96 - 2.09 (m, 2 H) 2.26 - 2.43 (m, 2 H) 3.70 (s, 2 H) 3.98 (q, J = 6.78 Hz, 2 H) 4.06 (t, J = 6.05 Hz, 2 H) 6.78 (d, J = 8.80 Hz, 2 H) 6.92 (d, J = 8.80 Hz, 2 H) 7.01 (d, J = 8.80 Hz, 2 H) 7.58 (d, J = 8.80 Hz, 2 H).
93 Rac		CF_3		$R^{13} = OCHF_2$	578.3	1.96 - 2.12 (m, 2 H) 2.28 - 2.45 (m, 2 H) 3.63 - 3.85 (m, 2 H) 4.07 (t, J = 6.05 Hz, 2 H) 6.95 - 7.08 (m, 7 H) 7.59 (d, J = 8.80 Hz, 2 H).

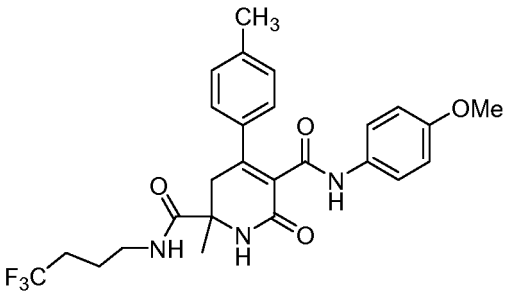
Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
94 Isómero S		CF_3		$R^{13} = CH_3$	661.3	1.97 - 2.08 (m, 2 H) 2.29 (s, 3 H) 2.32 - 2.40 (m, 2 H) 3.50 (d, J = 17.05 Hz, 1 H) 3.65 (d, J = 17.60 Hz, 1 H) 4.06 (t, J = 6.05 Hz, 2 H) 6.98 (d, J = 8.80 Hz, 2 H) 7.14 (dd, J = 16.77, 8.52 Hz, 4 H) 7.28 (d, J = 8.25 Hz, 2 H) 7.43 (d, J = 9.35 Hz, 2 H) 7.52 (d, J = 8.80 Hz, 2 H).
95 Isómero S		CF_3		$R^{11} = F$ $R^{13} = OCH_3$	560.3	1.95 - 2.08 (m, 2 H) 2.28 - 2.42 (m, 2 H) 3.58 - 3.71 (m, 2 H) 3.76 (s, 3 H) 4.06 (t, J = 6.05 Hz, 2 H) 6.59 (dd, J = 12.92, 2.47 Hz, 1 H) 6.69 (dd, J = 8.80, 2.75 Hz, 1 H) 6.91 - 6.96 (m, 1 H) 7.00 (d, J = 8.80 Hz, 2 H) 7.57 (d, J =

Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
						8.80 Hz, 2 H).
96 Rac		CF_3		$R^{12} = CH_3$	526.3	
97 Rac		CF_3		All H	512.2	
98 Rac		CF_3		$R^{13} = CF_3$	580.3	7.60 (t, *J* = 8.2 Hz, 4H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 4.08 (t, *J* = 6.0 Hz, 2H), 3.80 (d, *J* = 18.1 Hz, 1H), 3.69 (d, *J* = 18.1 Hz, 1H), 2.45 - 2.31 (m, 2H), 2.11 - 1.93 (m, 2H).
99 Rac		CF_3		$R^{12} = Cl$	546.2	

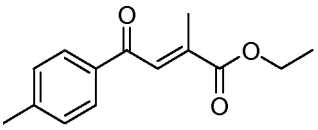
Ejemplo	R^1	R^2	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, MeOD)
100 Rac		CF_3		$R^{12} = OCH_3$	542.3	
101 Rac		CF_3		$R^{13} = Cl$	546.2	

*Datos reportados como peso molecular del compuesto con base en los resultados de la espectrometría de masas por electroaspersión.

Ejemplo 102. N^5-(4-metoxifenil)-2-metil-6-oxo-4-*p*-tolil-N^2-(4,4,4-trifluorobutil)-1,2,3,6-tetrahidropiridin-2,5-dicarboxamida



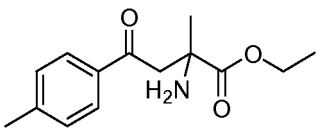
Intermediario 102A. 2-metil-4-oxo-4-*p*-tolilbut-2-enoato de (*E*)-etilo



Una solución del Intermediario 2D (3.02 g, 7.65 mmol) y 2-oxopropanoato de etilo (0.74 g, 6.37 mmol) en THF (12 ml) en un vial de 5 ml para microondas equipado con un agitador magnético se calentó a 150°C en condiciones de microondas durante 20 min. El solvente se retiró al vacío, y el residuo se purificó mediante cromatografía en gel de sílice (80 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el producto deseado (1.067 g, 72%) como un aceite amarillo. LCMS Anal. calc. para $C_{14}H_{16}O_3$ 232.11, encontrado [M+H] 233.1. RMN 1H (500 MHz, $CDCl_3$) δ ppm 7.87 (d, *J* = 8.25 Hz, 2 H), 7.69 (q, *J* = 1.56 Hz, 1 H), 7.28 (d, *J*

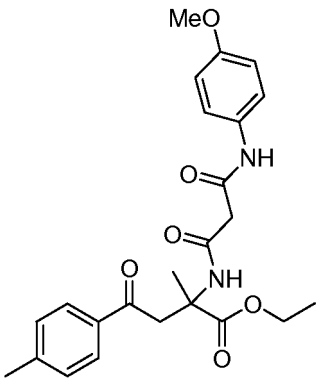
= 7.98 Hz, 2 H), 4.30 (q, *J* = 7.15 Hz, 2 H), 2.42 (s, 3 H), 2.16 (d, *J* = 1.38 Hz, 3 H), 1.36 (t, *J* = 7.02 Hz, 3 H).

Intermediario 102B. 2-amino-2-metil-4-oxo-4-*p*-tolilbutanoato de etilo



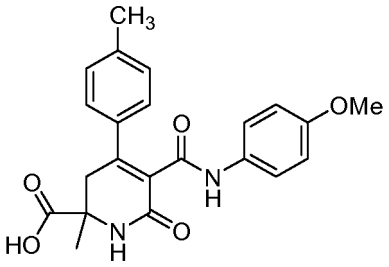
A una solución del Intermediario 102A (1.067 g, 4.59 mmol) en DMSO (20 ml) en argón, se agregó NH_4OH (18.04 ml, 271 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con EtOAc (75 ml) y se lavó secuencialmente con agua (40 ml) y salmuera (20 ml). La fase orgánica se secó en $MgSO_4$ y se concentró al vacío para obtener un aceite amarillo. El aceite se purificó mediante cromatografía en gel de sílice (120 g de gel de sílice) para obtener el producto deseado (0.632 g, 55%) como un aceite transparente. LCMS Anal. calc. para $C_{14}H_{19}NO_3$ 249.14, encontrado [M+H] 250.1. RMN 1H (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.25 Hz, 2 H), 7.24 (d, *J* = 7.98 Hz, 2 H), 4.14 (dd, *J* = 7.15, 2.75 Hz, 2 H), 3.65 (d, *J* = 17.61 Hz, 1 H), 3.20 (d, *J* = 17.61 Hz, 1 H), 2.40 (s, 3 H), 2.18 - 2.27 (m, 2 H), 1.39 (s, 3 H), 1.19 (t, *J* = 7.01 Hz, 3 H).

Intermediario 102C. 2-(3-(4-metoxifenilamino)-3-oxopropanamido)-2-metil-4-oxo-4-*p*-tolilbutanoato de etilo



A una solución del Intermediario 6B (0.388 g, 1.855 mmol) en DCM (10 ml) en argón, se agregó 1-cloro-*N*,*N*,2-trimetilprop-1-en-1-amina (0.293 g, 2.192 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 20 min. Se agregó una solución del Intermediario 102B (0.4204 g, 1.686 mmol) en DCM (1.000 ml) y luego piridina (0.409 ml, 5.06 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 2.5 h. La mezcla de reacción se concentró para obtener un aceite oscuro que se disolvió en EtOAc (15 ml) y se lavó con agua (5 ml). La fase orgánica se secó en $MgSO_4$, se filtró y se concentró. El residuo se purificó mediante cromatografía en gel de sílice (80 g de gel de sílice) para obtener el producto deseado (0.650 g, 88%) como un aceite naranja. LCMS Anal. calc. para $C_{24}H_{28}N_2O_6$ 440.19, encontrado [M+H] 441.2. RMN 1H (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.25 Hz, 2 H), 7.24 (d, *J* = 7.98 Hz, 2 H), 4.14 (dd, *J* = 7.15, 2.75 Hz, 2 H), 3.65 (d, *J* = 17.61 Hz, 1 H), 3.20 (d, *J* = 17.61 Hz, 1 H), 2.40 (s, 3 H), 2.18 - 2.27 (m, 2 H), 1.39 (s, 3 H), 1.19 (t, *J* = 7.01 Hz, 3 H).

Intermediario 102D. Ácido 5-(4-metoxifenilcarbamoil)-2-metil-6-oxo-4-*p*-tolil-1,2,3,6-tetrahidropiridin-2-carboxílico



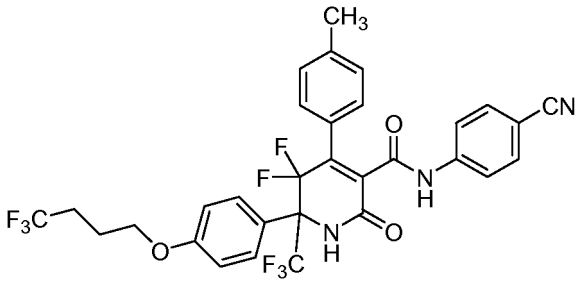
A una solución del Intermediario 102C (0.033 g, 0.075 mmol) en THF (8 ml) y agua (1.600 ml), se agregó hidróxido de litio monohidrato (3.77 mg, 0.090 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se acidificó con AcOH (5 gotas) y se diluyó con EtOAc (10 ml) y agua (3 ml). Las fases se separaron, y la fase acuosa se extrajo con EtOAc (10 ml). Las fases orgánicas se combinaron y se secaron en $MgSO_4$, se filtraron y se concentraron al vacío para obtener el producto deseado (0.0213 g, 72%) como un sólido blanco. LCMS Anal. calc. para $C_{22}H_{22}N_2O_5$ 394.15, encontrado [M+H] 395.0.

Ejemplo 102

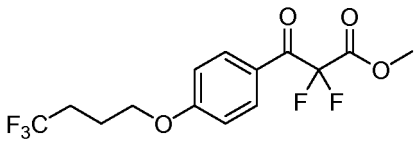
A una solución del Intermediario 102D (0.0213 g, 0.054 mmol) en DCM (2 ml) en argón, se agregaron EDC (0.014 g, 0.076 mmol), HOBT (9.92 mg, 0.065 mmol), 4,4,4-trifluorobutan-1-amina (8.24 mg, 0.065 mmol) y DIEA (0.019 ml, 0.108 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 3 días. La mezcla de reacción se diluyó con

EtOAc (5 ml), y la solución se lavó con agua (2 ml) y salmuera (2 ml). La fase orgánica se secó en $MgSO_4$, se filtró y se concentró al vacío para obtener un sólido naranja que se purificó mediante HPLC preparativa (ACN/H_2O/TFA) para obtener el producto deseado (4.6 mg, 15%) como un sólido amarillo pálido. LCMS Anal. calc. para $C_{26}H_{28}F_3N_3O_4$ 503.2, encontrado [M+H] 504.1. RMN 1H (500 MHz, $CDCl_3$) δ 8.46 (br. s., 1 H), 7.61 (br. s., 1 H), 7.24 - 7.32 (m, 4 H), 7.16 (d, *J* = 7.83 Hz, 2 H), 6.79 (d, *J* = 8.84 Hz, 2 H), 3.75 (s, 3 H), 3.56 (d, *J* = 17.18 Hz, 1 H), 3.22 - 3.37 (m, 2 H), 3.14 (br. s., 1 H), 2.73 (d, *J* = 17.18 Hz, 1 H), 2.34 (s, 3 H), 2.00 - 2.15 (m, 2 H), 1.70 - 1.80 (m, 2 H), 1.54 (s, 3 H).

Ejemplo 103. *N*-(4-cianofenil)-5,5-difluoro-2-oxo-4-*p*-tolil-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carboxamida

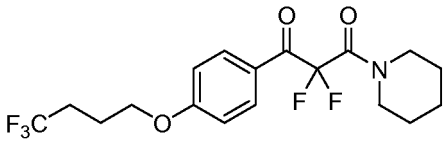


Intermediario 103A. 2,2-difluoro-3-oxo-3-(4-(4,4,4-trifluorobutoxi)fenil)propanoato de metilo



A una solución del Intermediario 14A (3 g, 9.86 mmol) y selectFluor (10.48 g, 29.6 mmol) en acetonitrilo (10 ml), se agregó hidróxido de tetrabutilamonio metanólico 1 M (19.72 ml, 19.72 mmol). La mezcla de reacción se calentó a 82°C durante 10 min en condiciones de microondas. La reacción se diluyó con 1:1 de ACN y MeOH y se enjuagó filtrándolo con 1:1 de ACN en MeOH (50 ml). El filtrado se evaporó hasta secarse, y el producto crudo se purificó mediante cromatografía en gel de sílice (80 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el producto deseado (2.34 g, 69%) como un aceite incoloro transparente. RMN 1H (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.08 Hz, 2 H), 6.98 (d, *J* = 9.08 Hz, 2 H), 4.13 (t, *J* = 6.05 Hz, 2 H), 3.93 (s, 3 H), 2.27 - 2.39 (m, 2 H), 2.07 - 2.15 (m, 2 H).

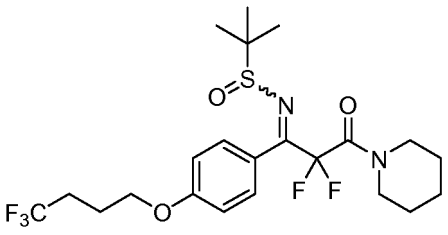
Intermediario 103B. 2,2-difluoro-1-(piperidin-1-il)-3-(4-(4,4,4-trifluorobutoxi)fenil)propan-1,3-diona



Se agregó lentamente piperidina (175 µl, 1.763 mmol) al Intermediario 103A (500 mg, 1.470 mmol) a temperatura ambiente. La reacción se agitó a temperatura ambiente durante 3 h. La reacción se diluyó con CH_2Cl_2, se cargó en una columna de SiO_2 de 12 g y se eluyó con EtOAc en hexanos. Las fracciones que contenían el producto se

combinaron y se evaporaron hasta secarse para obtener el producto (520 mg, 81%) como un aceite transparente. LCMS Anal. calc. para $C_{18}H_{20}F_5NO_3$ 393.14, encontrado [M+H] 394.2. RMN 1H (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9.1 Hz, 2 H), 6.98 - 6.91 (m, 2 H), 4.10 (t, *J* = 5.9 Hz, 2 H), 3.61 - 3.56 (m, 2 H), 3.54 - 3.50 (m, 2 H), 2.39 - 2.26 (m, 2 H), 2.14 - 2.05 (m, 2 H), 1.69 - 1.61 (m, 2 H), 1.60 - 1.51 (m, 4 H).

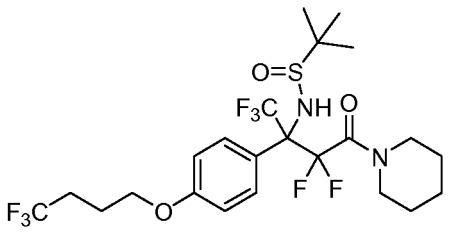
Intermediario 103C. *N*-(2,2-difluoro-3-oxo-3-(piperidin-1-il)-1-(4-(4,4,4-trifluorobutoxi)fenil)propiliden)-2-metilpropan-2-sulfinamida



A una solución del Intermediario 103B (1.97 g, 5.01 mmol) y 2-metilpropan-2-sulfinamida (1.821 g, 15.02 mmol) en THF anhidro (25.04 ml), se agregó $Ti(OEt)_4$ (5.19 ml, 25.04 mmol). La reacción se calentó a temperatura de reflujo durante la noche. La reacción se enfrió a temperatura ambiente, se vertió en salmuera, se diluyó con EtOAc y se agitó durante 30 min. El óxido de titanio se retiró mediante filtración a través de un tapón de Celite®. Las capas de filtrado se separaron, y la capa orgánica se lavó con salmuera, se secó en Na_2SO_4, se filtró y se concentró. El residuo se purificó mediante cromatografía en gel de sílice

(80 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el producto deseado (1.62 g, 59%) como un aceite amarillo. RMN 1H (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.80 Hz, 2 H), 6.95 (d, *J* = 9.08 Hz, 2 H), 4.07 (t, *J* = 6.05 Hz, 2 H), 3.62 - 3.69 (m, 1 H), 3.52 - 3.58 (m, 1 H), 3.39 (t, *J* = 5.09 Hz, 2 H), 2.26 - 2.37 (m, 2 H), 2.05 - 2.11 (m, 2 H), 1.53 - 1.70 (m, 7 H), 1.25 (s, 9 H).

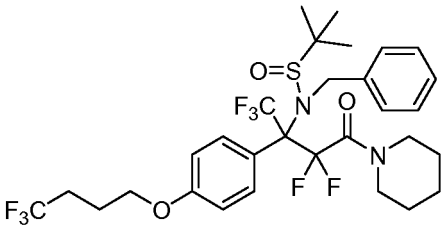
Intermediario 103D. 2-metil-*N*-(1,1,1,3,3-pentafluoro-4-oxo-4-(piperidin-1-il)-2-(4-(4,4,4-trifluorobutoxi)fenil)butan-2-il)propan-2-sulfinamida



A una solución de TBAT (3.43 g, 6.36 mmol) en DMF (5.89 ml), se agregó una solución del Intermediario 103C (1.17 g, 2.356 mmol) en THF (5.89 ml). La solución se enfrió a 0°C, y luego se agregó por goteo $TMSCF_3$ 2 M (3.53 ml, 7.07 mmol) en THF. La reacción se agitó a 0°C durante 1 h y luego se inactivó con salmuera (20 ml) a 0°C. La mezcla se calentó a temperatura ambiente y se diluyó con agua y EtOAc. Las capas se separaron. La capa acuosa se lavó con EtOAc. Las capas orgánicas combinadas se lavaron con salmuera, se secaron en Na_2SO_4, se filtraron y se concentraron. El residuo se purificó mediante cromatografía en gel de sílice (80 g de

gel de sílice, eluido con EtOAc en hexanos) para obtener el producto deseado (773 mg, 58%) como una goma amarilla. LCMS Anal. calc. para $C_{23}H_{30}F_8N_2O_3S$ 566.18, encontrado [M+H] 567.1. RMN 1H (500 MHz, CD_3OD) δ 7.69 (d, *J* = 8.53 Hz, 2 H), 6.91 (d, *J* = 9.08 Hz, 2 H), 4.03 (t, *J* = 5.91 Hz, 2 H), 3.50 - 3.62 (m, 2 H), 3.34 - 3.45 (m, 2 H), 2.23 - 2.35 (m, 2 H), 1.98 - 2.07 (m, 2 H), 1.48 - 1.69 (m, 6 H), 1.26 (s, 9 H).

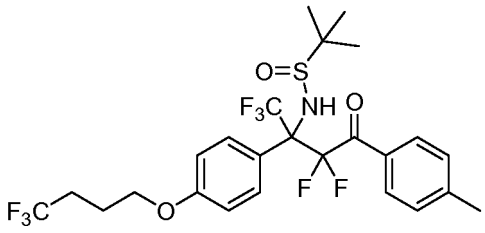
Intermediario 103E. *N*-bencil-2-metil-*N*-(1,1,1,3,3-pentafluoro-4-oxo-4-(piperidin-1-il)-2-(4-(4,4,4-trifluorobutoxi)fenil)butan-2-il)propan-2-sulfinamida



Se agregó una solución del Intermediario 103D (461 mg, 0.814 mmol) en DMF anhidro (0.5 ml) a una suspensión de NaH (65 mg, 1.627 mmol) (60% en aceite mineral) a 0°C. Después de agitar durante 5 min, se agregó BnBr (0.484 ml, 4.07 mmol). La mezcla de reacción se calentó a temperatura ambiente y se agitó durante 1 h. La reacción se diluyó con EtOAc, se lavó con salmuera, se secó en Na_2SO_4, se filtró y se concentró. El residuo se purificó mediante cromatografía en gel de sílice (4 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el producto deseado (260 mg, 44%) como una goma amarilla. RMN 1H (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.5

Hz, 2 H), 7.33 - 7.27 (m, 3 H), 7.14 (dd, *J* = 7.3, 2.1 Hz, 2 H), 6.80 (d, *J* = 9.1 Hz, 2 H), 4.46 - 4.38 (m, 2 H), 4.00 - 3.95 (m, 2 H), 3.72 (br. s., 1 H), 3.51 (br. s., 1 H), 3.35 - 3.10 (m, 2 H), 2.37 - 2.25 (m, 2 H), 2.09 - 1.99 (m, 2 H), 1.70 - 1.39 (m, 6 H), 1.34 - 1.29 (m, 9 H).

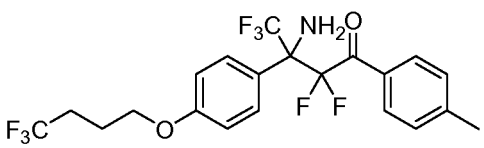
Intermediario 103F. 2-metil-*N*-(1,1,1,3,3-pentafluoro-4-oxo-4-*p*-tolil-2-(4-(4,4,4-trifluorobutoxi)fenil)butan-2-il)propan-2-sulfinamida



Las virutas de Mg se suspendieron en HCl acuoso 0.1 N durante algunos minutos, se enjuagaron con agua y MeOH y se secaron al vacío. Un matraz secado al fuego equipado con una barra agitadora se cargó con virutas de Mg (0.243 g, 10 mmol), THF anhidro (4.4 ml) y 4-bromotolueno (1.71 g, 10 mmol) en THF anhidro (4.4 ml), seguido de varias gotas de 1,2-dibromoetano. La reacción comenzó algunos minutos después, y la mezcla se calentó. La concentración aproximada del reactivo de Grignard fue de 1 M. La mezcla se diluyó con 10 ml de THF anhidro para producir una solución transparente de bromuro de p-tolilmagnesio (~0.5 M). A una solución del Intermediario 103E (260 mg, 0.396 mmol) en THF (3959 µl) a 0°C, se agregó

el bromuro de p-tolilmagnesio recién preparado (3959 µl, 1.980 mmol). La reacción se calentó a temperatura ambiente, se concentró a la mitad del volumen original y se agitó durante 3 h. La reacción se enfrió a 0°C, se inactivó con NH_4Cl acuoso saturado y luego se diluyó con EtOAc. Las capas se separaron, y la capa orgánica se lavó con salmuera, se secó en $MgSO_4$, se filtró y se concentró. El residuo se purificó mediante cromatografía en gel de sílice (24 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el producto deseado (60 mg, 24%) como una goma amarilla. RMN 1H (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 2*H*), 7.55 (d, *J* = 8.5 Hz, 2*H*), 7.19 (d, *J* = 8.0 Hz, 2*H*), 6.83 (d, *J* = 8.8 Hz, 2*H*), 4.19 (s, 1*H*), 4.01 (br. s., 2*H*), 2.40 (s, 3H), 2.31 (dd, *J* = 16.2, 10.2 Hz, 2*H*), 2.10 - 1.99 (m, 2*H*), 1.25 (s, 9H).

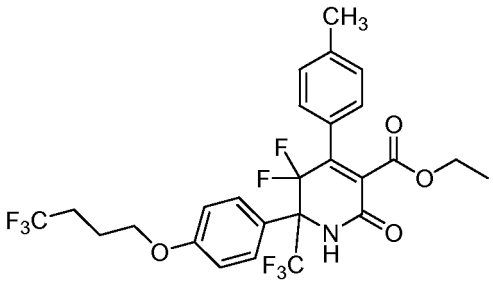
Intermediario 103G. 3-amino-2,2,4,4,4-pentafluoro-1-*p*-tolil-3-(4-(4,4,4-trifluorobutoxi)fenil)butan-1-ona, HCl



A una solución del Intermediario 103F (30 mg, 0.052 mmol) en MeOH (0.5 ml), se agregó HCl 4.0 M (0.026 ml, 0.105 mmol) en dioxano. La reacción se agitó a

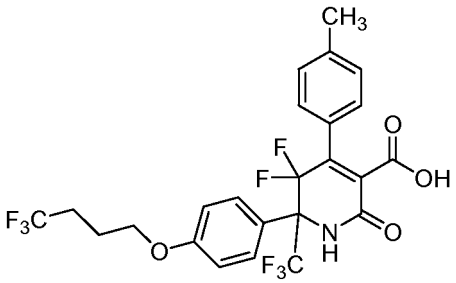
temperatura ambiente durante 1 h. La reacción se concentró, y el producto crudo se usó en la siguiente etapa sin purificación adicional. LCMS Anal. calc. para $C_{21}H_{19}F_8NO_2$ 469.13, encontrado [M+H] 470.1.

Intermediario 103H. 5,5-difluoro-2-oxo-4-*p*-tolil-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carboxilato de etilo



Se disolvió el Intermediario 103G (268 mg, 0.530 mmol) en MeOH y luego se hizo pasar a través de una resina de NaHCO3 (500 mg, 0.9 mmol). La solución se concentró para obtener la base libre (230 mg). La base libre se disolvió en 9:1 de CH_2Cl_2/piridina (3 ml), y se agregó 3-cloro-3-oxopropanoato de etilo (160 mg, 1.060 mmol). La mezcla resultante se agitó a temperatura ambiente durante 24 h y luego se concentró. El residuo se absorbió con EtOH (1 ml) y se trató con piperidina (20 ul). La mezcla resultante se agitó a 65°C durante 24 h y luego se concentró. El residuo se purificó mediante HPLC preparativa (MeOH/H_2O/TFA) para obtener el producto deseado (100 mg, 33%) como una espuma. LCMS Anal. calc. para $C_{26}H_{23}F_8NO_4$ 565.15, encontrado [M+H] 566.1.

Intermediario 103I. Ácido 5,5-difluoro-2-oxo-4-*p*-tolil-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carboxílico



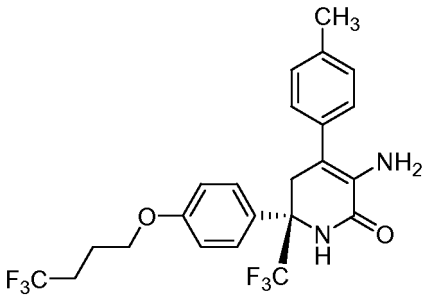
A una solución del Intermediario 103H (100 mg, 0.177 mmol) en MeOH (2 ml), se agregó LiOH 2 M (0.4 ml, 0.800 mmol). La mezcla resultante se agitó a 100°C durante 15 min. La LC-MS indicó que el producto era el componente principal junto con una cantidad mínima de SM y 14% del metiléster correspondiente. Luego se agregó LiOH 2 M (100 ul), y la reacción se agitó a 100°C durante 15 min más. La reacción se concentró, se acidificó con HCl 1 N y se extrajo con EtOAc. La capa orgánica se lavó con salmuera, se secó en $MgSO_4$, se filtró y se concentró para obtener el producto deseado (75 mg, 78%) como un sólido. LCMS Anal. calc. para $C_{24}H_{19}F_8NO_4$ 537.12, encontrado [M+H] 537.9.

Ejemplo 103

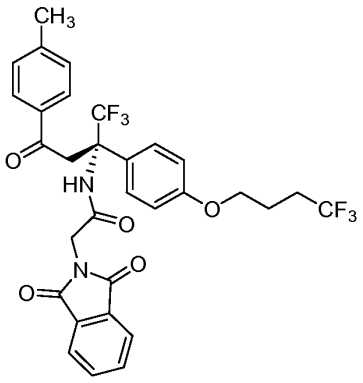
A una solución del Intermediario 103I (20 mg, 0.037 mmol) en MeCN (1 ml), se agregaron 3*H*-[1,2,3]triazolo[4,5-*b*]piridin-3-ol (7.60 mg, 0.056 mmol), 4-aminobenzonitrilo (6.59 mg, 0.056 mmol) y EDC (10.70 mg, 0.056 mmol). La mezcla

resultante se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con MeCN y se purificó mediante HPLC preparativa (MeCN/H_2O/TFA) para obtener el producto deseado (11 mg, 46%) como un sólido. LCMS Anal. calc. para $C_{31}H_{23}F_8N_3O_3$ 637.16, encontrado [M+H] 637.9. RMN 1H (500 MHz, CD_3OD) δ 7.67 (d, *J* = 9.08 Hz, 2 H), 7.56 - 7.63 (m, 4 H), 7.22 - 7.26 (m, 2 H), 7.15 - 7.20 (m, 2 H), 7.04 - 7.09 (m, 2 H), 4.12 (t, *J* = 6.05 Hz, 2 H), 2.33 - 2.44 (m, 2 H), 2.30 (s, 3 H), 2.02 - 2.09 (m, 2 H).

Ejemplo 104. (*S*)-3-amino-4-*p*-tolil-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-5,6-dihidropiridin-2(1*H*)-ona



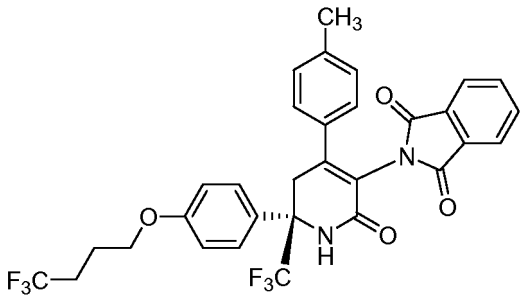
Intermediario 104A. (*S*)-2-(1,3-dioxoisoindolin-2-il)-*N*-(1,1,1-trifluoro-4-oxo-4-*p*-tolil-2-(4-(4,4,4-trifluorobutoxi)fenil)butan-2-il)acetamida



A una solución de ácido 2-(1,3-dioxoisoindolin-2-

il)acético (592 mg, 2.88 mmol) en DCM seco (10 ml), se agregó PPh_3 (2269 mg, 8.65 mmol) bastante rápido y luego se agregó por goteo CCl_3CN (500 mg, 3,46 mmol). La mezcla se agitó a temperatura ambiente durante 3 h, y se agregaron una solución del Intermediario 2F, isómero 2 (500 mg, 1.15 mmol) en DCM seco (3 ml) y luego piridina (0.3 ml). La mezcla se agitó a temperatura ambiente durante la noche. La mezcla se diluyó con DCM (10 ml) y se lavó con NaHCO3 saturado (2 x 8 ml). La capa orgánica se secó en $MgSO_4$ anhidro, se filtró y se concentró. El residuo se purificó mediante cromatografía en gel de sílice para obtener el producto deseado (620 mg, 87%). LCMS Anal. calc. para $C_{31}H_{26}F_6N_2O_5$ 620.17, encontrado [M+H] 621.3.

Intermediario 104B. (*S*)-2-(2-oxo-4-*p*-tolil-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-il)isoindolin-1,3-diona



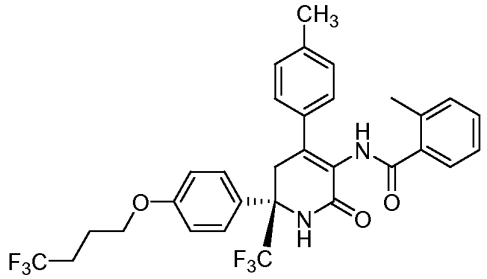
Se disolvió el Intermediario 104A (145 mg, 0.234 mmol) en MeOH (2.2 ml), y luego se agregó NaOH 1 N (0.2 ml). La mezcla se agitó a 69°C durante 45 min, y se agregaron 0.2 ml más de NaOH 1 N. La reacción se calentó a 130°C en condiciones de microondas durante 10 min. La mezcla se

neutralizó con HCl 1 N y luego se concentró. El residuo se purificó mediante cromatografía en gel de sílice (12 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el producto deseado (80 mg, 57%). LCMS Anal. calc. para $C_{31}H_{24}F_6N_2O_4$ 602.16, encontrado [M+H] 603.3.

Ejemplo 104

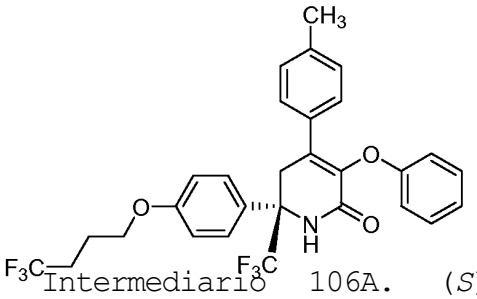
A una solución del Intermediario 104B (80 mg, 0.133 mmol) en 1 ml de EtOH, se agregó 1 ml de $MeNH_2$ 2 N en MeOH. La mezcla se agitó a 67°C durante 24 h. El solvente se retiró al vacío, y el producto crudo se purificó mediante cromatografía en gel de sílice (4 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el producto deseado (32.3 mg, 52%) como un sólido marrón claro. LCMS Anal. calc. para $C_{23}H_{22}F_6N_2O_2$ 472.16, encontrado [M+H] 473.2. RMN 1H (500 MHz, CD_3OD) δ 7.49 (d, *J* = 8.8 Hz, 2 H), 7.31 - 7.17 (m, 4 H), 7.04 - 6.92 (m, 2 H), 4.08 (s, 2 H), 3.46 (d, *J* = 16.2 Hz, 1 H), 3.21 (d, *J* = 16.2 Hz, 1 H), 2.44 - 2.30 (m, 5 H), 2.09 - 1.99 (m, 2 H).

Ejemplo 105. (*S*)-2-metil-*N*-(2-oxo-4-*p*-tolil-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-il)benzamida

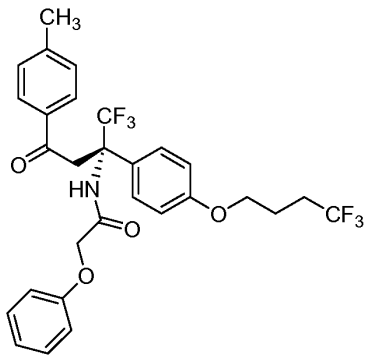


A una solución de 104 (15 mg, 0.032 mmol) en DCM seco (0.5 ml), se agregaron cloruro de 2-metilbenzoilo (5.4 mg, 0.035 mmol) y piridina (2.8 µl, 0.035 mmol). La mezcla se agitó a temperatura ambiente durante 2 h y luego se concentró. El residuo se purificó mediante HPLC preparativa ($MeCN/H_2O/TFA$) para obtener el producto deseado. LCMS Anal. calc. para $C_{31}H_{28}F_6N_2O_3$ 590.20. encontrado [M+H] 591.3. RMN 1H (500 MHz, CD_3OD) δ 7.56 (d, *J* = 8.80 Hz, 2 H), 7.11 - 7.29 (m, 8 H), 6.98 (d, *J* = 9.08 Hz, 2 H), 4.06 (t, *J* = 6.05 Hz, 2 H), 3.73 (d, *J* = 17.06 Hz, 1 H), 3.46 (d, *J* = 16.78 Hz, 1 H), 2.33 (s, 3 H), 2.30 - 2.42 (m, 2 H), 2.22 (s, 3 H), 1.98 - 2.06 (m, 2 H).

Ejemplo 106. (*S*)-3-fenoxi-4-*p*-tolil-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-5,6-dihidropiridin-2(1*H*)-ona



Intermediario 106A. (*S*)-2-fenoxi-N-(1,1,1-trifluoro-4-oxo-4-*p*-tolil-2-(4-(4,4,4-trifluorobutoxi)fenil)butan-2-il)acetamida



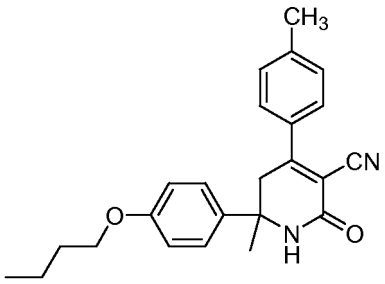
A una mezcla of trifenilfosfina (138 mg, 0.318 mmol) en DCM seco (0.8 ml), se agregó ácido 2-fenoxiacético (26 mg, 0.173 mmol) y luego tricloroacetonitrilo (30 mg, 0.208 mmol). La mezcla se agitó a temperatura ambiente durante 2.5 h. A la mezcla se agregó una solución del Intermediario 2F, isómero 2 (30 mg, 0.069 mmol) en DCM seco (0.5 ml) y luego piridina (17 µl, 0.208 mmol). La reacción se agitó a temperatura ambiente durante la noche. La mezcla se concentró y se purificó mediante HPLC preparativa (MeOH/H_2O/TFA) para obtener el producto deseado (27 mg, 69%) como un aceite marrón. LCMS Anal. calc. para $C_{29}H_{27}F_6NO_4$ 567.18, encontrado [M+H] 568.3.

Ejemplo 106

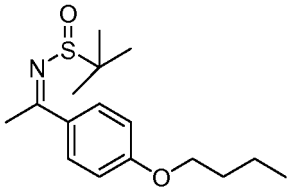
A una solución del Intermediario 106A (26 mg, 0.046 mmol) en MeOH (0.5 ml), se agregó NaOH 1 N (60 µl). La mezcla se calentó a 130°C en condiciones de microondas durante 10 min. La mezcla se neutralizó con HCl 1 N y se concentró. El residuo se purificó mediante HPLC preparativa (MeCN/H_2O/TFA) para obtener el producto deseado (1.5 mg, 6%) como un aceite marrón claro. LCMS Anal. calc. para $C_{29}H_{25}F_6NO_3$ 549.17, encontrado [M+H] 550.3. RMN 1H (500 MHz, CD_3OD) δ 7.59 (d, *J* = 8.80 Hz, 2 H), 7.33 (d, *J* = 8.25 Hz, 2 H), 7.13 (d, *J* = 8.25 Hz, 2 H), 7.01 - 7.08 (m, 4 H), 6.85 - 6.90 (m, 1 H), 6.38 (dd, *J* = 8.67, 0.96 Hz, 2 H), 4.10 - 4.15 (m, 2 H), 3.71 - 3.76 (m, 1 H), 3.61 - 3.67 (m, 1 H), 2.34 - 2.45 (m, 2 H),

2.30 (s, 3 H), 2.02 - 2.11 (m, 2 H).

Ejemplo 107. 6-(4-butoxifenil)-6-metil-2-oxo-4-*p*-tolil-1,2,5,6-tetrahidropiridin-3-carbonitrilo



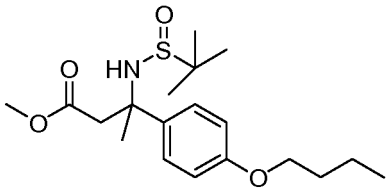
Intermediario 107A. (*Z*)-*N*-(1-(4-butoxifenil)etiliden)-2-metilpropan-2-sulfinamida



A una solución agitada de 1-(4-butoxifenil)etanona (3 g, 15.60 mmol) y 2-metilpropan-2-sulfinamida (2.84 g, 23.41 mmol) en THF (50 ml), se agregó tetraetoxititanio (8.90 g, 39.0 mmol). La reacción se calentó a 70°C durante 3 días. Se agregó agua fría, y la reacción se agitó vigorosamente durante 20 min. La mezcla se filtró a través de Celite®, y el filtrado se diluyó con EtOAc. La solución orgánica se lavó con H_2O y salmuera, se secó en $MgSO_4$, se filtró y se concentró. El producto crudo se purificó mediante cromatografía en gel de sílice (220 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el producto deseado

(4 g, 87%) como un aceite amarillo. RMN 1H (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.80 Hz, 2 H), 6.91 (d, *J* = 8.80 Hz, 2 H), 4.02 (t, *J* = 6.46 Hz, 2 H), 2.73 (s, 3 H), 1.75 - 1.83 (m, 2 H), 1.46 - 1.56 (m, 2 H), 1.32 (s, 9 H), 0.99 (t, *J* = 7.43 Hz, 3 H).

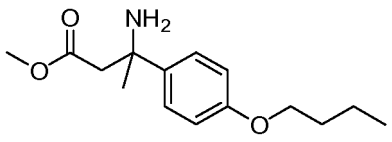
Intermediario 107B. 3-(4-butoxifenil)-3-(1,1-dimetiletilsulfinamido)butanoato de metilo



A una solución agitada of diisopropilamina (3.86 ml, 27.1 mmol) en THF (40 ml) a -78°C, se agregó por goteo n-butil litio (22.57 ml, 27.1 mmol). La reacción se calentó lentamente hasta -20°C y se agitó durante 45 min. La reacción se enfrió a -78°C, y se agregó por goteo acetato de metilo (2.006 g, 27.1 mmol). Después de 30 min, se agregó por goteo triisopropóxido de clorotitanio (8.09 ml, 33.8 mmol) en THF (40 ml). La reacción se agitó a -78°C durante 1 h. Se agregó por goteo el Intermediario 107A (4 g, 13.54 mmol) en THF (15 ml), y la reacción se agitó a -78°C durante 2 h. La reacción se inactivó mediante la adición de solución saturada de NH_4Cl y se agitó vigorosamente mientras se calentaba a temperatura ambiente. La mezcla se filtró a través de Celite® y se lavó con EtOAc. El filtrado se lavó con H_2O y salmuera, se secó en $MgSO_4$, se filtró y se concentró. El producto crudo se

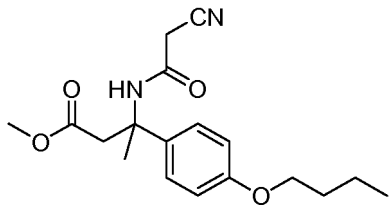
purificó mediante cromatografía en gel de sílice (220 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el producto deseado (4.33 g, 87%) como un aceite amarillo claro. LCMS Anal. calc. para $C_{19}H_{31}NO_4S$ 369.20. encontrado [M+H] 370.2. RMN 1H (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.80 Hz, 2 H), 6.85 (d, *J* = 8.80 Hz, 2 H), 3.95 (t, *J* = 6.46 Hz, 2 H), 3.62 (s, 3 H), 2.05 (s, 2 H), 1.74 - 1.80 (m, 2 H), 1.74 (s, 3 H), 1.44 - 1.54 (m, 2 H), 1.29 (s, 9 H), 0.98 (t, *J* = 7.43 Hz, 3 H).

Intermediario 107C. 3-amino-3-(4-butoxifenil)butanoato de metilo



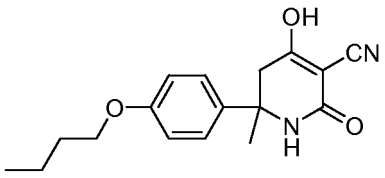
A una solución agitada del Intermediario 107B (1 g, 2.71 mmol) en MeOH (6 ml), se agregó HCl 4 N (3.38 ml, 13.53 mmol). La reacción se agitó a temperatura ambiente durante 4 h. La mezcla de reacción se concentró al vacío y se diluyó con EtOAc. La capa orgánica se lavó con NaHCO3 saturado, se secó en $MgSO_4$, se filtró y se concentró para obtener el producto deseado (700 mg, 97%) como un aceite amarillo. RMN 1H (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.80 Hz, 2 H), 6.86 (d, *J* = 8.80 Hz, 2 H), 3.95 (t, *J* = 6.46 Hz, 2 H), 3.59 (s, 3 H), 1.73 - 1.80 (m, 2 H), 1.53 (s, 2 H), 1.45 - 1.52 (m, 2 H), 1.19 (s, 3 H), 0.98 (t, *J* = 7.29 Hz, 3 H).

Intermediario 107D. 3-(4-butoxifenil)-3-(2-cianoacetamido)butanoato de metilo



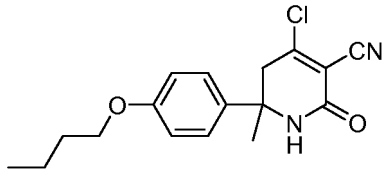
A una solución agitada de ácido 2-cianoacético (128 mg, 1.507 mmol) en CH_2Cl_2 (5 ml), se agregaron cloruro de oxalilo (0.754 ml, 1.507 mmol) y 1 gota de DMF. La reacción se agitó a temperatura ambiente durante 1 h y luego se concentró. El cloruro ácido resultante se disolvió en CH_2Cl_2 (1 ml) y luego se agregó al Intermediario 107C (200 mg, 0.754 mmol) y piridina (0.183 ml, 2.261 mmol) en CH_2Cl_2 (5 ml). La reacción se agitó a temperatura ambiente durante 5 h. La mezcla de reacción se concentró, y el residuo se diluyó con EtOAc. La capa orgánica se lavó con NH_4Cl saturado, se secó en $MgSO_4$, se filtró y se concentró. El producto crudo se purificó mediante cromatografía en gel de sílice (24 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el producto deseado (218 mg, 87%) como un aceite transparente. RMN 1H (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.80 Hz, 2 H), 6.85 (d, *J* = 8.80 Hz, 2 H), 3.94 (t, *J* = 6.46 Hz, 2 H), 3.65 (s, 3 H), 3.30 (s, 2 H), 3.03 (d, *J* = 15.13 Hz, 1 H), 2.85 (d, *J* = 15.13 Hz, 1 H), 1.80 (s, 3 H), 1.71 - 1.78 (m, 2 H), 1.44 - 1.53 (m, 2 H), 0.97 (t, *J* = 7.29 Hz, 3 H).

Intermediario 107E. 6-(4-butoxifenil)-4-hidroxi-6-metil-2-oxo-1,2,5,6-tetrahidropiridin-3-carbonitrilo



A una solución agitada del Intermediario 107D (218 mg, 0.656 mmol) en MeOH (5 ml), se agregó NaOMe 4.37 M (0.750 ml, 3.28 mmol) en solución de metanol. La reacción se calentó a 55°C durante 5 h. La mezcla de reacción se concentró, y el residuo se diluyó con EtOAc. La capa orgánica se lavó con HCl 1 M, se secó en $MgSO_4$, se filtró y se concentró para obtener el producto deseado (200 mg, 102%) como un sólido amarillo claro. LCMS Anal. calc. para $C_{17}H_{20}N_2O_3$ 300.15, encontrado [M+H] 301.1.

Intermediario 107F. 6-(4-butoxifenil)-4-cloro-6-metil-2-oxo-1,2,5,6-tetrahidropiridin-3-carbonitrilo



A una solución agitada del Intermediario 107E (130 mg, 0.433 mmol) en $ClCH_2CH_2Cl$ (3 ml), se agregaron $POCl_3$ (0.056 ml, 0.606 mmol) y base de Hunig (0.113 ml, 0.649 mmol). La reacción se agitó a temperatura ambiente durante 30 min y luego se calentó a 85°C durante 3 h. La mezcla de reacción se concentró, y el residuo se diluyó con EtOAc. La

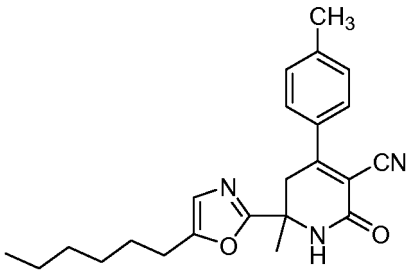
capa orgánica se lavó con NH_4Cl saturado, se secó en $MgSO_4$, se filtró y se concentró. El producto crudo se purificó mediante cromatografía en gel de sílice (24 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el producto deseado (102 mg, 74%) como un sólido blanco. LCMS Anal. calc. para $C_{17}H_{19}ClN_2O_2$ 318.11, encontrado [M+H] 319.2. RMN 1H (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.80 Hz, 2 H), 6.90 (d, *J* = 8.80 Hz, 2 H), 3.97 (t, *J* = 6.60 Hz, 2 H), 2.05 (s, 2 H), 1.74 - 1.82 (m, 2 H), 1.69 (s, 3 H), 1.46 - 1.55 (m, 2 H), 0.99 (t, *J* = 7.43 Hz, 3 H).

Ejemplo 107

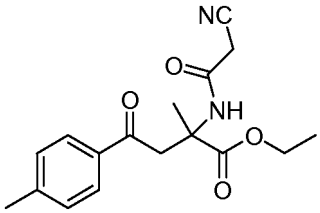
A una solución agitada del Intermediario 107F (11 mg, 0.035 mmol), ácido *p*-tolilborónico (5.63 mg, 0.041 mmol) y dicloruro de 1,1'-bis(di-*ter*-butilfosfino)ferrocenpaladio (2.270 mg, 3.45 µmol) en dioxano (1 ml), se agregó CsF (10.48 mg, 0.069 mmol). La reacción se desgasificó durante 10 min y se calentó a 80°C durante 2 h. La mezcla de reacción se concentró. El residuo se diluyó con EtOAc, se lavó con H_2O y salmuera, se secó en $MgSO_4$, se filtró y se concentró. El material crudo se purificó mediante HPLC preparativa (MeOH/H_2O/TFA) para obtener el producto deseado (5.7 mg, 44%) como un sólido marrón. LCMS Anal. calc. para $C_{24}H_{26}N_2O_2$ 374.20. encontrado [M+H] 375.2. RMN 1H (400 MHz, CD_3OD) δ 7.41 (d, *J* = 8.14 Hz, 2 H), 7.32 (d, *J* = 8.80 Hz, 2 H), 7.28 (d, *J* = 8.14 Hz, 2 H), 6.89 (d, *J* = 8.80 Hz, 2 H), 3.96 (t, *J* = 6.38

Hz, 2 H), 3.46 (d, *J* = 18.05 Hz, 1 H), 3.24 (d, *J* = 17.83 Hz, 1 H), 2.38 (s, 3 H), 1.69 - 1.78 (m, 2 H), 1.65 (s, 3 H), 1.43 - 1.55 (m, 2 H), 0.97 (t, *J* = 7.48 Hz, 3 H).

Ejemplo 108. 6-(5-hexiloxazol-2-il)-6-metil-2-oxo-4-*p*-tolil-1,2,5,6-tetrahidropiridin-3-carbonitrilo



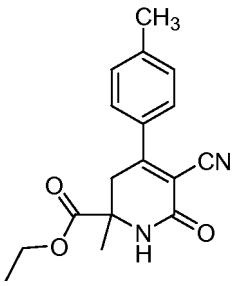
Intermediario 108A. 2-(2-cianoacetamido)-2-metil-4-oxo-4-*p*-tolilbutanoato de etilo



A una solución del Intermediario 3C (2.192 g, 21.18 mmol) en DCM (30 ml) en argón, se agregaron el Intermediario 102C (1.2 g, 4.81 mmol), piridina (0.779 ml, 9.63 mmol) y DMAP (0.059 g, 0.481 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se cargó en gel de sílice (25 g) y se lavó con EtOAc (4 x 50 ml). El filtrado se concentró al vacío hasta obtener un aceite rojo oscuro. El aceite se disolvió en EtOAc (100 ml) y se lavó con agua (2 x 50 ml). La fase orgánica se secó en

$MgSO_4$ y se concentró al vacío. El residuo se purificó mediante cromatografía en gel de sílice (80 g de gel de sílice, eluido con EtOAc en hexanos) para obtener el producto deseado (1.28 g, 84%) como un aceite amarillo. LCMS Anal. calc. para $C_{17}H_{20}N_2O_4$ 316.1, encontrado [M+H] 317.1. RMN 1H (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 2 H), 7.39 (s, 1 H), 7.24 - 7.29 (m, 2 H), 4.45 (d, *J* = 18.2 Hz, 1 H), 4.22 - 4.31 (m, 2 H), 3.47 (d, *J* = 18.2 Hz, 1 H), 3.28 - 3.38 (m, 2 H), 2.42 (s, 3 H), 1.74 (s, 3 H), 1.24 (t, *J* = 7.0 Hz, 3 H).

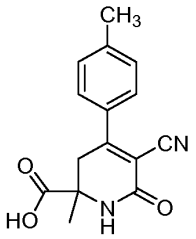
Intermediario 108B. 5-ciano-2-metil-6-oxo-4-*p*-tolil-1,2,3,6-tetrahidropiridin-2-carboxilato de etilo



Se disolvió el Intermediario 108A (1.2837 g, 4.06 mmol) en una mezcla de THF (15 ml) y agua (3.00 ml) en un matraz de 25 ml con forma de pera y un cuello, equipado con un agitador magnético. Se agregó hidróxido de litio monohidrato (0.204 g, 4.87 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se acidificó a pH 4 con AcOH, se diluyó con EtOAc (50 ml), y la solución se lavó con agua (20 ml). La fase orgánica se secó en $MgSO_4$ y se concentró al vacío para

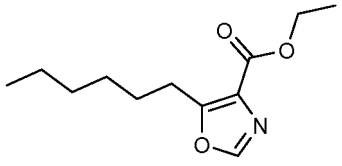
obtener el producto deseado (1.40 g, 115%) como un aceite amarillo. LCMS Anal. calc. para $C_{17}H_{18}N_2O_3$ 298.1, encontrado [M+H] 299.1.

Intermediario 108C. Ácido 5-ciano-2-metil-6-oxo-4-*p*-tolil-1,2,3,6-tetrahidropiridin-2-carboxílico



El Intermediario 108B (1.211 g, 4.06 mmol) se disolvió en ácido acético (95 ml) en un matraz de 250 ml con forma de pera y un cuello, equipado con un agitador magnético. Se agregó HCl (11.67 ml, 142 mmol), y la mezcla de reacción se agitó a 60°C durante la noche. La mezcla de reacción se concentró al vacío para obtener el producto deseado como un sólido amarillo pálido. LCMS Anal. calc. para $C_{15}H_{14}N_2O_3$ 270.1, encontrado [M+H] 271.0. RMN 1H (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.3 Hz, 2 H), 7.23 (d, *J* = 7.7 Hz, 2 H), 3.39 (d, *J* = 18.2 Hz, 1 H), 2.83 (d, *J* = 18.2 Hz, 1 H), 2.35 (s, 3 H), 1.54 (s, 3 H).

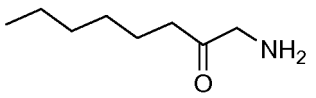
Intermediario 108D. 5-hexiloxazol-4-carboxilato de etilo



Se disolvió 2-isocianoacetato de etilo (1.0 g, 8.84

mmol) en DMF (5 ml) en un matraz de 25 ml con forma de pera y un cuello, equipado con un agitador magnético y una entrada de Ar. Se agregaron DBU (1.999 ml, 13.26 mmol) y cloruro de heptanoilo (1.770 ml, 11.49 mmol), y la mezcla de reacción se agitó a 80°C durante 6 h. La mezcla de reacción se vertió en agua (50 ml) y se extrajo con EtOAc (3 x 30 ml). Las fases se separaron, y la fase orgánica se secó en $MgSO_4$ y se concentró al vacío hasta obtener un aceite oscuro. El producto deseado se aisló mediante distilación a 90-95°C a 0.3 mmHg como un aceite transparente (0.89 g, 45%). LCMS Anal. calc. para $C_{12}H_{19}NO_3$ 225.1, encontrado [M+H] 226.1. RMN 1H (500 MHz, $CDCl_3$) δ 7.76 (s, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 3.03 (t, *J* = 7.6 Hz, 2H), 1.71 - 1.64 (m, 2H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.35 - 1.26 (m, 6H), 0.86 (t, *J* = 6.3 Hz, 3H).

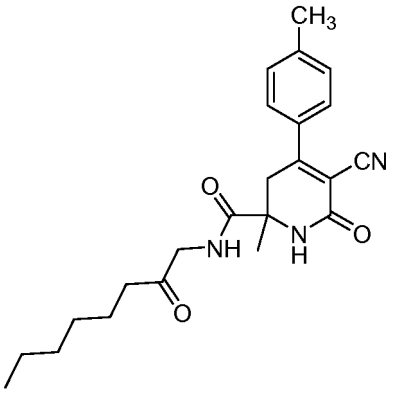
Intermediario 108E. 1-aminooctan-2-ona, sal de HCl



Se agitó el Intermediario 108D (0.8889 g, 3.95 mmol) en HCl (16.44 ml, 99 mmol) en un matraz de 100 ml con forma de pera y un cuello, equipado con un agitador magnético. La mezcla de reacción se calentó a 100°C y se agitó durante 6 h. La mezcla de reacción se concentró al vacío hasta obtener un sólido de color tostado que se trituró en éter (15 ml). La suspensión se filtró y se lavó con éter (3 ml). La torta de filtro se secó al vacío para obtener el

producto deseado (0.57 g, 80%) como un sólido blancuzco. RMN 1H (500 MHz, MeOD) δ 3.97 (s, 2 H), 2.56 (t, *J* = 7.4 Hz, 2 H), 1.62 (quin, *J* = 7.4 Hz, 2 H), 1.26 - 1.40 (m, 6 H), 0.88 - 0.93 (m, 3 H).

Intermediario 108F. 5-ciano-2-metil-6-oxo-N-(2-oxooctil)-4-*p*-tolil-1,2,3,6-tetrahidropiridin-2-carboxamida

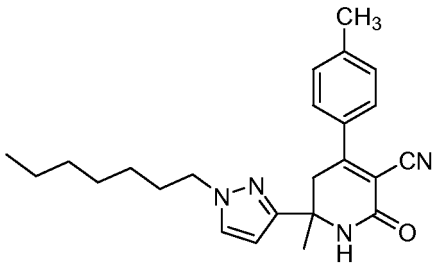


Se disolvió Intermediario 108C (0.1 g, 0.370 mmol) en DCM (4 ml) en un matraz de 10 ml con forma de pera y un cuello, equipado con un agitador magnético y una entrada de Ar. Se agregaron EDC (0.099 g, 0.518 mmol), HOBT (0.068 g, 0.444 mmol), Intermediario 108E (0.080 g, 0.444 mmol) y DIEA (0.194 ml, 1.110 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró al vacío hasta obtener un aceite naranja que se purificó mediante cromatografía en gel de sílice (40 g de gel de sílice, eluido con 0-100% de EtOAc en hexanos) para obtener el producto deseado (0.09 g, 61%) como un aceite amarillo.

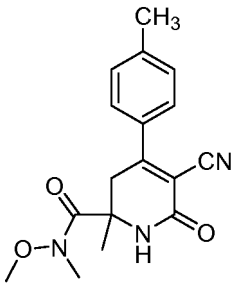
Ejemplo 108

Se disolvió el Intermediario 108F (0.045 g, 0.114 mmol) en 1,2-dicloroetano (2 ml) en un matraz de 10 ml con forma de pera y un cuello, equipado con un agitador magnético y una entrada de Ar. Se agregaron $POCl_3$ (0.042 ml, 0.455 mmol) y DIEA (0.089 ml, 0.512 mmol), y la mezcla de reacción se agitó a 85°C durante la noche. La mezcla de reacción se enfrió en un baño de hielo/agua y se inactivó con agua (3 ml). La mezcla se extrajo con EtOAc (2 x 5 ml), y las fases orgánicas se combinaron, se secaron en $MgSO_4$ y se concentraron al vacío para obtener un aceite marrón. El producto crudo se purificó mediante HPLC preparativa (MeOH/H2O/TFA) para obtener el producto deseado (3.5 mg, 8%) como un sólido amarillo. LCMS Anal. calc. para $C_{23}H_{27}N_3O_2$ 377.2, encontrado [M+H] 378.2. RMN 1H (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 6.81 (br. s., 1 H), 3.65 (d, *J* = 17.9 Hz, 1 H), 3.09 (d, *J* = 17.9 Hz, 1 H), 2.63 (t, *J* = 7.4 Hz, 2 H), 2.43 (s, 3 H), 1.76 (s, 3 H), 1.57 - 1.67 (m, 2 H), 1.23 - 1.42 (m, 6 H), 0.89 (t, *J* = 6.7 Hz, 3 H).

Ejemplo 109. 6-(1-heptil-1*H*-pirazol-3-il)-6-metil-2-oxo-4-*p*-tolil-1,2,5,6-tetrahidropiridin-3-carbonitrilo

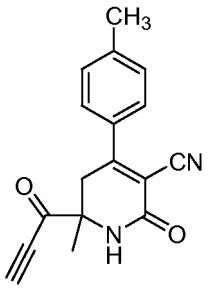


Intermediario 109A. 5-ciano-*N*-metoxi-*N*,2-dimetil-6-oxo-4-*p*-tolil-1,2,3,6-tetrahidropiridin-2-carboxamida



Se disolvió el Intermediario 108C (0.25 g, 0.925 mmol) en DCM (15 ml) en un matraz de 25 ml de fondo redondo y un cuello, equipado con un agitador magnético y una entrada de Ar. Se agregaron *N*,*O*-dimetilhidroxilamina (0.062 g, 1.017 mmol), EDC (0.195 g, 1.017 mmol) y *N*-metilmorfolina (0.112 ml, 1.017 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante la noche. El solvente de reacción se retiró al vacío. El residuo se disolvió en EtOAc (10 ml) y se lavó con agua (5 ml). La fase orgánica se secó en $MgSO_4$ y se concentró al vacío hasta obtener un sólido oscuro. El producto crudo se purificó mediante cromatografía en gel de sílice (40 g de gel de sílice, eluido con 0-100% de EtOAc en hexanos) para obtener el producto deseado (0089 g, 31%) como un sólido blanco. LCMS Anal. calc. para $C_{17}H_{19}N_3O_3$ 313.3, encontrado [M+H] 314.1. RMN 1H (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.3 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 3.81 (s, 3 H), 3.69 - 3.75 (m, 1 H), 3.22 (s, 3 H), 2.72 (d, *J* = 17.6 Hz, 1 H), 2.42 (s, 3 H), 1.63 (s, 3 H).

Intermediario 109B. 6-metil-2-oxo-6-propioloil-4-*p*-tolil-1,2,5,6-tetrahidropiridin-3-carbonitrilo



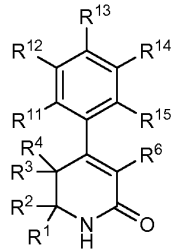
Se disolvió el Intermediario 109A (0.0887 g, 0.283 mmol) en tetrahidrofurano (1 ml) en un matraz de 25 ml con forma de pera y un cuello, equipado con un agitador magnético y una entrada de Ar. Se agregó por goteo bromuro de etinilmagnesio (5.66 ml, 2.83 mmol), y la mezcla de reacción se agitó a 35°C durante 4 h. La mezcla de reacción se enfrió a temperatura ambiente, se inactivó con NH_4Cl acuoso saturado (5 ml) y se extrajo con EtOAc (2 x 10 ml). Las fases orgánicas se combinaron y se concentraron al vacío. El residuo se purificó mediante cromatografía en gel de sílice (24 g de gel de sílice, eluido con 0-100% de EtOAc en hexanos) para obtener el producto deseado (0.06 g, 78%) como un sólido naranja. LCMS Anal. calc. para $C_{17}H_{14}N_2O_2$ 278.1, encontrado [M+H] 279.0.

Ejemplo 109

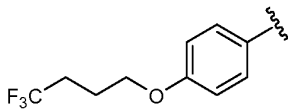
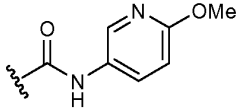
Se disolvió el Intermediario 109B (0.0613 g, 0.220 mmol) en etanol (3 ml) en un matraz de 25 ml con forma de pera y un cuello, equipado con un agitador magnético. Se

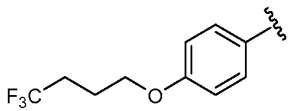
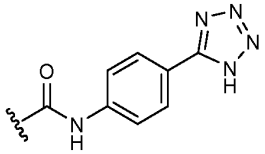
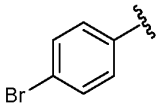
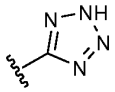
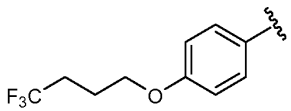
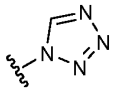
agregaron heptilhidrazina, HCl (0.073 g, 0.441 mmol) y TEA (0.061 ml, 0.441 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró y se purificó mediante HPLC preparativa (MeOH/H_2O/TFA) para obtener el producto deseado (3.2 mg, 4%) como un sólido blanco. LCMS Anal. calc. para $C_{24}H_{30}N_4O$ 390.2, encontrado [M+H] 391.2. RMN 1H (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.3 Hz, 2 H), 7.25 - 7.30 (m, 2 H), 6.35 (s, 1 H), 6.15 (d, *J* = 1.7 Hz, 1 H), 3.98 - 4.08 (m, 2 H), 3.57 (d, *J* = 17.9 Hz, 1 H), 3.01 (d, *J* = 17.9 Hz, 1 H), 2.41 (s, 3 H), 1.81 (quin, *J* = 7.3 Hz, 2 H), 1.70 - 1.77 (m, 2 H), 1.68 (s, 3 H), 1.16 - 1.34 (m, 6 H), 0.87 (t, *J* = 7.0 Hz, 3 H).

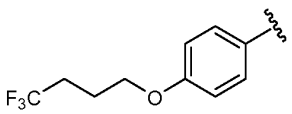
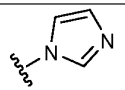
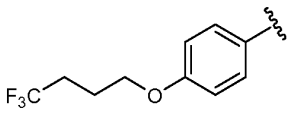
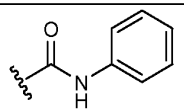
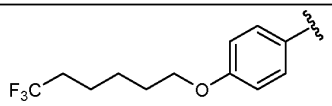
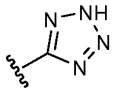
Los ejemplos 110-273 expresados mediante la Fórmula (II), a menos que se indiquen en la tabla, pueden ser realizados por una persona del oficio del nivel medio mediante la aplicación adecuada de los procedimientos descritos para los Ejemplos 1-16 y los Ejemplos 102-. R^{11} a R^{15} son hidrógeno, a menos que se indique en la tabla.

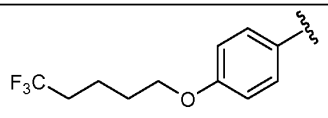
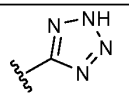
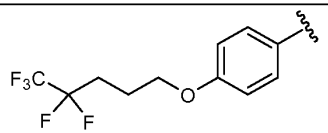
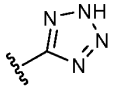
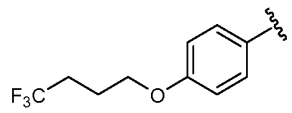
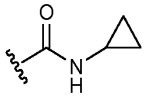


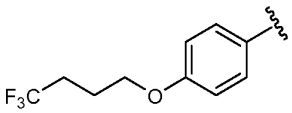
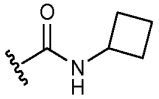
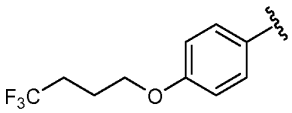
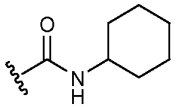
(II)

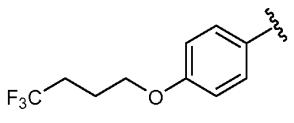
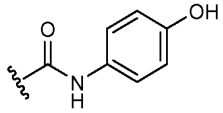
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
110 Isómero S		CF_3	H		$R^{13} = CH_3$	608.1	8.13 (d, *J* = 2.5 Hz, 1H), 7.93 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.46 (d, *J* = 9.1 Hz, 2H), 7.22 (s, 1H), 7.20 - 7.15 (m, 2H), 7.13 - 7.08 (m, 2H), 6.94 (d, *J* = 9.1 Hz, 2H), 6.67 (d, *J* = 9.1 Hz, 1H), 4.02 (t, *J* = 5.9 Hz, 2H), 3.90 (br. s., 3H), 3.56 - 3.38 (m, 2H), 2.39 - 2.25 (m, 5H), 2.10 - 2.01 (m, 2H).

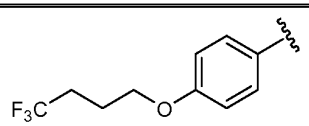
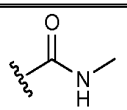
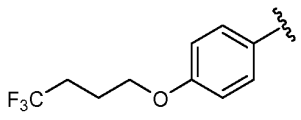
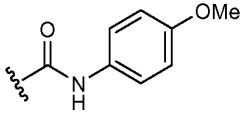
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
111 Isómero S		CF_3	H		$R^{13} = CH_3$	645.2	7.88 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 7.7 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 4.07 (t, J = 5.9 Hz, 2H), 3.75 - 3.46 (m, 2H), 2.43 - 2.32 (m, 2H), 2.29 (s, 3H), 2.11 - 1.97 (m, 2H).
112 Rac		CF_3	H		$R^{13} = CH_3$	480.0	
113 Isómero S		CF_3	H		$R^{13} = CH_3$	526.1	9.07 (d, *J* = 1.1 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.16 - 7.09 (m, *J* = 8.0 Hz, 2H), 7.09 - 7.03 (m, 2H), 6.93 - 6.86 (d, *J* = 7.7 Hz, 2H), 4.12 (t, *J* = 6.1 Hz, 2H), 4.00 (s, 1H), 3.92 (d, *J* =

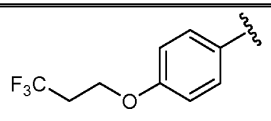
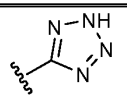
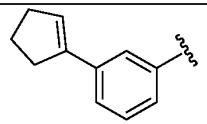
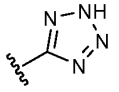
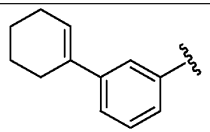
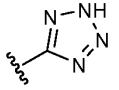
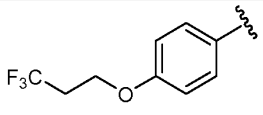
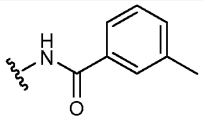
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							17.6 Hz, 1H), 3.77 (d, *J* = 17.6 Hz, 1H), 2.46 - 2.34 (m, 2H), 2.30 (s, 3H), 2.12 - 2.02 (m, 2H).
114 Isómero S		CF_3	H		$R^{13} = CH_3$	524.1	
115 Isómero S		CF_3	H		$R^{13} = CH_3$	577.2	
116 Rac		CF_3	H		$R^{13} = CH_3$	554.2	7.42 (d, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.10 (br. s., 1H), 6.95 (dd, *J* = 15.0, 8.4 Hz, 4H), 3.97 (t, *J* = 6.3 Hz, 2H), 3.59 (d, *J* = 5.5 Hz, 2H), 2.36 (s, 3H), 2.16 - 2.04 (m, 2H), 1.86 - 1.77 (m, 2H), 1.69 - 1.59 (m, 2H), 1.59 - 1.50 (m, 2H),

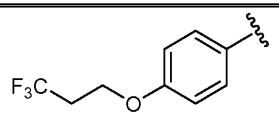
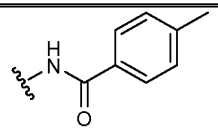
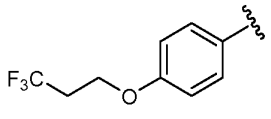
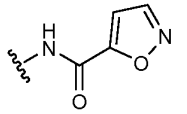
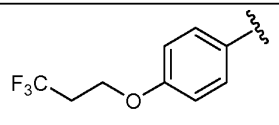
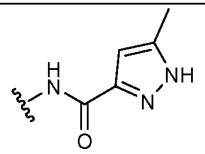
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							0.93 - 0.79 (m, 3H)
117 Rac		CF_3	H		$R^{13} = CH_3$	540.1	7.43 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 7.7 Hz, 2H), 7.03 - 6.91 (m, 5H), 3.99 (t, *J* = 5.9 Hz, 2H), 3.65 - 3.53 (m, 2H), 2.37 (s, 3H), 2.23 - 2.11 (m, 2H), 1.92 - 1.82 (m, 2H), 1.82 - 1.72 (m, 2H)
118 Rac		CF_3	H		$R^{13} = CH_3$	576.1	7.44 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.96 (dd, *J* = 11.4, 8.7 Hz, 4H), 6.80 (br. s., 1H), 4.07 - 4.01 (m, 2H), 3.59 (d, *J* = 7.4 Hz, 2H), 2.37 (s, 3H), 2.33 - 2.19 (m, 2H), 2.10 (dd, *J* = 9.5, 5.6 Hz, 2H)
119 Isómero S		CF_3	H		$R^{13} = CH_3$	541.2	7.44 (d, *J* = 8.3 Hz, 2H), 7.21 - 7.16 (m, 2H), 7.14 -

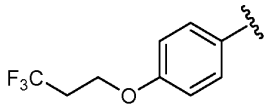
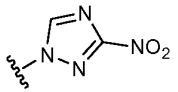
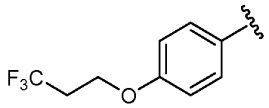
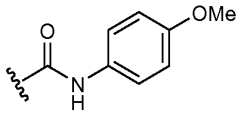
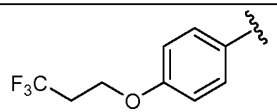
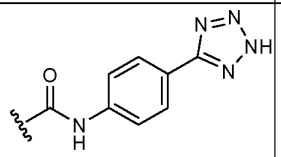
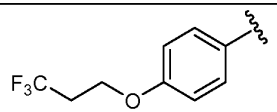
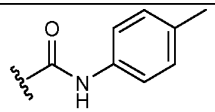
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							7.09 (m, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 4.06 (t, *J* = 5.9 Hz, 3H), 3.58 - 3.27 (m, 2H), 2.48 - 2.27 (m, 5H), 2.09 (dd, *J* = 9.5, 5.9 Hz, 2H), 0.97 - 0.80 (m, 2H), 0.75 - 0.61 (m, 2H), 0.38 (d, *J* = 3.6 Hz, 2H)
120 Isómero S		CF_3	H		$R^{13} = CH_3$	555.2	7.43 (d, *J* = 8.5 Hz, 2H), 7.20 - 7.03 (m, 5H), 6.97 - 6.88 (m, 2H), 4.36 - 4.22 (m, 1H), 4.08 - 3.98 (m, 2H), 3.53 - 3.27 (m, 2H), 2.44 - 2.16 (m, 8H), 2.12 - 2.02 (m, 2H), 1.78 - 1.51 (m, 4H)
121 Isómero S		CF_3	H		$R^{13} = CH_3$	583.3	7.49 - 7.37 (m, 2H), 7.22 - 7.07 (m, 4H), 6.97 - 6.84 (m, 3H), 6.74 (d, *J* = 8.0 Hz, 1H), 4.10 - 3.95 (m, 3H),

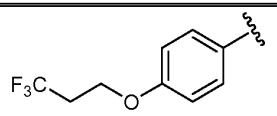
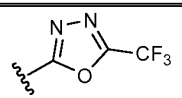
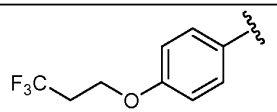
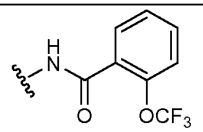
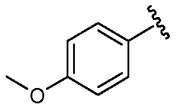
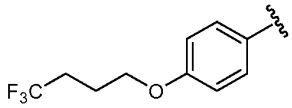
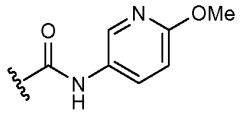
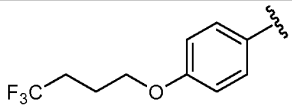
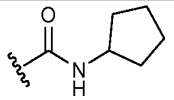
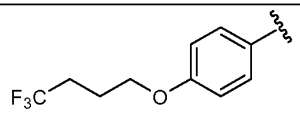
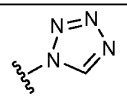
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							3.77 - 3.62 (m, 1H), 3.52 - 3.26 (m, 2H), 2.42 - 2.25 (m, 6H), 2.15 - 1.96 (m, 3H), 1.86 - 1.64 (m, 2H), 1.64 - 1.44 (m, 4H), 1.35 - 1.16 (m, 3H), 1.14 - 0.93 (m, 4H)
122 Isómero S		CF_3	H		$R^{13} = CH_3$	593.3	7.55 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.14 - 7.09 (d, *J* = 8.8 Hz, 2H), 7.02 - 6.97 (d, *J* = 8.8 Hz, 2H), 6.68 - 6.62 (m, 2H), 4.08 (t, *J* = 6.1 Hz, 2H), 3.67 (d, *J* = 17.1 Hz, 1H), 3.51 (d, *J* = 17.1 Hz, 1H), 2.45 - 2.35 (m, 2H), 2.34 (s, 3H), 2.09 - 2.00 (m, 2H).

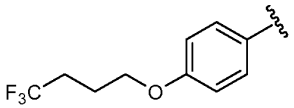
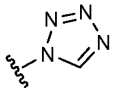
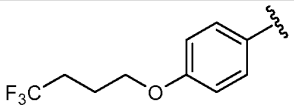
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
123 Isómero S		CF_3	H		$R^{13} = CH_3$	515.2	7.57 - 7.50 (m, *J* = 8.8 Hz, 2H), 7.27 - 7.23 (m, *J* = 8.3 Hz, 2H), 7.23 - 7.19 (m, *J* = 8.3 Hz, 2H), 7.02 - 6.97 (m, *J* = 9.1 Hz, 2H), 4.08 (t, *J* = 6.1 Hz, 2H), 3.60 (d, *J* = 17.1 Hz, 1H), 3.46 (d, *J* = 17.1 Hz, 1H), 2.57 (s, 3H), 2.45 - 2.37 (m, 2H), 2.36 (s, 3H), 2.11 - 1.99 (m, 2H).
124 Rac		CF_3	F		$R^{13} = CH_3$	643.3	7.90 (s, 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.25 - 7.17 (m, 6H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.95 (br. s., 1H), 6.78 (d, *J* = 9.1 Hz, 2H), 4.05 (t, *J* = 5.9 Hz, 2H), 3.81 - 3.71 (m, 3H), 2.44 - 2.27 (m, 5H), 2.13 - 2.03 (m, 2H)

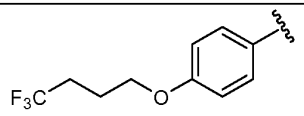
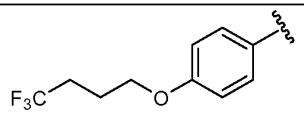
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
125 Rac		CF_3	H		$R^{13} = CH_3$	512.1	7.45 (d, *J* = 8.5 Hz, 3H), 7.13 (d, *J* = 7.7 Hz, 2H), 6.93 (d, *J* = 7.7 Hz, 4H), 4.18 (t, *J* = 6.5 Hz, 2H), 3.68 - 3.52 (m, 2H), 2.67 - 2.56 (m, 2H)
126 Rac		CF_3	H		$R^{13} = CH_3$	466.2	
127 Rac		CF_3	H		$R^{13} = CH_3$	480.1	7.50 - 7.40 (m, 4H), 7.16 (d, *J* = 7.7 Hz, 2H), 7.09 (br. s., 1H), 6.98 (d, *J* = 7.7 Hz, 2H), 6.17 (br. s., 1H), 2.36 (s, 5H), 2.21 (d, *J* = 3.6 Hz, 2H), 1.82 - 1.74 (m, 2H), 1.70 - 1.62 (m, 2H)
128 Isómero S		CF_3	H		$R^{13} = CH_3$	591.3	

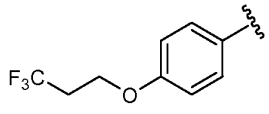
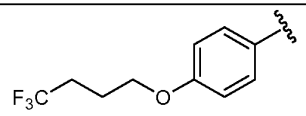
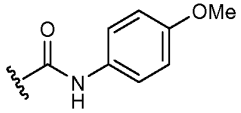
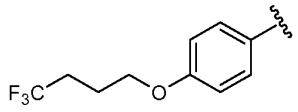
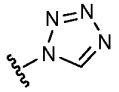
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
129 Isómero S		CF_3	H		$R^{13} = CH_3$	591.3	
130 Isómero S		CF_3	H		$R^{13} = CH_3$	568.2	8.47 (d, *J* = 1.9 Hz, 1H), 7.61 - 7.54 (ab cuarteto, *J* = 8.8 Hz, 2H), 7.24 - 7.20 (ab cuarteto, *J* = 8.3 Hz, 2H), 7.19 - 7.15 (ab cuarteto, *J* = 8.3 Hz, 2H), 7.04 - 6.98 (m, 2H), 6.93 - 6.87 (m, 1H), 4.09 (t, *J* = 6.1 Hz, 2H), 3.75 (d, *J* = 17.1 Hz, 1H), 3.51 (d, *J* = 16.8 Hz, 1H), 2.46 - 2.34 (m, 2H), 2.32 (s, 3H), 2.12 - 2.01 (m, 3H).
131 Isómero S		CF_3	H		$R^{13} = CH_3$	581.3	

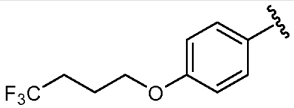
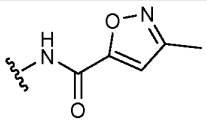
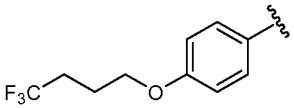
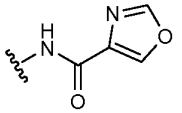
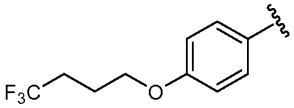
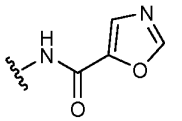
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
132 Isómero S		CF_3	H		$R^{13} = CH_3$	570.2	
133 Rac		CF_3	F		$R^{13} = CH_3$	643.1	8.07 (br. s., 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.24 - 7.15 (m, 6H), 6.96 (d, *J* = 9.1 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 4.09 - 3.97 (m, 2H), 3.75 (s, 3H), 2.39 - 2.25 (m, 5H), 2.12 - 2.02 (m, 2H)
134 Rac		CF_3	F		$R^{13} = CH_3$	680.9	
135 Rac		CF_3	F		$R^{13} = CH_3$	626.9	

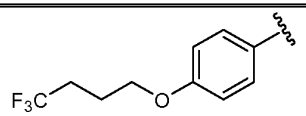
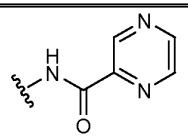
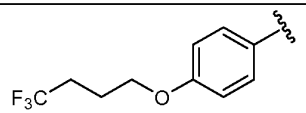
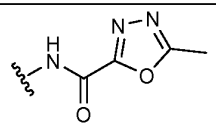
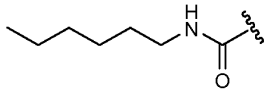
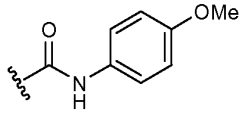
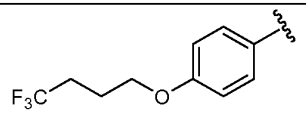
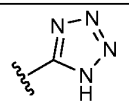
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
136 Isómero S		CF_3	H		$R^{13} = CH_3$	594.1	
137 Isómero S		CF_3	H		$R^{13} = CH_3$	661.1	
138 Rac		CF_3	F	CN	$R^{13} = CH_3$	422.8	
140 Rac		CF_3	F		$R^{13} = CH_3$	643.9	
141 Rac		CF_3	F		$R^{13} = CH_3$	604.9	
142 Isómero S		CF_3	H		$R^{11} = F$ $R^{13} = OCH_3$	560.1	9.17 (s, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.07 - 7.00 (m, 2H), 6.95 (t, J = 8.5 Hz, 1H), 6.69 (dd, J = 8.8, 2.5 Hz, 1H), 6.63 (dd, J = 12.7, 2.5 Hz,

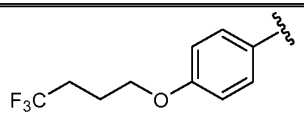
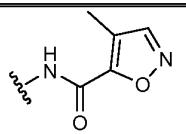
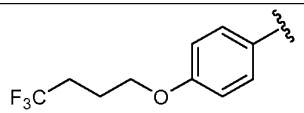
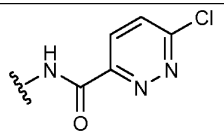
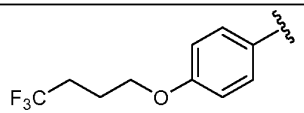
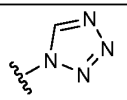
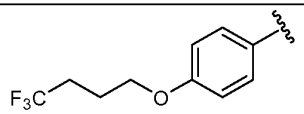
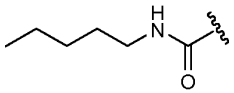
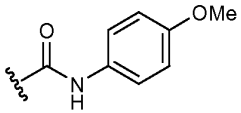
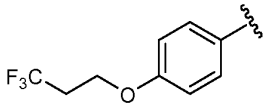
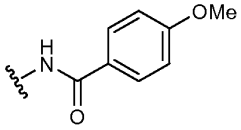
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							1H), 4.09 (t, J = 6.1 Hz, 2H), 3.90 - 3.81 (m, 1H), 3.76 (s, 3H), 3.74 - 3.66 (m, 1H), 2.47 - 2.30 (m, 2H), 2.12 - 1.94 (m, 2H).
143 Isómero S		CF_3	H		$R^{13} = OCH_3$	542.1	9.05 (s, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 9.1 Hz, 2H), 6.97 - 6.88 (m, 1H), 6.86 - 6.76 (m, 1H), 4.09 (t, J = 6.1 Hz, 2H), 3.92 - 3.70 (m, 2H), 3.75 (S, 3H), 2.45 - 2.29 (m, 2H), 2.10 - 1.94 (m, 2H).
144 Isómero S		CF_3	H	CN	$R^{13} = OCHF_2$	535.1	7.65 (br. s., 2H), 7.53 (d, J = 9.1 Hz, 2H), 7.32 - 7.24 (m, 2H), 7.05 - 6.98 (m, 2H), 6.96 (t, J = 75 Hz, 1H), 4.14 - 3.97 (m, 2H), 3.73 (d, J =

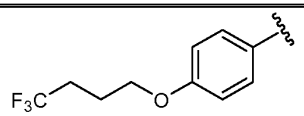
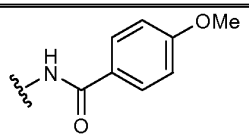
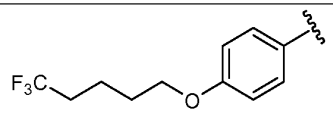
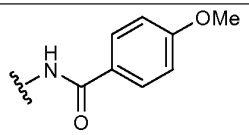
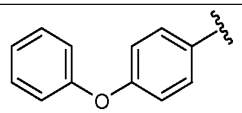
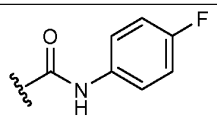
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							3.3 Hz, 2H), 2.42 - 2.27 (m, 2H), 2.09 - 1.96 (m, 2H).
145 Isómero S		CF_3	H	CN	R^{13} = OCH_2CH_3	513.1	7.64 (d, J = 9.1 Hz, 2H), 7.52 (d, J = 9.1 Hz, 2H), 7.03 (d, J = 9.1 Hz, 4H), 4.12 (d, J = 6.9 Hz, 2H), 4.08 - 4.03 (m, 2H), 3.82 - 3.58 (m, 2H), 2.45 - 2.26 (m, 2H), 2.08 - 1.95 (m, 2H), 1.41 (t, J = 6.9 Hz, 3H).
146 Isómero S		CF_3	H	CN	R^{12} and R^{13} 	519.1	8.15 (d, J = 1.7 Hz, 1H), 8.01 - 7.96 (m, 2H), 7.93 (d, J = 8.0 Hz, 1H), 7.67 - 7.54 (m, 5H), 7.06 - 7.00 (m, 2H), 4.08 (s, 2H), 3.93 - 3.77 (m, 2H), 2.48 - 2.25 (m, 2H), 2.13 - 1.92 (m, 2H).

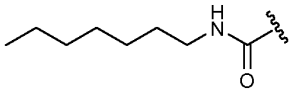
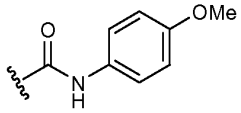
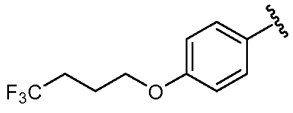
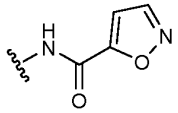
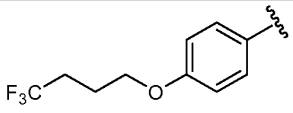
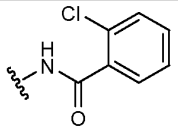
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
147 Isómero S		CF_3	H	CN	$R^{13} = CH_3$	469.1	7.55 (d, J = 8.8 Hz, 2H), 7.52 - 7.49 (m, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.04 - 6.99 (m, 2H), 4.24 (t, J = 6.1 Hz, 2H), 3.77 - 3.66 (m, 2H), 2.75 - 2.63 (m, 2H), 2.41 (s, 3H).
148 Isómero S		CF_3	H		$R^{11} = CH_3$ $R^{13} = CH_3$	621.2	7.49 - 7.41 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.03 - 6.65 (m, 7H), 4.07 - 3.99 (m, 2H), 3.71 (s, 3H), 3.51 - 3.42 (m, 1H), 3.28 – 3.14 (m, 1H), 2.38 - 2.21 (m, 8H), 2.11 - 1.99 (m, 2H).
149 Isómero S		CF_3	H		$R^{13} = OCHF_2$	578.1	9.09 (s, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.08 - 7.03 (m, 6H), 6.97 – 6.68 (m, 1H), 4.09 (t, *J* = 6.1 Hz, 2H), 3.92 (d, *J* = 17.9 Hz, 1H), 3.77 (d,

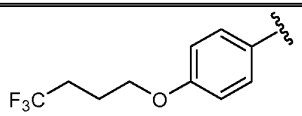
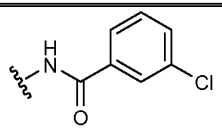
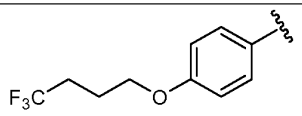
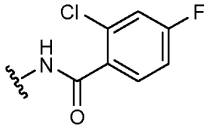
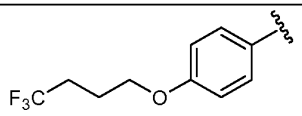
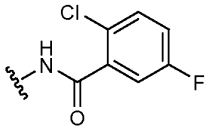
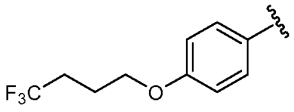
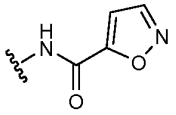
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							J = 17.9 Hz, 1H), 2.43 - 2.31 (m, 2H), 2.10 - 1.98 (m, 2H).
150 Isómero S		CF_3	F		$R^{13} = CH_3$	582.2	7.54 (d, *J* = 8.8 Hz, 2H), 7.23 - 7.11 (m, 4H), 7.03 - 6.94 (m, 2H), 6.71 (s, 1H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.98 (s, 1H), 3.71 (d, *J* = 17.1 Hz, 1H), 3.47 (d, *J* = 16.8 Hz, 1H), 2.45 - 2.31 (m, 2H), 2.29 (d, *J* = 6.3 Hz, 6H), 2.12 - 1.96 (m, 2H).
151 Isómero S		CF_3	H		$R^{13} = CH_3$	568.2	
152 Isómero S		CF_3	H		$R^{13} = CH_3$	568.2	

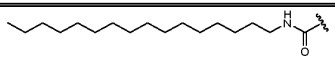
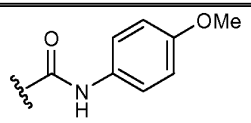
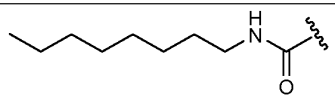
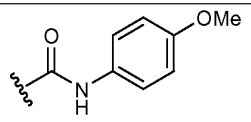
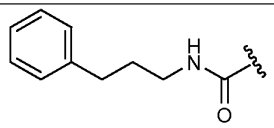
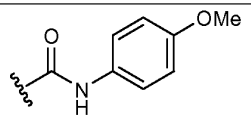
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
153 Isómero S		CF_3	H		$R^{13} = CH_3$	579.2	
154 Isómero S		CF_3	H		$R^{13} = CH_3$	583.1	7.58 - 7.49 (ab cuarteto, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 7.03 - 6.92 (m, 2H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.72 (d, *J* = 17.3 Hz, 1H), 3.49 (d, *J* = 17.1 Hz, 1H), 2.55 (s, 3H), 2.43 - 2.33 (m, 2H), 2.30 (s, 3H), 2.09 - 1.97 (m, 2H).
155 Rac		CH_3	H		$R^{13} = CH_3$	478.4	
156 Isómero S		CF_3	H		$R^{11} = CH_3$ $R^{13} = CH_3$	540.1	

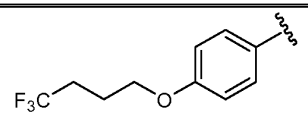
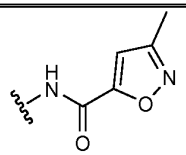
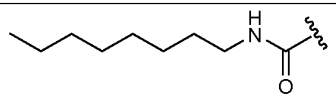
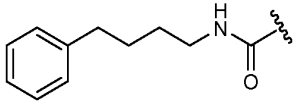
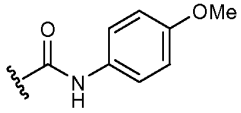
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
157 Isómero S		CF_3	H		$R^{13} = CH_3$	582.2	
158 Isómero S		CF_3	H		$R^{13} = CH_3$	613.2	
159 Rac		CF_3	F		$R^{13} = CH_3$	562.2	
160 Rac		CF_3	F	CN	$R^{13} = CH_3$	519.2	
161 Rac		CH_3	H		$R^{13} = CH_3$	464.3	
162 Rac		CF_3	F		$R^{13} = CH_3$	628.9	

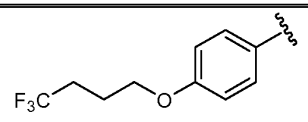
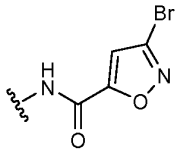
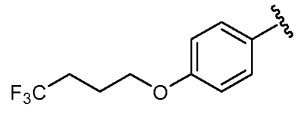
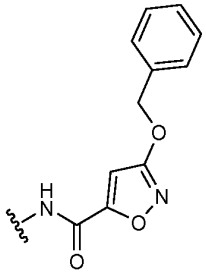
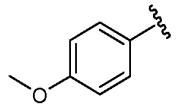
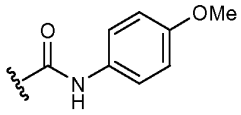
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
163 Rac		CF_3	F		$R^{13} = CH_3$	656.9	8.05 (s, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.25 - 7.16 (m, 6H), 7.02 - 6.94 (m, 2H), 6.82 - 6.73 (m, 2H), 6.60 (br. s., 1H), 4.01 (td, *J* = 6.1, 1.4 Hz, 2H), 3.75 (s, 3H), 2.35 (s, 3H), 2.24 - 2.10 (m, 2H), 1.93 - 1.85 (m, 2H), 1.83 - 1.74 (m, 2H), 1.67 (br. s., 3H)
164 Rac		CF_3	F		$R^{13} = CH_3$	671.0	
165 Isómero S		CF_3	H		$R^{13} = CH_3$	561.2	7.59 (d, *J* = 8.8 Hz, 2H), 7.42 - 7.36 (m, 2H), 7.35 - 7.28 (m, 4H), 7.20 - 7.16 (m, 3H), 7.06 - 6.99 (m, 4H), 6.98 - 6.93 (m, 2H), 3.66 (d,

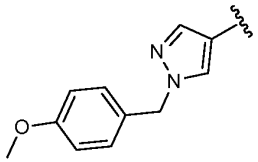
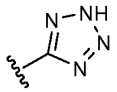
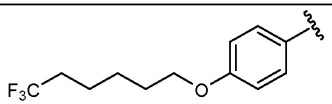
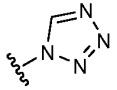
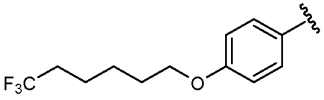
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							J = 17.3 Hz, 1H), 3.52 (d, *J* = 17.3 Hz, 1H), 2.30 (s, 3H).
166 Rac		CH_3	H		$R^{13} = CH_3$	492.2	
167 Isómero S		CF_3	H		$R^{13} = OHCF_2$	620.2	8.38 (d, *J* = 1.7 Hz, 1H), 7.61 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.34 - 7.24 (m, 2H), 7.13 - 7.04 (ab quartet, *J* = 8.8 Hz, 2H), 6.99 - 6.92 (m, 2H), 6.86 (s, 1H), 4.26 (br. s., 1H), 4.05 (t, *J* = 5.9 Hz, 2H), 3.69 (d, *J* = 17.1 Hz, 1H), 3.42 (d, *J* = 17.1 Hz, 1H), 2.41 - 2.27 (m, 2H), 2.10 - 1.97 (m, 2H).
168 Isómero S		CF_3	H		$R^{13} = CH_3$	611.2	

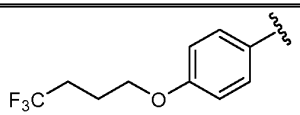
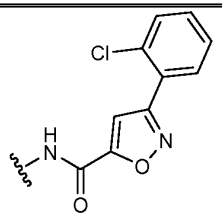
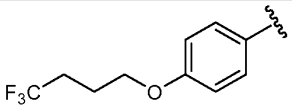
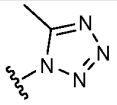
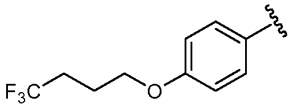
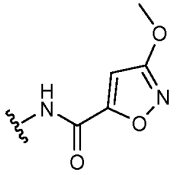
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
169 Isómero S		CF_3	H		$R^{13} = CH_3$	611.2	
170 Isómero S		CF_3	H		$R^{13} = CH_3$	629.2	
171 Isómero S		CF_3	H		$R^{13} = CH_3$	629.3	
172 Isómero S		CF_3	H		$R^{13} = OCH_3$	584.2	8.37 (d, *J* = 1.7 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.28 - 7.17 (m, 2H), 6.99 - 6.91 (m, 2H), 6.89 - 6.82 (m, 3H), 4.05 (t, *J* = 6.1 Hz, 2H), 3.78 (s, 3H), 3.68 (d, *J* = 16.8 Hz, 1H), 3.42 (d, *J* = 17.1 Hz, 1H), 2.45 - 2.23 (m, 2H), 2.10 - 1.98 (m, 2H).

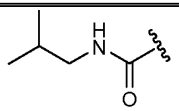
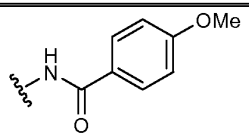
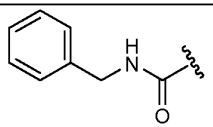
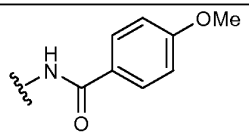
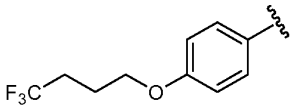
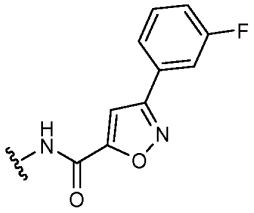
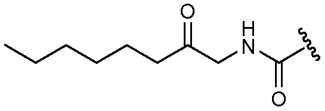
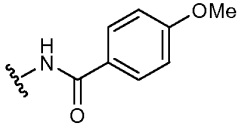
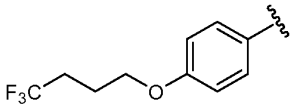
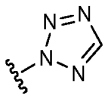
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
173 Rac		CH_3	H		$R^{13} = CH_3$	618.4	7.34 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 9.1 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.79 (d, *J* = 9.1 Hz, 2H), 3.76 (s, 3H), 3.43 - 3.37 (d, *J* = 17.5 Hz, 1H), 3.22 (t, *J* = 7.1 Hz, 2H), 2.86 - 2.80 (d, *J* = 17.2 Hz, 1H), 2.32 (s, 3H), 1.53 (s, 3H), 1.31 - 1.21 (m, 28H), 0.88 (t, *J* = 7.1 Hz, 3H)
174 Rac		CH_3	H		$R^{13} = CH_3$	506.4	
175 Rac		CH_3	H		$R^{13} = CH_3$	512.4	

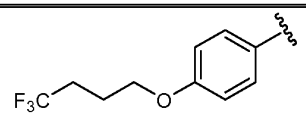
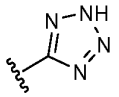
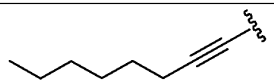
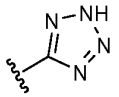
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
176 Isómero S		CF_3	H		$R^{13} = OCH_3$	598.2	7.54 (d, *J* = 8.8 Hz, 2H), 7.32 - 7.23 (m, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.73 (s, 1H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.76 (s, 3H), 3.71 (d, *J* = 17.1 Hz, 1H), 3.49 (d, *J* = 17.1 Hz, 1H), 2.45 - 2.32 (m, 2H), 2.31 - 2.26 (m, 3H), 2.08 - 1.97 (m, 2H).
177 Rac		CH_3	H	CN	$R^{13} = CH_3$	382.3	
178 Rac		CH_3	H		$R^{13} = CH_3$	526.4	

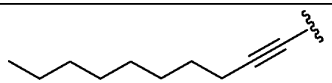
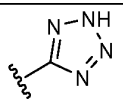
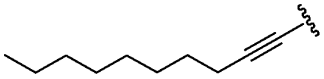
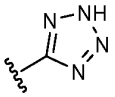
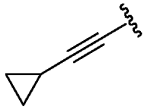
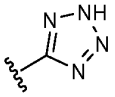
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
179 Isómero S		CF_3	H		$R^{13} = CH_3$	648.2	7.54 (d, *J* = 8.8 Hz, 2H), 7.23 - 7.11 (m, 4H), 7.03 - 6.93 (m, 3H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.72 (d, *J* = 16.9 Hz, 1H), 3.48 (d, *J* = 17.2 Hz, 1H), 2.44 - 2.32 (m, 2H), 2.30 (s, 3H), 2.08 - 1.97 (m, 2H).
180 Isómero S		CF_3	H		$R^{13} = CH_3$	674.3	
181 Rac		CF_3	F		$R^{13} = CH_3$	547.0	

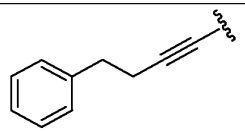
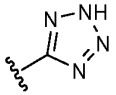
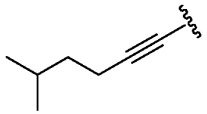
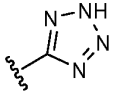
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
182 Rac		CF_3	H		$R^{13} = CH_3$	510.3	
183 Rac Isómero S		CF_3	H		$R^{13} = CH_3$	554.3	7.57 - 7.48 (m, 2H), 7.13 - 7.05 (m, 2H), 7.02 - 6.94 (m, 2H), 6.88 - 6.77 (m, 2H), 4.07 - 3.99 (m, 2H), 2.29 (s, 3H), 2.19 - 2.07 (m, 2H), 1.89 - 1.78 (m, 2H), 1.69 - 1.55 (m, 4H)
184 Isómero S		CF_3	H	CN	$R^{13} = CH_3$	511.1	7.46 (dd, *J* = 12.1, 8.5 Hz, 4H), 7.31 (d, *J* = 8.3 Hz, 2H), 6.95 (d, *J* = 9.1 Hz, 2H), 4.32 - 4.22 (m, 1H), 4.00 (s, 2H), 3.67 - 3.55 (m, 1H), 2.41 (s, 3H), 2.23 - 1.99 (m, 2H), 1.88 - 1.76 (m, 2H), 1.70 - 1.50 (m, 5H)

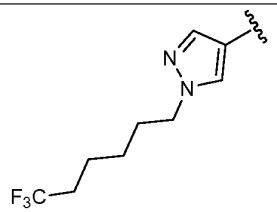
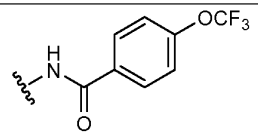
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
185 Isómero S		CF_3	H		$R^{13} = CH_3$	678.3	
186 Isómero S		CF_3	H		$R^{13} = CH_3$	540.3	
187 Isómero S		CF_3	H		$R^{13} = CH_3$	598.3	7.57 - 7.50 (m, *J* = 8.8 Hz, 2H), 7.21 - 7.12 (m, 4H), 7.01 - 6.94 (m, 2H), 6.48 (s, 1H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.95 (s, 3H), 3.71 (d, *J* = 17.1 Hz, 1H), 3.47 (d, *J* = 17.1 Hz, 1H), 2.44 - 2.32 (m, 2H), 2.30 (s, 3H), 2.07 - 1.98 (m, 2H).

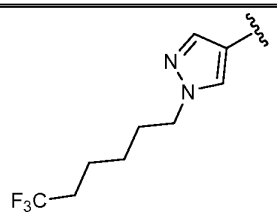
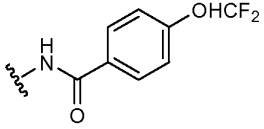
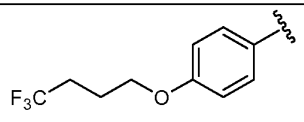
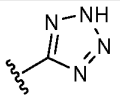
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
188 Rac		CH_3	H		$R^{13} = CH_3$	450.1	
189 Rac		CH_3	H		$R^{13} = CH_3$	484.1	
190 Isómero S		CF_3	H		$R^{13} = CH_3$	662.3	
191 Rac		CH_3	H		$R^{13} = CH_3$	520.2	
192 Isómero S		CF_3	H		$R^{13} = CH_3$	526.3	

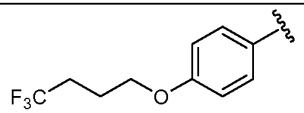
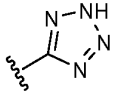
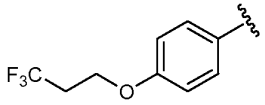
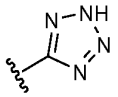
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
193 Isómero S		CF_3	H		$R^{13} = OCH_3$	542.1	^{1}H NMR (500 MHz, $CDCl_3$: MeOD (1:1)) δ 7.65 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 4.07 (t, *J* = 6.0 Hz, 2H), 3.77 (s, 3H), 3.69 (d, *J* = 17.7 Hz, 1H), 3.60 (d, *J* = 17.7 Hz, 1H), 2.41 - 2.28 (m, 2H), 2.06 (dq, *J* = 12.1, 6.3 Hz, 2H).
194 Rac		CF_3	H		$R^{13} = CH_3$	432.3	7.21 (d, *J* = 7.9 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.25 (s, 1H), 3.39 (d, *J* = 18.5 Hz, 1H), 3.34 (d, *J* = 18.9 Hz, 1H), 2.39 (s, 3H), 2.23 (t, *J* = 7.2 Hz, 2H), 1.55 - 1.47 (m, 2H), 1.40 - 1.23

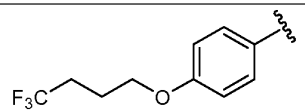
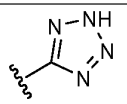
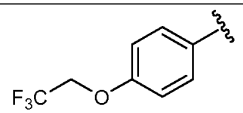
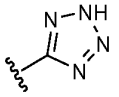
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							(m, 6H), 0.87 (t, *J* = 6.9 Hz, 3H).
195 Rac		CF_3	H		$R^{13} = CH_3$	460.4	7.21 (d, *J* = 7.9 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.32 (s, 1H), 3.37 (AB quartet, *J* = 18.7 Hz, 2H), 2.39 (s, 3H), 2.23 (t, *J* = 7.0 Hz, 2H), 1.51 (quin, *J* = 7.2 Hz, 2H), 1.39 - 1.20 (m, 10H), 0.91 - 0.84 (m, 3H).
196 Isómero R		CF_3	H		$R^{13} = CH_3$	460.4	7.17 (d, *J* = 7.9 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 6.74 (s, 1H), 3.43 - 3.32 (m, 2H), 2.37 (s, 3H), 2.23 (t, *J* = 7.0 Hz, 2H), 1.55 - 1.47 (m, 2H), 1.37 - 1.22 (m, 10H).
197 Isómero S		CF_3	H		$R^{13} = CH_3$	388.3	7.20 (d, *J* = 7.9 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 2H),

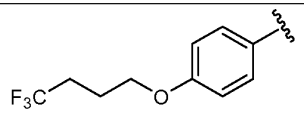
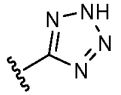
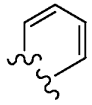
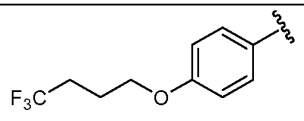
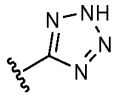
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							6.34 (s, 1H), 3.38, 3.32 (ABq, *J* = 18.9 Hz, 2H), 2.39 (s, 3H), 1.28 (tt, *J* = 8.3, 5.0 Hz, 1H), 0.89 - 0.83 (m, 2H), 0.76 - 0.71 (m, 2H).
198 Isómero S		CF_3	H		$R^{13} = CH_3$	452.3	7.30 - 7.23 (m, 2H), 7.22 - 7.13 (m, 5H), 6.99 (d, *J* = 8.1 Hz, 2H), 6.57 (s, 1H), 3.33 (d, *J* = 18.9 Hz, 1H), 3.26 (d, *J* = 18.9 Hz, 1H), 2.85 - 2.80 (m, 2H), 2.57 - 2.53 (m, 2H), 2.38 (s, 3H)
199 Isómero S		CF_3	H		$R^{13} = CH_3$	418.3	7.19 (d, *J* = 7.9 Hz, 2H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.68 (s, 1H), 3.38, 3.35 (ABq, *J* = 18.9 Hz, 2H), 2.37 (s, 3H), 2.24 (t, *J* = 7.4 Hz, 2H), 1.63 (dquin, *J* = 13.4,

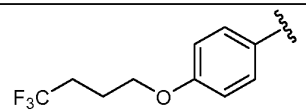
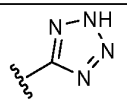
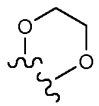
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							6.7 Hz, 1H), 1.41 (q, *J* = 7.3 Hz, 2H), 0.88 (d, *J* = 6.6 Hz, 6H)
200 Rac		CF_3	H		$R^{13} = CH_3$	663.2	9.63 (s, 1H), 7.62 (s, 1H), 7.54 (s, 1H), 7.50 (d, *J* = 8.9 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.87 (s, 1H), 4.13 (t, *J* = 7.2 Hz, 2H), 3.48 (d, *J* = 18.4 Hz, 1H), 3.25 (d, *J* = 18.4 Hz, 1H), 2.42 - 2.31 (m, 3H), 2.08 - 2.03 (m, 2H), 1.96 - 1.85 (m, 2H), 1.62 - 1.53 (m, 2H), 1.41 - 1.31 (m, 2H)

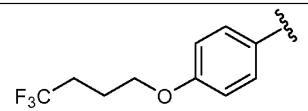
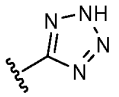
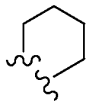
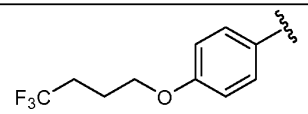
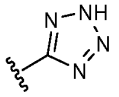
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
201 Rac		CF_3	H		$R^{13} = CH_3$	645.3	10.16 (s, 1H), 9.00 (s, 1H), 7.99 (s, 1H), 7.70 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 2H), 7.12 (t, *J* = 74.3 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 4.11 (t, *J* = 6.9 Hz, 2H), 3.41-3.37 (d, *J* = 17.4 Hz, 1H), 3.35 - 3.31 (d, *J* = 17.4 Hz, 1H), 2.28 (s, 3H), 2.23 - 2.17 (m, 2H), 1.85 - 1.75 (m, 2H), 1.52 - 1.44 (m, 2H), 1.31 - 1.22 (m, 2H).
202 Isómero S		CF_3	H		R^{13} = CH_2OCH_3	556.3	^{1}HNMR (500 MHz, DMSO-d_6) δ 9.57 (s, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.04 (d, *J* = 8.8

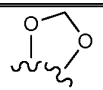
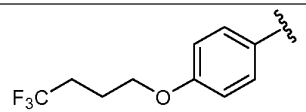
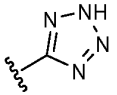
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							Hz, 2H), 6.99 (d, *J* = 7.9 Hz, 2H), 4.36 (s, 2H), 4.09 (t, *J* = 6.1 Hz, 2H), 3.75 (d, *J* = 17.5 Hz, 1H), 3.69 (d, *J* = 17.5 Hz, 1H), 3.27 (s, 3H), 2.48 - 2.37 (m, 2H), 2.01 - 1.89 (m, 2H)
203 Isómero S		CF_3	H		R^{12} = F R^{13} = OCH_2CH_3	574.3	
204 Isómero S		CF_3	H		$R^{13} = CH_3$	512.1	^{1}H NMR (500 MHz, MeOD:$CDCl_3$ (1:1)) δ 7.61 (s, 2H), 7.55 (d, *J* = 8.6 Hz, 2H), 6.97 (dd, *J* = 10.4, 8.3 Hz, 4H), 6.84 (d, *J* = 8.1 Hz, 2H), 4.24 (t, *J* = 6.4 Hz, 2H), 3.71 (d, *J* = 17.2 Hz, 1H), 3.50 (d, *J* = 17.2 Hz, 1H),

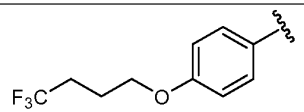
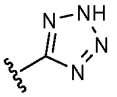
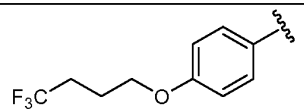
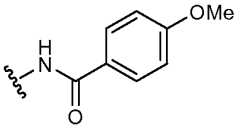
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							3.08 - 3.03 (m, 4H), 2.67 (qt, *J* = 10.8, 6.3 Hz, 2H), 1.78 (dq, *J* = 11.3, 5.5 Hz, 4H), 1.69 (q, *J* = 5.9 Hz, 2H).
205 Isómero S		CF_3	H		$R^{13} = OCHF_2$	578.1	^{1}H NMR (500 MHz, $CDCl_3$: MeOD (1:1)) δ 7.61 (s, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.05 - 6.96 (m, 5H), 6.66 (t, *J* = 73.4 Hz, 1H), 4.07 (t, *J* = 6.0 Hz, 2H), 3.70 (d, *J* = 17.9 Hz, 1H), 3.57 (d, *J* = 17.8 Hz, 1H), 2.41 - 2.28 (m, 2H), 2.11 - 2.02 (m, 2H).
206 Isómero S		CF_3	H		$R^{13} = CH_3$	498.1	^{1}H NMR (500 MHz, MeOD-$CDCl_3$ (1:1)) δ 7.60 - 7.57 (m, 2H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 1H), 4.48 (q, *J* = 8.2 Hz,

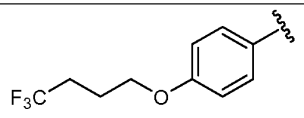
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							1H), 3.70 (d, *J* = 17.8 Hz, 1H), 3.58 (d, *J* = 17.8 Hz, 1H), 2.30 (s, 1H).
207 Isómero S		CF_3	H		R^{12} R^{13} = 	562.1	^{1}H NMR (500 MHz, $CDCl_3$: MeOD (1:1)) δ 7.81 - 7.73 (m, 2H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.61 (s, 1H), 7.60 - 7.55 (m, 3H), 7.53 - 7.46 (m, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.98 (dd, *J* = 8.5, 1.8 Hz, 1H), 4.08 (t, *J* = 6.0 Hz, 2H), 3.83 (d, *J* = 17.8 Hz, 1H), 3.70 (d, *J* = 17.8 Hz, 1H), 2.41 - 2.28 (m, 2H), 2.11 - 2.01 (m, 2H).
208 Isómero S		CF_3	H		R^{13} = OCH_2CH_3	556.1	^{1}H NMR (500 MHz, CDCl3: MeOD (1:1)) δ 7.62 (s, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J*

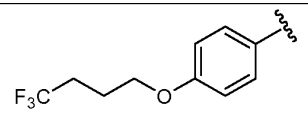
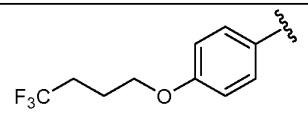
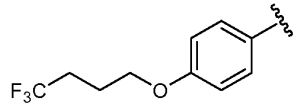
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							= 8.7 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 4.07 (t, *J* = 6.0 Hz, 2H), 4.00 (q, *J* = 7.0 Hz, 2H), 3.68 (d, *J* = 17.8 Hz, 1H), 3.59 (d, *J* = 17.7 Hz, 1H), 2.40 - 2.28 (m, 2H), 2.10 - 2.01 (m, 2H), 1.38 (t, *J* = 7.0 Hz, 3H).
209 Isómero S		CF_3	H		R^{12} R^{13} = 	570.2	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.57 (d, *J* = 2.2 Hz, 1H), 6.41 (dd, *J* = 8.5, 2.2 Hz, 1H), 4.25 - 4.14 (m, 4H), 4.06 (t, *J* = 6.2 Hz, 2H), 3.68 (d, *J* = 18.2 Hz, 1H), 3.63 (d, *J* = 18.5 Hz, 1H), 2.42 (ddd,

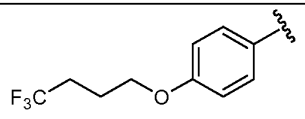
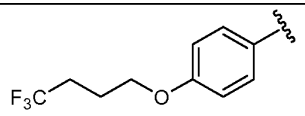
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							J = 16.4, 8.0, 5.1 Hz, 2H), 1.93 (dq, *J* = 12.3, 6.4 Hz, 2H).
210 Isómero S		CF_3	H		R^{12} R^{13} = 	566.1	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.42 (s, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.80 (s, 1H), 6.56 (d, *J* = 7.7 Hz, 1H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.67 (d, *J* = 17.8 Hz, 1H), 3.60 (d, *J* = 17.9 Hz, 1H), 2.61 (s, 2H), 2.56 (s, 2H), 2.42 (ddd, *J* = 11.4, 8.3, 5.2 Hz, 2H), 1.98 - 1.88 (m, 2H), 1.65 (p, *J* = 2.8 Hz, 4H).
211 Isómero S		CF_3	H		R^{12} R^{13} =	556.2	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.37 (s, 1H), 7.60 (d, *J*

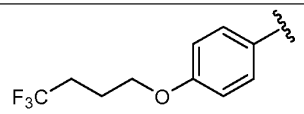
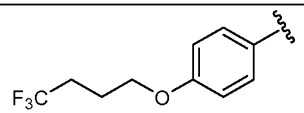
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							= 8.5 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.57 (s, 1H), 6.48 (d, *J* = 8.1 Hz, 1H), 5.97 (d, *J* = 3.1 Hz, 2H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.65 (d, *J* = 17.6 Hz, 1H), 3.58 (d, *J* = 17.7 Hz, 1H), 2.46 - 2.35 (m, 2H), 1.93 (dd, *J* = 9.9, 5.4 Hz, 2H).
212 Isómero S		CF_3	H		R^{11} R^{12} =  $R^{13} = OCH_3$	582.3	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.30 (s, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.71 (d, *J* = 8.2 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 4.12 - 4.01 (m, 2H), 3.70 (s, 3H), 3.67 (m, 1H), 3.60 (d, *J* = 17.4 Hz, 1H),

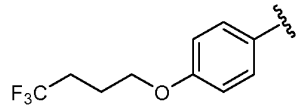
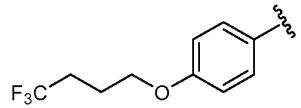
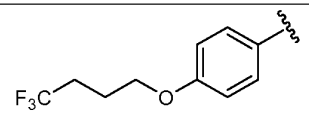
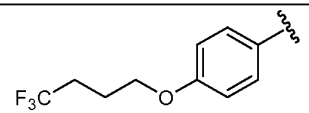
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							2.67 - 2.55 (m, 2H), 2.46 - 2.35 (m, 2H), 2.31 - 2.07 (m, 2H), 1.97 - 1.91 (m, 2H), 1.81 - 1.69 (m, 2H).
213 Isómero S		CHF_2	H		$R^{13} = CH_3$	508.3	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.10 (s, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 7.8 Hz, 2H), 7.02 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 7.9 Hz, 2H), 6.33 (t, J = 55.0 Hz, 1H), 4.07 (t, J = 6.2 Hz, 2H), 3.57 (d, J = 17.9 Hz, 1H), 3.41 (d, J = 18.2 Hz, 1H), 2.44 (ddd, J = 11.4, 8.1, 5.2 Hz, 2H), 1.99 - 1.91 (m, 2H).
214 Isómero R		H	H		$R^{13} = CH_3$	539.4	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.06 (s, 1H), 7.42 (d, J = 8.6 Hz,

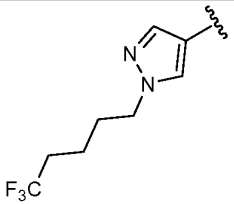
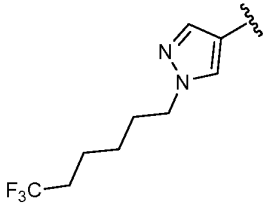
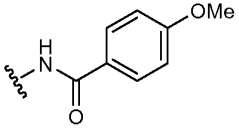
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							2H), 7.36 (dd, *J* = 10.3, 8.2 Hz, 4H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 4.82 - 4.73 (m, 1H), 4.05 (t, *J* = 6.2 Hz, 2H), 3.83 - 3.72 (m, 1H), 3.71 (s, 3H), 2.88 (qd, *J* = 17.0, 7.6 Hz, 1H), 2.48 - 2.35 (m, 2H), 2.25 (s, 3H), 1.94 (dq, *J* = 12.5, 6.4 Hz, 2H).
215 Isómero S		CF_3	H	CN	$R^{12} = CH_3$ $R^{13} = OCH_3$	513.1	^{1}H NMR (500 MHz, MeOD) δ 7.61 (s, 1H), 7.58 (s, 1H), 7.54 - 7.41 (m, 1H), 7.30 (dd, J = 8.4, 2.0 Hz, 1H), 7.22 (s, 1H), 7.03 (d, J = 9.4 Hz, 1H), 6.96 (d, J = 8.9 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 4.32 (s,

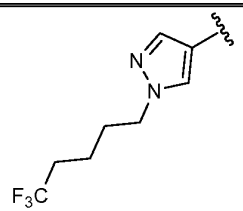
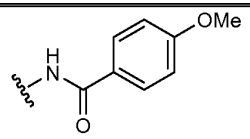
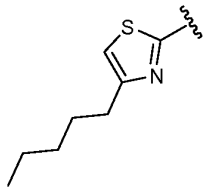
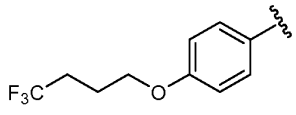
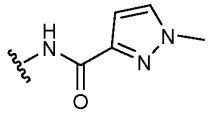
Example	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							2H), 4.10 - 4.03 (m, 2H), 3.86 (s, 2H), 3.67 - 3.55 (m, 1H), 2.40 - 2.27 (m, 2H), 2.27 - 2.23 (m, 1H), 2.22 (s, 2H), 2.10 - 2.00 (m, 2H)
216 S-isomer		CF_3	H	CN	$R^{12} = OCH_3$ $R^{13} = OCH_3$	529.1	
217 S-isomer		CF_3	H	CN	$R^{12} = CH_3$ $R^{13} = CH_3$	497.1	^{1}H NMR (500 MHz, MeOD) δ 7.61 (s, 1H), 7.49 - 7.43 (m, 2H), 7.35 - 7.23 (m, 3H), 6.99 - 6.94 (m, 2H), 4.32 (s, 2H), 4.06 (t, J = 5.9 Hz, 2H), 3.61 (s, 2H), 2.38 - 2.33 (m, 2H), 2.31 - 2.28 (m, 1H), 2.09 - 2.01 (m, 2H)
218 S-isomer		CF_3	H	CN	$R^{12} = F$ $R^{13} = OCH_3$	517.1	^{1}H NMR (500 MHz, MeOD) δ 7.49 - 7.43 (m, 3H), 7.40 (dd, J = 11.9, 2.0 Hz, 1H),

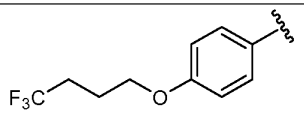
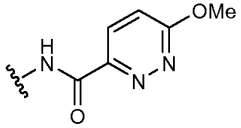
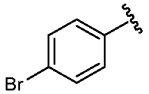
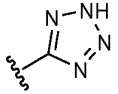
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							7.14 (t, J = 8.4 Hz, 1H), 7.00 - 6.93 (m, 2H), 4.32 (s, 2H), 4.05 (t, J = 5.9 Hz, 2H), 3.96 (s, 3H), 3.61 (d, J = 3.0 Hz, 2H), 2.39 - 2.27 (m, 2H), 2.09 - 2.01 (m, 2H)
219 Isómero S		CF_3	H	CN	R^{12} = F R^{13} = CH_3	501.1	^{1}H NMR (500 MHz, MeOD) δ 7.49 - 7.43 (m, 2H), 7.39 - 7.32 (m, 1H), 7.30 - 7.21 (m, 2H), 7.00 - 6.93 (m, 2H), 4.29 (s, 1H), 4.08 - 4.04 (m, 2H), 3.60 (d, J = 2.0 Hz, 2H), 2.35 (d, J = 5.4 Hz, 1H), 2.32 - 2.28 (m, 1H), 2.09 - 2.00 (m, 2H)
220 Isómero S		CF_3	H	CN	R^{11} = F R^{13} = Cl	521.0	^{1}H NMR (500 MHz, MeOD) δ 7.48 - 7.43 (m, 2H), 7.36 - 7.28 (m, 3H), 7.00 - 6.95 (m,

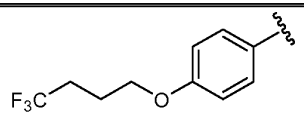
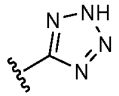
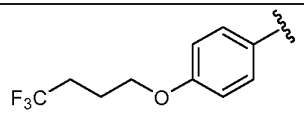
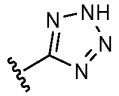
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							2H), 4.07 (t, J = 5.9 Hz, 2H), 3.59 (q, J = 1.0 Hz, 2H), 2.40 - 2.28 (m, 2H), 2.10 - 2.02 (m, 2H)
221 Isómero S		CF_3	H	CN	$R^{12} = CH_3$ $R^{13} = Cl$	517.1	^{1}H NMR (500 MHz, MeOD) δ 7.61 (s, 1H), 7.58 (s, 1H), 7.54 - 7.41 (m, 1H), 7.30 (dd, J = 8.4, 2.0 Hz, 1H), 7.22 (s, 1H), 7.03 (d, J = 9.4 Hz, 1H), 6.96 (d, J = 8.9 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 4.32 (s, 2H), 4.10 - 4.03 (m, 2H), 3.86 (s, 2H), 3.67 - 3.55 (m, 1H), 2.40 - 2.27 (m, 2H), 2.27 - 2.23 (m, 1H), 2.22 (s, 2H), 2.10 - 2.00 (m, 2H)
222 Isómero S		CF_3	H	CN	$R^{12} = Cl$ $R^{13} = Cl$	539.0	

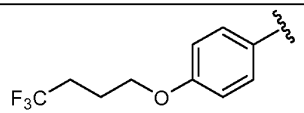
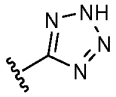
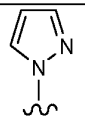
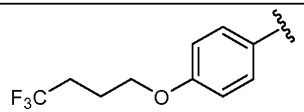
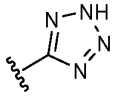
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
223 Isómero S		CF_3	H	CN	R^{11} = Cl R^{13} = OCH_3	532.8	
224 Isómero S		CF_3	H	CN	R^{13} = CN	493.9	
225 Isómero S		CF_3	H	CN	R^{13} = $NHSO_2CH_3$	562.1	
226 Isómero S		CF_3	H	CN	R^{11} = Cl R^{13} = OCH_2CH_3	547.1	^{1}H NMR (500 MHz, MeOD) δ 7.61 - 7.58 (m, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.06 - 7.00 (m, 2H), 7.00 - 6.95 (m, 2H), 6.89 (dd, J = 8.4, 2.5 Hz, 1H), 4.11 - 4.04 (m, 4H), 3.66 (d, J = 18.3 Hz, 1H), 3.43 (d, J = 18.3 Hz, 1H), 2.40 - 2.28 (m, 2H), 2.10 - 2.02 (m, 2H), 1.45 - 1.39 (m, 3H)

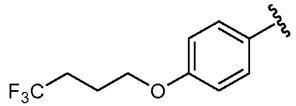
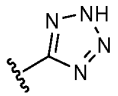
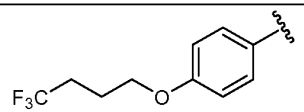
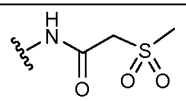
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
227 Rac		CF_3	H	CN	$R^{13} = CH_3$	471.2	
228 Rac		CF_3	H		$R^{13} = CH_3$	609.2	7.86 (s, 1H), 7.66 (s, 1H), 7.37 (d, J = 8.25 Hz, 2H), 7.26 (d, J = 9.08 Hz, 2H), 7.21 (d, J = 7.98 Hz, 2H), 6.82 (d, J = 9.08 Hz, 2H), 4.18 (t, J = 6.88 Hz, 2H), 3.76 (s, 3H), 3.58 (d, J = 17.33 Hz, 1H), 3.35 (d, J = 17.33 Hz, 1H), 2.34 (s, 3H), 2.13 (m, 2H), 1.89 (m, 2H), 1.57 (m, 2H), 1.35 (m, 2H).

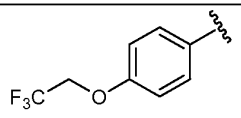
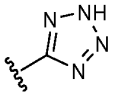
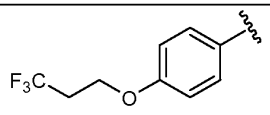
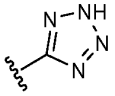
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
229 Rac		CF_3	H		$R^{13} = CH_3$	595.2	
230 Rac		CF_3	H	CN	$R^{13} = CH_3$	434.0	
231 Isómero S		CF_3	H		$R^{13} = CH_3$	581.4	^{1}H NMR (500 MHz, DMSO-d_6) δ 10.43 (s, 1H), 9.23 (s, 1H), 7.54 (d, J = 8.80 Hz, 2H), 7.48 (d, J = 1.65 Hz, 1H), 7.29 (d, J = 7.98 Hz, 2H), 7.15 (d, J = 7.98 Hz, 2H), 7.00 (d, J = 8.80 Hz, 2H), 6.34 (d, J = 1.93 Hz, 1H), 4.07 (t, J = 6.05 Hz, 2H), 3.67 (s, 3H), 3.48 (d, J

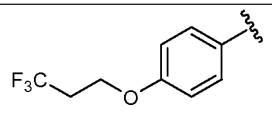
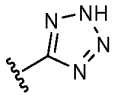
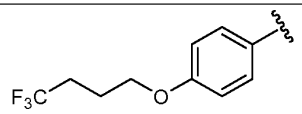
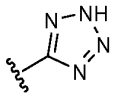
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							= 17.06 Hz, 1H), 3.39 (d, J = 17.06 Hz, 1H), 2.43 (m, 2H), 2.27 (s, 3H), 1.95 (m, 2H).
232 Isómero S		CF_3	H		$R^{13} = CH_3$	609.1	8.13 (d, J = 9.63 Hz, 1H), 7.54 (d, J = 8.80 Hz, 2H), 7.26 (d, J = 8.25 Hz, 2H), 7.23 (d, J = 9.63 Hz, 1H), 7.17 (d, J = 7.99 Hz, 2H), 6.99 (d, J = 9.08 Hz, 2H), 4.07 (t, J = 6.05 Hz, 2H), 4.01 (s, 3H), 3.67 (d, J = 17.33 Hz, 1H), 3.53 (d, J = 17.06 Hz, 1H), 2.37 (m, 2H), 2.29 (s, 3H), 2.03 (m, 2H).
233 Isómero S		CF_3	H		$R^{13} = CH_3$	479.8	

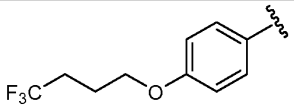
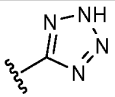
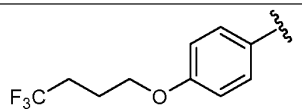
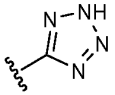
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
234 Isómero S		CF_3	H		R^{13} = Br	589.9	7.54 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 6.97 (dd, *J* = 8.7, 2.3 Hz, 4H), 6.85 (br. s., 1H), 4.04 (t, *J* = 5.8 Hz, 2H), 3.69 - 3.59 (m, 1H), 3.56 - 3.46 (m, 1H), 2.40 - 2.26 (m, 2H), 2.08 (dd, *J* = 9.4, 6.1 Hz, 2H).
235 Isómero S		CF_3	H		R^{13} = 		^{1}H NMR (500 MHz, DMSO) δ 9.55 (br. s., 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.98 - 6.92 (m, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 4.07 (t, *J* = 6.1 Hz, 2H), 3.80 - 3.61 (m, 2H), 2.46 - 2.29 (m, 2H), 2.00 - 1.90 (m, 2H), 1.89 - 1.79 (m, 1H), 1.00 - 0.88 (m, 2H), 0.69 -

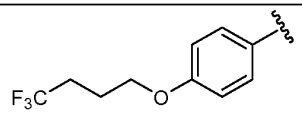
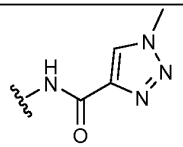
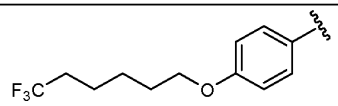
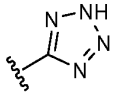
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							0.54 (m, 2H).
236 Isómero S		CF_3	H			578.0	^{1}H NMR (500MHz, DMSO) δ 9.42 (br. s., 1H), 8.47 (d, *J* = 2.5 Hz, 1H), 7.73 (d, *J* = 1.1 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 1.9 Hz, 1H), 4.08 (t, *J* = 6.2 Hz, 2H), 3.78 - 3.63 (m, 2H), 2.46 - 2.34 (m, 2H), 2.02 - 1.86 (m, 2H).
237 Isómero S		CF_3	H		R^{12} R^{13} = 	554.0	^{1}H NMR (500MHz, DMSO) δ 9.42 (br. s., 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.97 (s, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 6.59

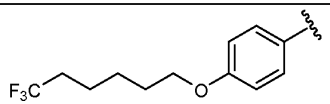
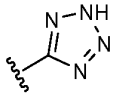
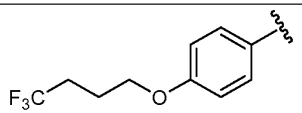
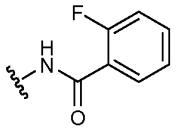
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							(d, *J* = 8.3 Hz, 1H), 4.50 (t, *J* = 8.7 Hz, 2H), 4.07 (t, *J* = 6.2 Hz, 2H), 3.65 (br. s., 2H), 3.06 (t, *J* = 8.7 Hz, 2H), 2.47 - 2.34 (m, 2H), 2.00 - 1.89 (m, 2H).
238 Isómero S		CF_3	H		R^{13} = 	555.1	^{1}H NMR (500 MHz, DMSO) δ 9.41 (br. s., 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 6.52 (d, *J* = 8.8 Hz, 2H), 4.06 (t, *J* = 5.9 Hz, 2H), 3.75 - 3.55 (m, 2H), 2.89 (s, 6H), 2.42 (dd, *J* = 16.5, 11.0 Hz, 2H), 2.02 - 1.84 (m, 2H).
239 Isómero S		CF_3	H		$R^{13} = CH_3$	593.3	^{1}H NMR (400 MHz, MeOD) δ 7.52 (d, *J* = 8.8 Hz, 2H), 7.24 - 7.15 (m, 4H), 6.96 (d,

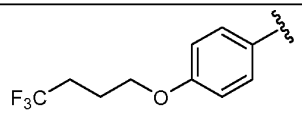
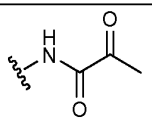
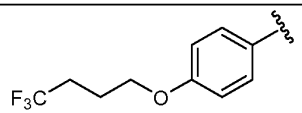
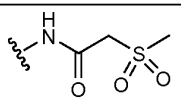
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							J = 8.8 Hz, 2H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.97 (s, 2H), 3.67 (d, *J* = 16.9 Hz, 1H), 3.43 (d, *J* = 16.9 Hz, 1H), 2.93 (s, 3H), 2.44 - 2.28 (m, 5H), 2.09 - 1.96 (m, 2H).
240 Isómero S		CF_3	H		$R^{13} = OCH_3$	514.3	^{1}H NMR (400 MHz, MeOD) δ 7.65 (d, *J* = 9.0 Hz, 2H), 7.13 - 7.08 (m, 2H), 6.97 - 6.93 (m, 2H), 6.84 - 6.78 (m, 2H), 4.57 (q, *J* = 8.4 Hz, 2H), 3.75 (s, 3H), 3.72 (d, *J* = 2.4 Hz, 2H).
241 Isómero S		CF_3	H		$R^{13} = OCH_3$	528.3	^{1}H NMR (400 MHz, MeOD) δ 7.61 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H),

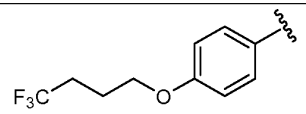
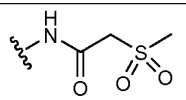
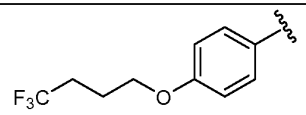
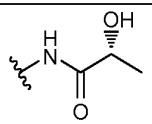
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							4.25 (t, *J* = 6.1 Hz, 2H), 3.76 (s, 3H), 3.71 (d, *J* = 1.5 Hz, 2H), 2.77 - 2.63 (m, 2H).
242 Isómero S		CF_3	H		$R^{13} = OCF_3$	582.2	^{1}H NMR (400 MHz, MeOD) δ 7.62 (d, *J* = 8.8 Hz, 2H), 7.23 - 7.17 (m, 2H), 7.14 - 7.09 (m, 2H), 7.08 - 7.02 (m, 2H), 4.26 (t, *J* = 6.2 Hz, 2H), 3.83 - 3.66 (m, 2H), 2.77 - 2.63 (m, 2H).
243 Isómero S		CF_3	H		$R^{13} = OCF_3$	596.3	^{1}H NMR (400 MHz, MeOD) δ 7.61 (d, *J* = 8.8 Hz, 2H), 7.22 - 7.17 (m, 2H), 7.15 - 7.09 (m, 2H), 7.06 - 7.00 (m, 2H), 4.08 (t, *J* = 6.1 Hz, 2H), 3.82 - 3.65 (m, 2H), 2.44 - 2.30 (m, 2H), 2.09 - 1.99 (m, 2H).

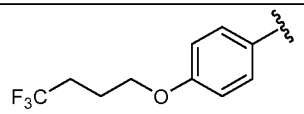
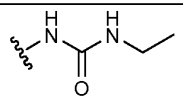
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
244 Isómero S		CF_3	H		$R^{13} = OCH_3$	556.3	^{1}H NMR (400 MHz, MeOD) δ 7.58 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.04 (t, *J* = 6.1 Hz, 2H), 3.76 (s, 3H), 3.70 (d, *J* = 1.3 Hz, 2H), 2.31 - 2.17 (m, 2H), 1.92 - 1.83 (m, 2H), 1.80 - 1.70 (m, 2H).
245 Isómero S		CF_3	H		R^{13} = $OCHCF_2$	592.1	^{1}H NMR (400 MHz, MeOD) δ 7.59 (d, *J* = 8.6 Hz, 2H), 7.05 (s, 4H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.87 (t, *J* = 74.6 Hz, 1H), 4.04 (t, *J* = 6.1 Hz, 2H), 3.74, 3.70 (ABq, *J* = 18.0 Hz, 2H), 2.31 - 2.17 (m, 2H), 1.92 - 1.84 (m, 2H),

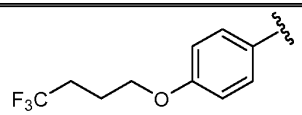
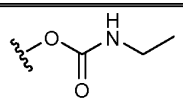
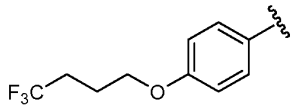
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							1.80 - 1.70 (m, 2H)
246 Isómero S		CF_3	H		$R^{13} = CH_3$	582.3	^{1}H NMR (400 MHz, MeOD) δ 8.18 (s, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.25 - 7.19 (m, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 4.09 (s, 3H), 4.07 - 4.03 (m, 2H), 3.71 (d, *J* = 16.9 Hz, 1H), 3.48 (d, *J* = 16.9 Hz, 1H), 2.44 - 2.31 (m, 2H), 2.28 (s, 3H), 2.08 - 1.98 (m, 2H).
247 Isómero S		CF_3	H		$R^{13} = OCH_3$	570.1	^{1}H NMR (400 MHz, MeOD) δ 7.57 (d, *J* = 8.8 Hz, 2H), 7.03 - 6.92 (m, 4H), 6.84 - 6.79 (m, 2H), 4.02 (t, *J* = 6.3 Hz, 2H), 3.76 (s, 3H), 3.70 (d, *J* = 1.5 Hz, 2H), 2.25 -

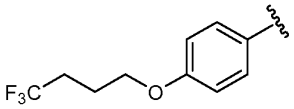
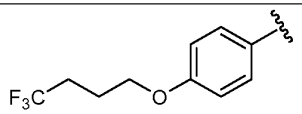
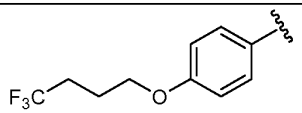
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							2.11 (m, 2H), 1.87 - 1.77 (m, 2H), 1.69 - 1.53 (m, 4H).
248 Isómero S		CF_3	H		R^{13} = $OCHCF_2$	606.3	^{1}H NMR (400 MHz, MeOD) δ 7.61 (d, *J* = 8.8 Hz, 2H), 7.08 (s, 4H), 7.05 - 7.01 (m, *J* = 9.0 Hz, 2H), 6.90 (t, *J* = 73.7 Hz, 1H), 4.05 (t, *J* = 6.2 Hz, 2H), 3.76, 3.73 (ABq, *J* = 18.5 Hz, 2H), 2.28 - 2.14 (m, 2H), 1.89 - 1.81 (m, 2H), 1.72 - 1.56 (m, 4H)
249 Isómero S		CF_3	H		$R^{13} = CH_3$	595.3	^{1}H NMR (400 MHz, MeOD) δ 7.62 - 7.53 (m, 3H), 7.51 - 7.45 (m, 1H), 7.27 - 7.09 (m, 6H), 7.01 - 6.95 (m, 2H), 4.07 (t, *J* = 6.1 Hz, 2H), 3.71 (d, *J* = 16.9 Hz, 1H), 3.48 (d, *J* = 16.9 Hz, 1H), 2.43 - 2.29

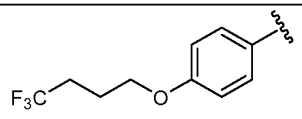
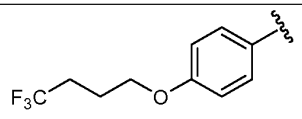
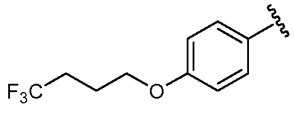
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							(m, 5H), 2.08 - 1.98 (m, 2H).
250 Isómero S		CF_3	H		$R^{13} = CH_3$	543.4	8.35 (br. s., 1H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.18 - 7.13 (m, 2H), 7.11 - 7.06 (m, 2H), 6.96 - 6.90 (m, 2H), 6.30 (s, 1H), 4.03 (t, *J* = 5.9 Hz, 2H), 3.61 (d, *J* = 17.2 Hz, 1H), 3.38 (d, *J* = 17.4 Hz, 1H), 2.41 - 2.25 (m, 8H), 2.11 - 2.02 (m, 2H).
251 Isómero S		CF_3	H		R^{13} = $OCHCF_2$	645.4	^{1}H NMR (400 MHz, MeOD) δ 7.52 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 7.04 - 6.63 (m, 1H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.98 (s, 2H), 3.69 (d, *J* = 16.9 Hz, 1H),

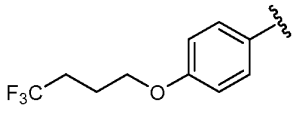
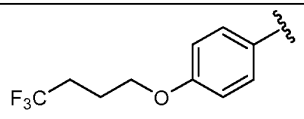
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							3.45 (d, *J* = 16.9 Hz, 1H), 2.93 (s, 3H), 2.44 - 2.29 (m, 2H), 2.09 - 1.98 (m, 2H).
252 Isómero S		CF_3	H		$R^{13} = OCH_3$	623.3	^{1}H NMR (400 MHz, MeOD) δ 7.51 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 9.0 Hz, 2H), 6.98 - 6.88 (m, 4H), 4.02 (t, *J* = 6.1 Hz, 2H), 3.99 (s, 2H), 3.79 (s, 3H), 3.66 (d, *J* = 16.9 Hz, 1H), 3.44 (d, *J* = 16.7 Hz, 1H), 2.97 (s, 3H), 2.30 - 2.16 (m, 2H), 1.90 - 1.81 (m, 2H), 1.79 - 1.69 (m, 2H).
253 Isómero S		CF_3	H		$R^{13} = CH_3$	545.4	^{1}H NMR (400 MHz, MeOD) δ 7.56 (d, *J* = 8.8 Hz, 2H), 7.22 - 7.17 (m, 4H), 7.03 - 6.96 (m, 2H), 4.09 (t, *J* = 6.1

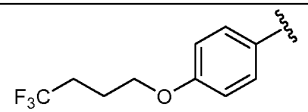
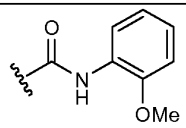
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							Hz, 2H), 4.02 (q, *J* = 6.8 Hz, 1H), 3.66 (d, *J* = 17.2 Hz, 1H), 3.47 (d, *J* = 16.9 Hz, 1H), 2.46 - 2.32 (m, 5H), 2.10 - 2.00 (m, 2H), 1.19 (d, *J* = 6.8 Hz, 3H).
254 Isómero S		CF_3	H		R^{13} = $OCHCF_2$	596.2	^{1}H NMR (400 MHz, MeOD) δ 7.53 (d, *J* = 8.8 Hz, 2H), 7.39 - 7.33 (m, 2H), 7.11 (d, *J* = 8.6 Hz, 2H), 7.00 - 6.95 (m, 2H), 7.02 - 6.63 (m, 1H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.65 (d, *J* = 16.9 Hz, 1H), 3.42 (d, *J* = 16.7 Hz, 1H), 2.96 (q, *J* = 7.3 Hz, 2H), 2.43 - 2.28 (m, 2H), 2.07 - 1.97 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H).

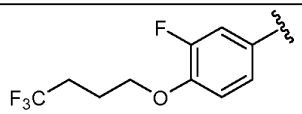
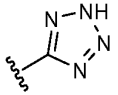
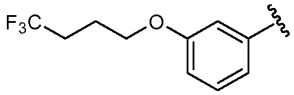
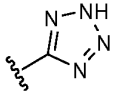
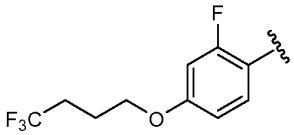
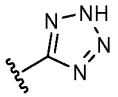
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
255 Isómero S		CF_3	H		$R^{13} = CH_3$	545.3	^{1}H NMR (400 MHz, MeOD) δ 7.53 (d, *J* = 8.8 Hz, 2H), 7.29 - 7.22 (m, 2H), 7.21 - 7.14 (m, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 4.06 (t, *J* = 6.2 Hz, 2H), 3.66 (d, *J* = 16.9 Hz, 1H), 3.45 (d, *J* = 16.7 Hz, 1H), 3.07 (q, *J* = 7.2 Hz, 2H), 2.45 - 2.29 (m, 5H), 2.02 (dd, *J* = 10.2, 5.8 Hz, 2H), 1.06 (t, *J* = 7.2 Hz, 3H).
256 Isómero S		CF_3	H	CN	$R^{11} = F$ $R^{13} = CH_3$	501.1	^{1}H NMR (400 MHz, MeOD) δ 1.96 - 2.13 (m, 2 H) 2.24 - 2.39 (m, 2 H) 2.41 (s, 3 H) 3.49 - 3.68 (m, 2 H) 3.75 (s, 1 H) 4.06 (t, *J* = 5.95 Hz, 2 H) 4.33 (s, 1 H) 6.97 (d, *J* = 1.00 Hz, 2 H) 7.00 - 7.14 (m,

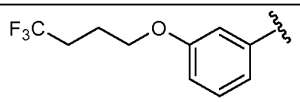
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							2 H) 7.24 (t, *J* = 7.68 Hz, 1 H) 7.45 (d, *J* = 1.00 Hz, 2 H) 7.61 (s, 1 H)
257 Isómero S		CF_3	H	CN	R^{13} = $NHCO_2Me$	541.5	
258 Isómero S		CF_3	H	CN	R^{12} = Cl R^{13} = OCH_3	533.1	
259 Isómero S		CF_3	H	CN	R^{12} = Cl R^{13} = CH_3	[M-H] 515.0	^{1}H NMR (500 MHz, MeOD) δ 2.05 (m, *J* = 9.90, 5.90 Hz, 2 H) 2.22 - 2.41 (m, 2 H) 2.24 - 2.42 (m, 2 H) 2.43 (s, 2 H) 3.62 (br. s., 1 H) 4.06 (t, *J* = 5.95 Hz, 2 H) 4.29 - 4.48 (m, 2 H) 6.98 (d, *J* = 8.92 Hz, 1 H) 7.40 (br. s., 1 H) 7.47 (d, *J* = 8.42 Hz, 1 H) 7.54 (s, 1 H) 7.63 (br. s., 1

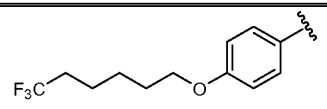
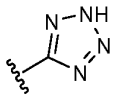
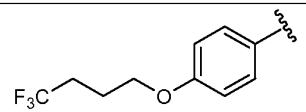
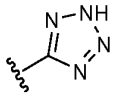
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							H)
260 Isómero S		CF_3	H	CN	R^{13} = CH_2OCH_3	513.1	^{1}H NMR (500 MHz, MeOD) δ 1.97 - 2.11 (m, 2 H) 2.33 (m, *J* = 5.40 Hz, 2 H) 3.43 (s, 3 H) 3.63 (s, 2 H) 4.06 (t, *J* = 5.95 Hz, 2 H) 4.53 (s, 2 H) 6.97 (d, *J* = 1.00 Hz, 2 H) 7.47 (d, *J* = 8.42 Hz, 4 H) 7.55 (d, *J* = 7.93 Hz, 2 H) 7.60 (s, 1 H)
261 Isómero S		CF_3	H	CN	R^{12} = F R^{13} = OCF_3	571.1	
262 Isómero S		CF_3	H	CN	R^{12} = OCH_3 R^{13} = CH_3	513.1	^{1}H NMR (500 MHz, MeOD) δ 1.95 - 2.12 (m, 2 H) 2.25 (s, 3 H) 2.27 - 2.44 (m, 2 H) 3.63 (d, *J* = 2.48 Hz, 2 H) 3.87 (s, 3 H) 4.05 (t, *J* = 5.95 Hz, 2 H) 6.97 (m, *J* = 8.92

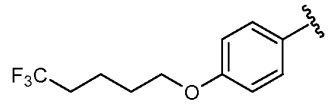
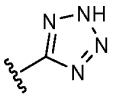
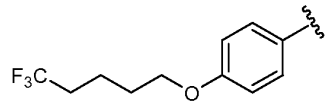
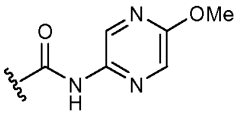
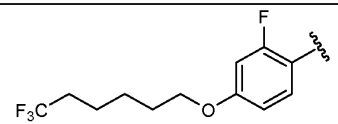
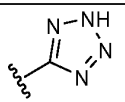
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							Hz, 2 H) 7.08 (d, *J* = 1.49 Hz, 1 H) 7.24 (s, 1 H) 7.47 (m, *J* = 8.92 Hz, 2 H) 7.60 (s, 1 H)
263 Isómero S		CF_3	H	CN	R^{12} = Cl R^{13} = OCH_2CH_3	547.1	^{1}H NMR (500 MHz, MeOD) δ 1.49 (t, *J* = 6.94 Hz, 3 H) 1.95 - 2.12 (m, 2 H) 2.23 - 2.41 (m, 2 H) 3.60 (s, 2 H) 4.05 (t, *J* = 5.95 Hz, 2 H) 4.19 (q, *J* = 6.90 Hz, 2 H) 6.96 (d, *J* = 9.41 Hz, 2 H) 7.08 (d, *J* = 8.92 Hz, 1 H) 7.46 (d, *J* = 8.92 Hz, 2 H) 7.55 (dd, *J* = 1.00 Hz, 1 H) 7.60 (s, 1 H) 7.64 (d, *J* = 1.00 Hz, 1 H)
264 Isómero S		CF_3	H	CN	R^{12} = F R^{13} =	[M-H] 529.1	^{1}H NMR (500 MHz, MeOD) δ 1.47 (t, *J* = 7.18 Hz, 3 H)

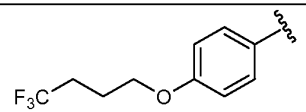
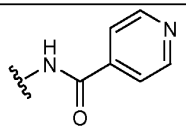
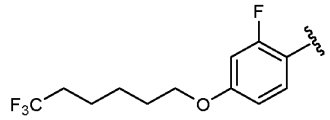
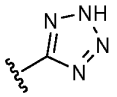
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
					OCH_2CH_3		1.95 - 2.12 (m, 2 H) 2.33 (s, 2 H) 4.06 (t, *J* = 5.95 Hz, 2 H) 4.19 (q, *J* = 6.90 Hz, 2 H) 6.97 (d, *J* = 8.92 Hz, 2 H) 7.12 (t, *J* = 1.00 Hz, 1 H) 7.37 - 7.53 (m, 4 H) 7.62 (s, 1 H)
265 Isómero S		CF_3	H		$R^{13} = CH_3$	607.1	^{1}H NMR (500 MHz, MeOD) δ 7.88 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.05 - 6.97 (m, 3H), 6.89 (d, *J* = 7.4 Hz, 1H), 6.85 - 6.80 (m, 1H), 4.07 (t, *J* = 6.1 Hz, 2H), 3.68 (s, 3H), 3.63 (d, *J* = 17.3 Hz, 1H), 3.51 (d, *J* = 17.3 Hz, 1H),

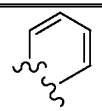
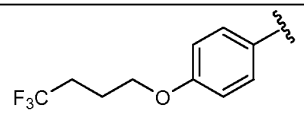
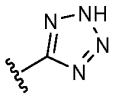
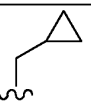
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							2.43 - 2.32 (m, 2H), 2.31 (s, 3 H), 2.07 - 1.98 (m, 2H).
266 Isómero S		CF_3	H		$R^{13} = CH_3$	544.1	^{1}H NMR (500 MHz, MeOD) δ 7.50 (dd, *J* = 12.7, 2.5 Hz, 1H), 7.45 - 7.38 (m, 1H), 7.18 (t, *J* = 8.7 Hz, 1H), 7.12 - 7.06 (m, 2H), 6.89 (d, *J* = 8.2 Hz, 2H), 4.16 (t, *J* = 6.1 Hz, 2H), 3.74 (d, J = 17.8 Hz, 1H), 3.68 (d, J = 17.8 Hz, 1H), , 2.52 - 2.32 (m, 2H), 2.29 (s, 3H), 2.13 - 1.98 (m, 2H).
267 Isómero S		CF_3	H		$R^{13} = CH_3$	526.2	
268 Isómero S		CF_3	H		$R^{13} = CH_3$	544.2	^{1}HNMR (500 MHz, DMSO-d_6) δ 9.58 (s, 1H), 7.59 (t, *J* = 9.2 Hz, 1H), 7.09 (d, *J* = 8.0

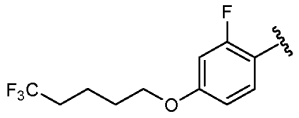
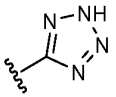
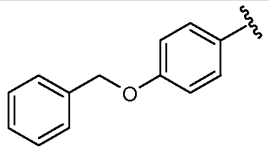
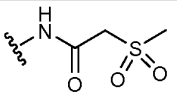
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							Hz, 2H), 6.99 – 6.92 (m, 2H), 6.89 (d, *J* = 8.1 Hz, 2H), 4.11 (t, *J* = 6.1 Hz, 2H), 3.81 (d, *J* = 17.7 Hz, 1H), 3.73 (d, *J* = 17.8 Hz, 1H), 2.49 – 2.30 (m, 2H), 2.25 (s, 3H), 2.03 – 1.78 (m, 2H).
269 Isómero S		CF_3	H	CN	$R^{13} = CH_3$	483.2	^{1}HNMR (400 MHz, MeOD) δ 8.18 (s, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.25 - 7.19 (m, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 4.09 (s, 3H), 4.07 - 4.03 (m, 2H), 3.71 (d, *J* = 16.9 Hz, 1H), 3.48 (d, *J* = 16.9 Hz, 1H), 2.44 - 2.31 (m, 2H), 2.28 (s, 3H), 2.08 - 1.98 (m, 2H).

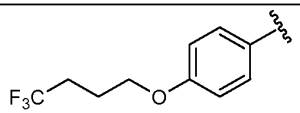
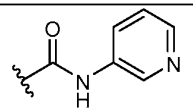
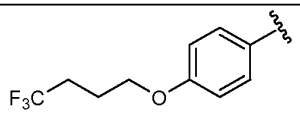
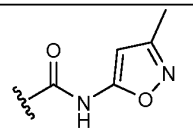
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
270 Isómero R		CF_3	H		$R^{13} = CH_3$	554.1	^{1}H NMR (400 MHz, MeOD) δ 7.51 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 9.0 Hz, 2H), 6.98 - 6.88 (m, 4H), 4.02 (t, *J* = 6.1 Hz, 2H), 3.99 (s, 2H), 3.79 (s, 3H), 3.66 (d, *J* = 16.9 Hz, 1H), 3.44 (d, *J* = 16.7 Hz, 1H), 2.97 (s, 3H), 2.30 - 2.16 (m, 2H), 1.90 - 1.81 (m, 2H), 1.79 - 1.69 (m, 2H).
271 Isómero S		CF_3	H		$R^{13} = CH_2CF_3$	594.1	^{1}H NMR (500 MHz, 1:1 MeOD/$CDCl_3$) δ 7.52 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.96 (dd, *J* = 8.4, 2.1 Hz, 4H), 4.04 (t, *J* = 6.1 Hz, 2H), 3.73 - 3.64 (m, 1H), 3.60 - 3.49 (m, 1H), 3.35 (d,

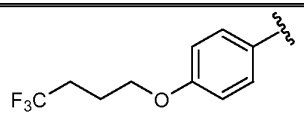
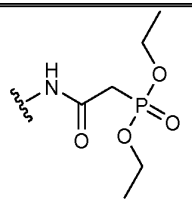
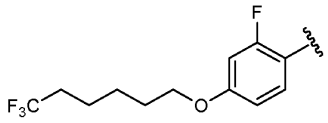
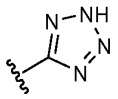
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							J = 10.7 Hz, 2H), 2.39 - 2.23 (m, 2H), 2.13 - 1.91 (m, 2H).
272 Isómero S		CF_3	H		$R^{13} = CH_3$	540.3	
273 Isómero S		CF_3	H		$R^{13} = CH_3$	608.2	1.98 – 2.11 (m, 2H), 2.29 (s, 3H), 2.33 - 2.49 (m, 2H), 3.71 - 3.47 (m, 2H), 3.91 (s, 3H), 4.20 - 4.02 (m, 2H), 6.95 – 7.03 (m, 2H), 7.15 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.86 (d, J = 1.4 Hz, 1H), 8.76 (d, J = 1.4 Hz, 1H).
274 Isómero S		CF_3	H		$R^{13} = OCHF_2$	624.1	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.63 (s, 1H), 7.58 (t, *J* = 9.3 Hz, 1H), 7.43 – 6.98 (m, 5H), 6.92 (d, *J* = 12.1

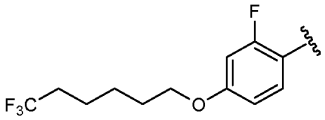
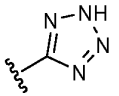
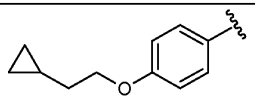
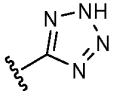
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							Hz, 2H), 4.03 (t, *J* = 6.4 Hz, 2H), 3.80 (d, *J* = 17.8 Hz, 1H), 3.76 (d, *J* = 17.9 Hz, 1H), 2.37 – 2.14 (m, 2H), 1.83 – 1.66 (m, 2H), 1.63 – 1.32 (m, 4H).
275 Isómero S		CF_3	H		R^{13} = $OCHF_2$	630.2	^{1}H NMR (400 MHz, MeOD) δ 8.75 (br. s., 2H), 7.87 (br. s., 2H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 7.04 - 6.62 (m, 3H), 4.08 (t, *J* = 5.8 Hz, 2H), 3.75 (br. s., 1H), 3.52 (d, *J* = 16.9 Hz, 1H), 2.45 - 2.29 (m, 2H), 2.09 - 1.99 (m, 2H).
276 Isómero S		CF_3	H		R^{12} R^{13} =	608.2	^{1}H NMR (500 MHz, MeOD) δ 7.83 – 7.66 (m, 3H), 7.61

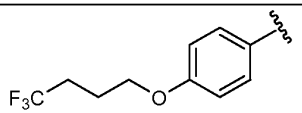
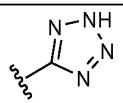
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							(s, 2H), 7.56 – 7.43 (m, 3H), 7.01 (d, *J* = 8.6 Hz, 1H), 6.85 – 6.67 (m, 2H), 4.05 (d, *J* = 18.0 Hz, 1H), 4.01 (t, *J* = 6.4 Hz, 2H), 3.76 (d, *J* = 17.9 Hz, 1H), 2.05-2.20 (m, 2H), 1.91 – 1.72 (m, 2H), 1.74 – 1.45 (m, 4H).
277 Isómero S		CF_3	H		R^{13} = 	567.1	^{1}H NMR (500 MHz, 1:1 $CDCl_3$:MeOD) δ 7.54 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 6.99 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 4.07 (t, J = 5.9 Hz, 2H), 3.79 - 3.66 (m, 1H), 3.63 - 3.50 (m, 1H), 2.49 (d, J = 6.9 Hz, 2H), 2.40 - 2.25 (m, 2H), 2.13 - 1.97 (m, 2H), 0.97 -

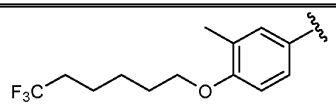
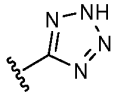
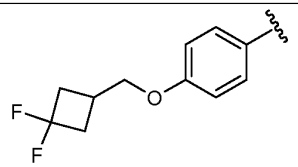
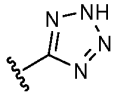
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							0.82 (m, 1H), 0.58 - 0.45 (m, 2H), 0.16 (q, J = 5.0 Hz, 2H).
278 Isómero S		CF_3	H		$R^{13} = CH_3$	558.2	^{1}H NMR (500 MHz, 1:1 $CDCl_3$:MeOD) δ 7.43 (t, *J* = 9.17 Hz, 1H), 7.02 (d, *J* = 7.93 Hz, 2H), 6.87 (d, *J* = 7.93 Hz, 2H), 6.75 (dd, *J* = 2.48, 8.92 Hz, 1H), 6.71 (dd, *J* = 2.23, 14.61 Hz, 1H), 3.99 (t, *J* = 5.95 Hz, 2H), 3.87 (d, *J* = 17.83 Hz, 1H), 3.61 (d, *J* = 17.83 Hz, 1H), 2.26 (s, 3H), 2.11-2.21 (m, 2H), 1.80-1.89 (m, 2H), 1.69-1.78 (m, 2H).
279 Isómero S		CF_3	H		$R^{13} = CH_3$	573.2	7.79 (br. s., 1H), 7.46 - 7.38 (m, 7H), 7.22 - 7.17 (m, 2H), 7.15 - 7.10 (m, 2H), 7.02 (d,

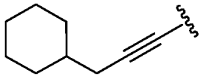
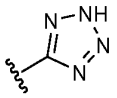
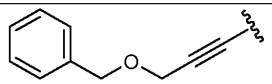
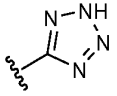
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							J = 9.0 Hz, 2H), 6.69 (br. s., 1H), 5.07 (s, 2H), 3.82 (br. s., 2H), 3.63 (d, *J* = 17.2 Hz, 1H), 3.37 (d, *J* = 17.2 Hz, 1H), 2.95 (s, 3H), 2.36 (s, 3H).
280 Isómero S		CF_3	H		$R^{13} = OCHF_2$	630.2	
281 Isómero S		CF_3	H		$R^{13} = CH_3$	582.2	^{1}H NMR (500MHz, MeOD) δ 7.56 (d, J = 8.92 Hz, 2H), 7.30 (d, J = 8.42 Hz, 2H), 7.10 (d, J = 7.93 Hz, 2H), 6.97 (d, J = 8.92 Hz, 2H), 6.37 (s, 1H), 4.06 (m, 2H), 3.59 (d, J = 17.83 Hz, 1H), 3.43 (d, J = 17.34 Hz, 1H), 2.32 (m, 2H), 2.30 (s, 3H), 2.22 (s, 3H), 2.06 (m, 2H).

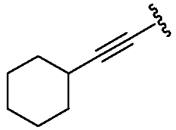
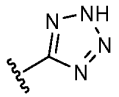
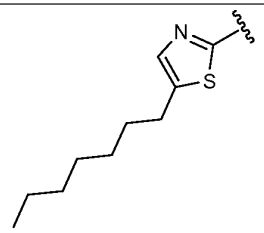
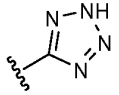
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
282 Isómero S		CF_3	H		$R^{13} = CH_3$	651.2	^{1}H NMR (500MHz, MeOD) δ 7.61 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 5.9 Hz, 4H), 6.93 (d, *J* = 8.9 Hz, 2H), 4.33 (br. s., 1H), 4.07 - 4.02 (m, 2H), 4.02 - 3.94 (m, 4H), 3.67 - 3.56 (m, 1H), 3.37 - 3.34 (m, 1H), 2.94 - 2.78 (m, 2H), 2.33 (s, 5H), 2.09 - 2.00 (m, 2H), 1.22 (d, *J* = 1.5 Hz, 6H).
283 Isómero S		CF_3	H		R^{13} = OCH_2CH_3	602.2	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.39 (s, 1H), 7.56 (t, *J* = 9.3 Hz, 1H), 6.92 (t, *J* = 8.6 Hz, 4H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.03 (t, *J* = 6.4 Hz, 2H), 3.99 (q, *J* = 6.9 Hz , 2H), 3.82 (d, *J* = 17.3 Hz, 1H),

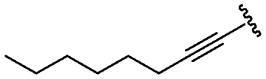
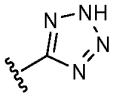
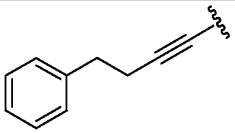
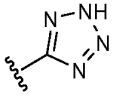
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							3.69 (d, *J* = 17.7 Hz, 1H), 2.34 – 2.15 (m, 2H), 1.85 – 1.70 (m, 2H), 1.65 – 1.42 (m, 4H), 1.29 (t, *J* = 6.9 Hz, 3H).
284 Isómero S		CF_3	H		$R^{13} = CH_2CF_3$	640.1	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.36 (w, 1H), 7.59 (t, *J* = 9.3 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 2H), 7.07 – 6.74 (m, 4H), 4.03 (t, *J* = 6.4 Hz, 2H), 3.76 (d, *J* = 17.4 Hz, 1H), 3.70 (d, *J* = 17.7 Hz, 1H), 3.58 (dd, *J* = 23.3, 11.7 Hz, 2H), 2.33 – 2.16 (m, 2H), 1.86 – 1.68 (m, 2H), 1.545-1.60 (m, 4H).
285 Isómero S		CF_3	H		$R^{13} = CH_3$	484.1	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.58 - 9.48 (m, 1H), 7.65 - 7.55 (m, 2H), 7.07 (d,

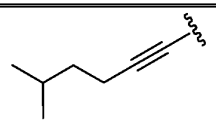
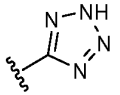
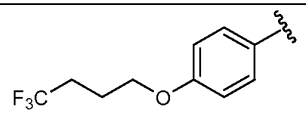
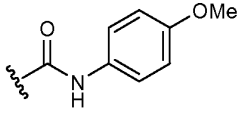
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							J = 8.0 Hz, 2H), 7.04 - 6.97 (m, 2H), 6.94 - 6.85 (m, 2H), 4.06 (s, 2H), 3.69 (s, 2H), 2.24 (s, 3H), 1.63 (q, *J* = 6.6 Hz, 2H), 1.35 - 1.08 (m, 1H), 0.94 - 0.77 (m, 1H), 0.51 - 0.38 (m, 2H), 0.16 - 0.06 (m, 2H)
286 Isómero S		CF_3	H		R^{11} = F R^{13} = CH_3	544.2	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.62 (d, J = 8.80 Hz, 2H), 7.02 (d, J = 8.80 Hz, 2H), 7.01 (m, 1H), 6.98 (t, J = 7.98 Hz, 1H), 6.93 (d, J = 11.55 Hz, 1H), 4.08 (t, J = 6.93 Hz, 2H), 3.68 (d, J = 18.16 Hz, 1H), 3.62 (d, J = 17.88 Hz, 1H), 2.42 (m, 2H), 2.28 (s, 3H), 1.95 (m, 2H).

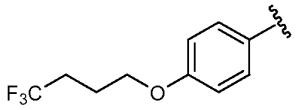
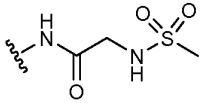
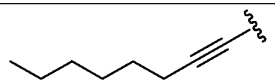
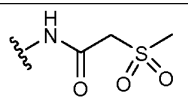
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
287 Isómero S		CF_3	H		$R^{13} = CH_3$	568.2	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.47 (s, 1H), 7.49 (s, 1H), 7.45 (d, *J* = 8.80 Hz, 1H), 7.07 (d, *J* = 7.98 Hz, 2H), 6.98 (d, *J* = 8.80 Hz, 1H), 6.89 (d, *J* = 8.25 Hz, 2H), 4.00 (t, *J* = 6.19 Hz, 2H), 3.66 (s, 2H), 2.24 (s, 3H), 2.20-2.32 (m, 2H), 2.17 (s, 3H), 1.71-1.80 (m, 2H), 1.47-1.61 (m, 4H).
288 Isómero S		CF_3	H		$R^{13} = CH_3$	520.0	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.67 (s, 1H), 8.15 (d, J = 4.1 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 4.1 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 4.03 (t, J = 6.2 Hz, 2H), 3.98 (d, J = 17.6 Hz, 1H),

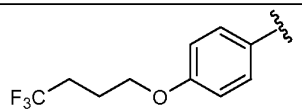
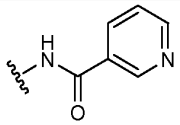
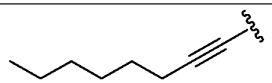
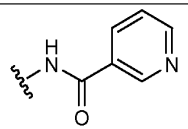
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							3.62 (d, J = 17.3 Hz, 1H), 2.45 - 2.33 (m, 2H), 2.31 - 2.23 (m, 1H), 1.94 - 1.79 (m, 2H), 1.23 - 1.11 (m, 2H), 0.87 - 0.77 (m, 2H).
289 Isómero S		CF_3	H		$R^{13} = CH_3$	444.1	7.17 (d, *J* = 7.9 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.84 (s, 1H), 3.39 (AB cuarteto, *J* = 18.7 Hz, 2H), 2.36 (s, 3H), 2.13 (d, *J* = 6.6 Hz, 2H), 1.77 - 1.60 (m, 5H), 1.55 - 1.42 (m, 1H), 1.29 - 0.88 (m, 5H).
290 Isómero S		CF_3	H		$R^{13} = CH_3$	468.1	7.36 - 7.27 (m, 5H), 7.18 (s, 1H), 7.13 (d, *J* = 7.9 Hz, 2H), 7.01 (d, *J* = 8.1 Hz, 2H), 4.57 (AB cuarteto, *J* = 11.7 Hz, 2H), 4.22 (s, 2H),

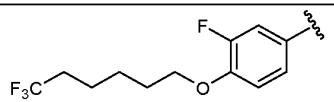
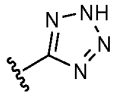
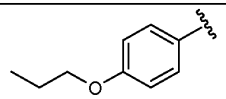
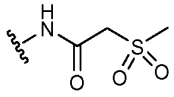
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							3.39 (AB cuarteto, J = 18.9 Hz, 2H), 2.34 (s, 3H).
291 Isómero S		CF_3	H		$R^{13} = CH_3$	430.1	7.19 (d, J = 7.9 Hz, 2H), 7.06 (d, J = 8.1 Hz, 2H), 6.59 (s, 1H), 3.38 (AB cuarteto, J = 18.9 Hz, 2H), 2.49 - 2.41 (m, 1H), 2.38 (s, 3H), 1.81 - 1.72 (m, 2H), 1.65 (dd, J = 5.9, 2.4 Hz, 2H), 1.54 - 1.40 (m, J = 12.5, 8.9, 8.9, 8.9 Hz, 3H), 1.38 - 1.28 (m, 3H).
292 Rac		CF_3	H		$R^{13} = CH_3$	394.5	

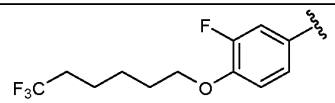
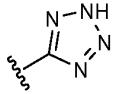
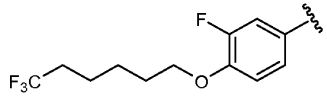
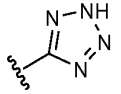
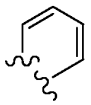
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
293 Isómero S		CF_3	H		$R^{13} = CH_3$	432.1	7.19 (d, *J* = 7.9 Hz, 2H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.67 (s, 1H), 3.38 (AB cuarteto, *J* = 18.9 Hz, 2H), 2.37 (s, 3H), 2.23 (t, *J* = 7.0 Hz, 2H), 1.51 (quin, *J* = 7.3 Hz, 2H), 1.40 - 1.22 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H).
294 Isómero S		CF_3	H		$R^{13} = OCH_3$	468.1	1H NMR (500 MHz, MeOD) δ 7.31 - 7.15 (m, 5H), 6.96 (d, J = 8.9 Hz, 2H), 6.81 (d, J = 8.9 Hz, 2H), 3.79 (s, 3H), 3.34 (AB cuarteto, J = 18.3 Hz, 2H, se traslapa parcialmente con solvente), 2.85 (t, J = 7.2 Hz, 2H), 2.58 (t, J = 7.4 Hz, 2H).

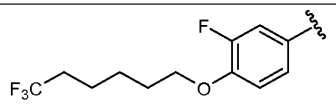
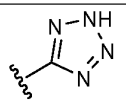
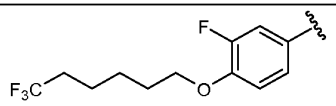
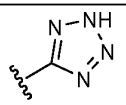
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
295 Isómero S		CF_3	H		$R^{13} = OCH_3$	434.1	1H NMR (500 MHz, MeOD) δ 7.01 (d, J = 8.9 Hz, 2H), 6.78 (d, J = 8.9 Hz, 2H), 3.77 (s, 3H), 3.40 (s, 2H), 2.29 (t, J = 7.4 Hz, 2H), 1.69 (dt, J = 13.5, 6.9 Hz, 1H), 1.45 (q, J = 7.4 Hz, 2H), 0.91 (dd, J = 6.9, 2.0 Hz, 6H).
296 Isómero S		CF_3	H		$R^{11} = F$ $R^{13} = CH_3$	625.2	^{1}H NMR (500 MHz, DMSO-d_6) δ 7.55 (d, J = 8.80 Hz, 2H), 7.31 (d, J = 9.08 Hz, 2H), 7.13 (m, 1H), 7.06 (d, J = 11.83 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 7.70 Hz, 1H), 6.80 (d, J = 9.08 Hz, 2H), 4.08 (m, 2H), 3.70 (m, 2H), 3.68 (s, 3H), 2.43 (m, 2H), 2.27 (s, 3H), 1.95

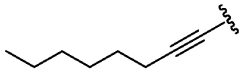
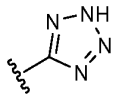
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							(m, 2H).
297 Isómero S		CF_3	H		$R^{13} = CH_3$	608.1	7.43 (d, *J* = 8.6 Hz, 2H), 7.20 - 7.16 (m, 2H), 7.15 - 7.10 (m, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.57 (s, 1H), 5.10 (br. s., 1H), 4.03 (t, *J* = 5.9 Hz, 2H), 3.72 (br. s., 2H), 3.62 (d, *J* = 17.6 Hz, 1H), 3.38 (d, *J* = 17.8 Hz, 1H), 2.80 - 2.74 (m, 3H), 2.40 - 2.24 (m, 5H), 2.12 - 2.02 (m, 2H)
298 Isómero S		CF_3	H		$R^{13} = CH_3$	499.1	7.74 (br. s., 1H), 7.26 - 7.20 (m, 4H), 5.88 (s, 1H), 3.84 (s, 2H), 3.29 (ABq, *J* = 17.6 Hz, 2H), 2.95 (s, 3H), 2.37 (s, 3H), 2.23 (t, *J* = 7.0 Hz, 2H), 1.57 - 1.48 (m, 2H),

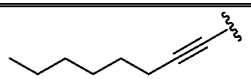
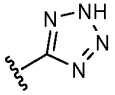
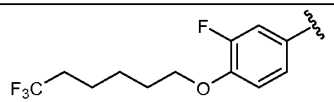
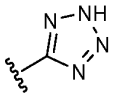
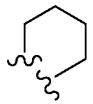
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							1.41 - 1.25 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H)
299 Isómero S		CF_3	H		$R^{13} = CH_3$	578.1	9.08 (br. s., 1H), 8.77 (d, *J* = 4.2 Hz, 1H), 8.37 (br. s., 1H), 8.25 (br. s., 1H), 7.65 (br. s., 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.19 - 7.11 (m, 4H), 6.95 (d, *J* = 9.0 Hz, 2H), 6.88 (s, 1H), 4.04 (t, *J* = 5.9 Hz, 2H), 3.66 (d, *J* = 17.6 Hz, 1H), 3.43 (d, *J* = 17.4 Hz, 1H), 2.40 - 2.25 (m, 5H), 2.12 - 2.03 (m, 2H).
300 Isómero S		CF_3	H		$R^{13} = CH_3$	484.2	^{1}H NMR (400 MHz, MeOD) δ 9.00 (br. s., 1H), 8.79 (dd, *J* = 5.3, 1.3 Hz, 1H), 8.46 (d, *J* = 7.3 Hz, 1H), 7.78 (dd, *J* = 8.0, 5.4 Hz, 1H), 7.33 (d, *J*

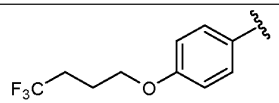
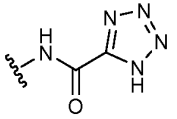
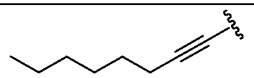
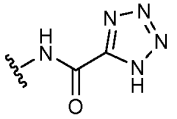
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							= 8.1 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 3.38 (s, 2H), 2.35 - 2.27 (m, 5H), 1.60 - 1.50 (m, 2H), 1.48 - 1.38 (m, 2H), 1.35 - 1.27 (m, 4H), 0.93 - 0.87 (m, 3H).
301 Isómero S		CF_3	H		$R^{13} = OCHF_2$	624.2	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.53 (s, 1H), 7.65 (dd, *J* = 13.0, 2.0 Hz, 1H), 7.49 (d, *J* = 7.4 Hz, 1H), 7.46 – 6.88 (m, 6H), 4.11 (t, *J* = 6.3 Hz, 2H), 3.77 (d, *J* = 17.9 Hz, 1H), 3.72 (d, *J* = 17.9 Hz, 1H), 2.36 – 2.08 (m, 2H), 1.88 – 1.71 (m, 2H), 1.67 – 1.34 (m, 4H).
302 Isómero S		CF_3	H		$R^{13} = CH_3$	525.0	^{1}HNMR (400 MHz, MeOD) δ 7.50 (d, *J* = 8.8 Hz, 2H),

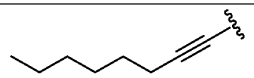
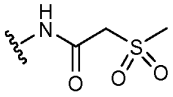
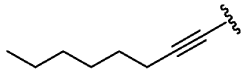
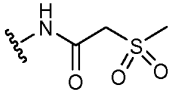
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							7.23 - 7.15 (m, 4H), 6.93 (d, *J* = 9.0 Hz, 2H), 4.00 - 3.92 (m, 4H), 3.66 (d, *J* = 17.2 Hz, 1H), 3.43 (d, *J* = 16.9 Hz, 1H), 2.93 (s, 3H), 2.32 (s, 3H), 1.79 (sxt, *J* = 7.0 Hz, 2H), 1.04 (t, *J* = 7.4 Hz, 3H).
303 Isómero S		CF_3	H		$R^{13} = CH_3$	572.3	
304 Isómero S		CF_3	H		R^{12} R13 = 	608.3	^{1}HNMR (500 MHz, DMSO-d_6) δ 9.57 (br. s., 1H), 7.84 (dd, *J* = 7.84, 13.34 Hz, 2H), 7.71-7.77 (m, 2H), 7.67 (d, *J* = 12.93 Hz, 1H), 7.47-7.57 (m, 3H), 7.26 (t, *J* = 8.94 Hz, 1H), 6.93 (d, *J* = 8.80 Hz, 1H), 5.56 (d, *J* = 7.70 Hz,

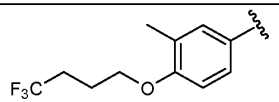
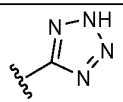
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							1H), 4.10 (t, *J* = 6.19 Hz, 2H), 3.79-3.92 (m, 2H), 2.20-2.33 (m, 2H), 1.68-1.83 (m, 2H), 1.45-1.65 (m, 4H).
305 Isómero S		CF_3	H		R^{13} = OCH_2CH_3	602.3	^{1}HNMR (500 MHz, DMSO-d_6) δ 9.38-9.54 (m, 1H), 7.63 (d, *J* = 13.20 Hz, 1H), 7.46 (d, *J* = 8.80 Hz, 1H), 7.24 (t, *J* = 8.80 Hz, 1H), 6.96 (d, *J* = 8.53 Hz, 2H), 6.79 (d, *J* = 8.53 Hz, 2H), 4.09 (t, *J* = 6.33 Hz, 2H), 3.98 (q, *J* = 6.88 Hz, 2H), 2.20-2.34 (m, 2H), 1.77 (quin, *J* = 6.81 Hz, 2H), 1.46-1.61 (m, 4H), 1.28 (t, *J* = 7.02 Hz, 3H).
306 Isómero S		CF_3	H		R^{13} = CH_2CF_3	640.2	^{1}HNMR (500 MHz, DMSO-d_6) δ 9.56 (br. s., 1H), 7.65

Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							(d, *J* = 12.93 Hz, 1H), 7.49 (d, *J* = 8.80 Hz, 1H), 7.20-7.28 (m, 3H), 7.03 (d, *J* = 7.98 Hz, 2H), 4.10 (t, *J* = 6.33 Hz, 2H), 3.71-3.81 (m, 2H), 3.61 (q, *J* = 11.55 Hz, 2H), 2.20-2.33 (m, 2H), 1.78 (quin, *J* = 6.74 Hz, 2H), 1.44-1.61 (m, 4H)
307 Isómero S		CF_3	H		R^{13} = $OCHF_2$	484.1	7.19 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.78 (br. s., 1H), 6.56 (t, *J* = 73.1 Hz, 1H), 3.37 (AB cuarteto, *J* = 18.9 Hz, 2H), 2.24 (t, *J* = 7.0 Hz, 2H), 1.52 (quin, *J* = 7.3 Hz, 2H), 1.41 - 1.21 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H).

Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
308 Isómero S		CF_3	H		R^{13} = OCH_2CH_3	462.1	7.10 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.72 (s, 1H), 4.04 (q, *J* = 7.0 Hz, 2H), 3.37 (AB quartet, *J* = 18.9 Hz, 2H), 2.22 (t, *J* = 7.2 Hz, 2H), 1.51 (quin, *J* = 7.3 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H), 1.39 - 1.22 (m, 6H), 0.87 (t, *J* = 6.6 Hz, 3H).
309 Isómero S		CF_3	H		R^{12} R13 = 	612.1	^{1}HNMR (500 MHz, DMSO-d_6) δ 9.52 (br. s., 1H), 7.63 (d, *J* = 13.20 Hz, 1H), 7.46 (d, *J* = 8.53 Hz, 1H), 7.25 (t, *J* = 8.94 Hz, 1H), 6.88 (d, *J* = 7.98 Hz, 1H), 6.83 (s, 1H), 6.58 (d, *J* = 7.98 Hz, 1H), 4.09 (t, *J* = 6.19 Hz, 2H), 3.64-3.75 (m, 2H), 2.54-2.67

Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							(m, 4H), 2.20-2.34 (m, 2H), 1.77 (quin, *J* = 6.74 Hz, 2H), 1.67 (br. s., 4H), 1.44-1.61 (m, 4H).
310 Isómero S		CF_3	H		$R^{13} = CH_3$	569.0	^{1}HNMR (400 MHz, MeOD) δ 7.56 (d, *J* = 8.8 Hz, 2H), 7.26 - 7.21 (m, 2H), 7.18 - 7.12 (m, 2H), 6.99 (d, *J* = 9.0 Hz, 2H), 4.07 (t, *J* = 6.2 Hz, 2H), 3.73 (d, *J* = 17.2 Hz, 1H), 3.51 (d, *J* = 16.9 Hz, 1H), 2.43 - 2.32 (m, 2H), 2.29 (s, 3H), 2.08 - 1.98 (m, 2H).
311 Isómero S		CF_3	H		$R^{13} = CH_3$	475.1	^{1}HNMR (400 MHz, MeOD) δ 7.34 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 3.37 (s, 2H), 2.34 - 2.26 (m,

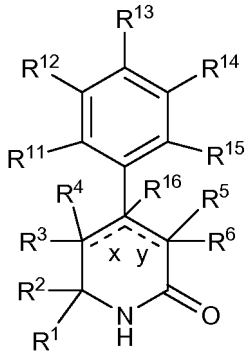
Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							5H), 1.53 (d, *J* = 7.3 Hz, 2H), 1.42 (br. s., 2H), 1.34 - 1.25 (m, 4H), 0.92 - 0.86 (m, 3H).
312 Isómero S		CF_3	H		R^{13} = OCH_2CH_3	529.4	7.73 (br. s., 1H), 7.31 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.91 (s, 1H), 4.06 (q, *J* = 7.0 Hz, 2H), 3.86 (s, 2H), 3.30, 3.28 (ABq, *J* = 18.3 Hz, 2H), 2.99 (s, 3H), 2.23 (t, *J* = 7.0 Hz, 2H), 1.52 (quin, *J* = 7.3 Hz, 2H), 1.43 (t, *J* = 6.9 Hz, 3H), 1.41 - 1.22 (m, 7H), 0.89 (t, *J* = 6.9 Hz, 2H).
313 Isómero S		CF_3	H		R^{13} = $OCHF_2$	551.0	7.85 (br. s., 1H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 8.6 Hz, 2H), 6.55 (t, *J* = 72.4

Ejemplo	R^1	R^2	$R^3 = R^4$	R^6	R^{11}-R^{15}	[M+H]	^{1}HNMR (400 MHz, $CDCl_3$)
							Hz, 1H), 5.97 (s, 1H), 3.84 (s, 2H), 3.30, 3.28 (ABq, *J* = 17.8 Hz, 2H), 2.89 (s, 3H), 2.24 (t, *J* = 7.0 Hz, 2H), 1.52 (dt, *J* = 14.6, 7.2 Hz, 2H), 1.43 - 1.23 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H).
314 Isómero S		CF_3	H		$R^{13} = CH_3$	540.3	

REIVINDICACIONES

Lo que se reivindica es:

1. Un compuesto de la Fórmula (I):



(I)

o un estereoisómero, un tautómero, una sal aceptable desde el punto de vista farmacéutico o un solvato de aquel, en donde:

--- indica un enlace simple o doble;

x e y pueden ser ambos un enlace simple; en donde x es un enlace doble, y es un enlace simple, y R^4 y R^{16} están ausentes; en donde y es un enlace doble, x es un enlace simple, y R^5 y R^{16} están ausentes;

R^1 se selecciona independientemente del grupo que consiste en: $-CONH(C_{4-18}$ alquilo), $-CONHC_{2-8}$ haloalquilo, $-CONH(CH_2)_{1-8}Ph$, $-CONHCH_2COC_{2-8}$alquilo,, $-(CH_2)_m-(C_{3-10}$ carbociclo sustituido con 0-2 R^b y 0-2 R^g), $-(CH_2)_m-$(heteroarilo de 5 a 6 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, NR^e, O y S; en donde el heteroarilo se sustituye con 0-1 R^b y 0-2 R^g), y una cadena de hidrocarburos C_{1-12} sustituida con 0-3 R^a; en donde la cadena de

hidrocarburos puede ser lineal o ramificada, saturada o insaturada;

R^2 se selecciona independientemente del grupo que consiste en: C_{1-4} alquilo, C_{3-4} cicloalquilo y C_{1-4} haloalquilo;

R^3 se selecciona independientemente del grupo que consiste en: H, F, Cl, C_{1-4} alquilo y CN;

R^4 y R^5 se seleccionan independientemente del grupo que consiste en: H, F, Cl y C_{1-4} alquilo;

en donde x es un enlace simple, R^3 y R^4 se pueden combinar con el átomo de carbono al que están unidos para formar un carbociclo de 3 a 6 miembros;

R^6 se selecciona independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo, CN, NO_2, R^c, $(CH_2)_n-(X)_t-(CH_2)_mR^c$, NH_2, $-CONH(C_{1-6}$ alquilo), $-NHCOX_1SO_2R^j$, $-NHCOCH_2PO(OEt)_2$, $-NHCOCOR^j$, $-NHCOCH(OH)R^j$, $-NHCOCH_2COR^j$, $-NHCONHR^j$ y $-OCONR^fR^j$;

X se selecciona independientemente del grupo que consiste en: O, S, NH, -CONH y NHCO;

X_1 es independientemente una cadena de hidrocarburos C_{1-4} opcionalmente sustituida con C_{1-4} alquilo o C_{3-4} cicloalquilo;

en donde y es un enlace simple, R^5 y R^6 se pueden combinar con el átomo de carbono al que están unidos para formar un carbociclo de 3 a 6 miembros;

R^{11}, R^{12}, R^{13}, R^{14} y R^{15} se seleccionan

independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo sustituido con 0-2 R^i, C_{1-4} alcoxi, C_{1-4} haloalquilo, C_{1-4} haloalcoxi, C_{3-6} cicloalquilo, CN, NR^fR^j, OR^j, SR^j, $NHCO_2(C_{1-4}$ alquilo), $NHSO_2(C_{1-4}$ alquilo) y un heterociclo de 4 a 6 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, NR^e, O y S;

de manera alternativa, R^{11} y R^{12}, junto con los átomos de carbono a los que están unidos, se combinan para formar un anillo carbocíclico de 5 a 6 miembros o un anillo heterocíclico de 5 a 6 miembros, que comprende átomos de carbono y 1-3 heteroátomos seleccionados de N, NR^e, O y S;

de manera alternativa, R^{12} y R^{13}, junto con los átomos de carbono a los que están unidos, se combinan para formar un anillo carbocíclico de 5 a 6 miembros o un anillo heterocíclico de 5 a 6 miembros, que comprende átomos de carbono y 1 3 heteroátomos seleccionados de N, NR^e, O y S;

R^{16} se selecciona independientemente del grupo que consiste en: H y C_{1-4} alquilo;

R^a, en cada caso, se selecciona independientemente del grupo que consiste en halo, OH, C_{1-6} alcoxi, C_{1-6} haloalquilo, C_{1-6} haloalcoxi, $N(C_{1-4}$ alquil$)_2$, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$ y $-(CH_2)_n-(CH_2O)_m-(CH_2)_nR^f$;

R^b, en cada caso, se selecciona independientemente del grupo que consiste en halo, OH, C_{1-10} alquilo, C_{1-10} alcoxi, C_{1-10} haloalquilo, C_{1-10} haloalcoxi, C_{1-10} alquiltio, C_{1-10}

haloalquiltio, $N(C_{1-4}$ alquil$)_2$, $-CONH(CH_2)_{4-20}H$, $O(CH_2)_sO(C_{1-6}$ alquilo), R^c, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$ y $-(CH_2)_n-(CH_2O)_m-(CH_2)_nR^f$;

R^c, en cada caso, se selecciona independientemente del grupo que consiste en: C_{3-6} cicloalquilo sustituido con 0-2 R^d, C_{3-6} cicloalquenilo sustituido con 0-2 R^d, $-(CH_2)_m-$(fenilo sustituido con 0-3 R^d) y un heterociclo de 5 a 6 miembros que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, NR^e, O y S; en donde el heterociclo se sustituye con 0-2 R^d;

R^d, en cada caso, se selecciona independientemente del grupo que consiste en halo, OH, CN, NO_2, C_{1-4} alquilo, C_{1-4} alcoxi, C_{1-4} haloalquilo, C_{1-4} haloalcoxi, tetrazolilo, OBn y fenilo sustituido con 0-2 R^h;

R^e, en cada caso, se selecciona independientemente del grupo que consiste en: H, C_{1-8} alquilo, C_{1-8} haloalquilo, bencilo opcionalmente sustituido con C_{1-4} alcoxi, $CO(C_{1-4}$ alquilo) y COBn;

R^f, en cada caso, se selecciona independientemente del grupo que consiste en: H y C_{1-4} alquilo;

R^g, R^h y R^i, en cada caso, se seleccionan independientemente del grupo que consiste en halo, C_{1-4} alquilo, C_{1-4} alcoxi, C_{1-4} haloalquilo y C_{1-4} haloalcoxi;

R^j, en cada caso, se selecciona independientemente del grupo que consiste en: C_{1-4} alquilo, C_{3-4} cicloalquilo y fenilo;

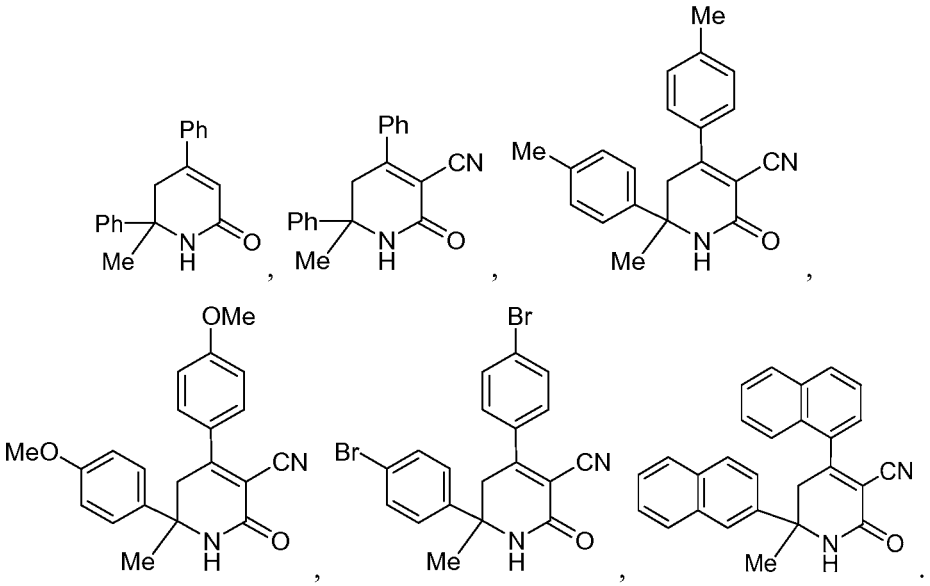
n, en cada caso, es independientemente 0 ó 1;

m, en cada caso, es independientemente 0, 1, 2, 3 ó 4;

s, en cada caso, es independientemente 1, 2 ó 3; y

t, en cada caso, es independientemente 0 ó 1;

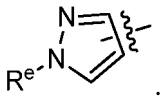
siempre que se excluyan los siguientes compuestos:



2. Un compuesto de acuerdo con la reivindicación 1, en donde:

R^1 se selecciona independientemente del grupo que consiste en: $-CONHC_{4-18}$ alquilo, $-CONH(CH_2)_{1-8}Ph$, C_{1-12} alquilo sustituido con 0-2 R^a, C_{1-12} alquenilo sustituido con 0-2 R^a, C_{1-12} alquinilo sustituido con 0-2 R^a, $-(CH_2)_m$-(fenilo sustituido con 0-1 R^b y 0-2 R^g), $-(CH_2)_m$-(C_{3-6} cicloalquilo sustituido con 0-1 R^b) y $-(CH_2)_m$-(heteroarilo de 5 a 6 miembros sustituido con 0-1 R^b y 0-2 R^g), en donde el

heteroarilo se selecciona de piridilo, oxazolilo, tiazolilo y



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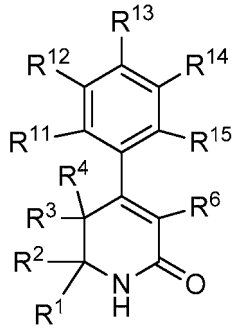
3. Un compuesto de acuerdo con la reivindicación 1 o la reivindicación 2, en donde:

R^{11} y R^{15} se seleccionan independientemente del grupo que consiste en: H, C_{1-4} alquilo y halo;

R^{12} y R^{14} se seleccionan independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo y C_{1-4} alcoxi; y

R^{13} se selecciona independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo sustituido con 0-1 Ri, C_{1-4} alcoxi, C_{1-4} haloalquilo, C_{1-4} haloalcoxi, C_{3-4} cicloalquilo, CN, NR^fR^j, SR^j, $NHCO_2(C_{1-4}$ alquilo), $NHSO_2(C_{1-4}$ alquilo) y un heterociclo de 4 a 6 miembros, que comprende átomos de carbono y 1-4 heteroátomos seleccionados de N, NR^e, O y S.

4. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 3, en donde el compuesto es de la Fórmula (II):



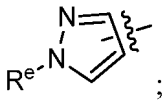
(II)

o un estereoisómero, un tautómero, una sal

aceptable desde el punto de vista farmacéutico o un solvato de aquel.

5. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 4, en donde:

R^1 se selecciona independientemente del grupo que consiste en: C_{1-6} alquilo, C_{3-6} cicloalquilo, $-CONHC_{4-18}$ alquilo, $-CONHC_{2-8}$ haloalquilo, $-CONH(CH_2)_{1-8}Ph$, $(CH_2)_m$-(fenilo sustituido con 1 R^b y 0-2 R^g) y un heteroarilo de 5 a 6 miembros sustituido con 0-1 R^b y 0-2 R^g, en donde el heteroarilo se selecciona de piridilo, oxazolilo, tiazolilo y



;

R^2 se selecciona independientemente del grupo que consiste en: C_{1-4} alquilo y C_{1-4} haloalquilo;

R^3 se selecciona independientemente del grupo que consiste en: H y F;

R^4 se selecciona independientemente del grupo que consiste en: H y F;

R^6 se selecciona independientemente del grupo que consiste en: CN, NH_2, $-CONH(C_{1-6}$ alquilo), R^c, $(CH_2)_n-(X)_t-(CH_2)_mR^c$, $-NHCO(CH_2)SO_2(C_{1-4}$ alquilo), $-NHCOCH_2PO(OEt)_2$, $-NHCOCO(C_{1-4}$ alquilo), $-NHCOCH(OH)(C_{1-4}$ alquilo), $-NHCOCH_2CO(C_{1-4}$ alquilo), $-NHCONH(C_{1-4}$ alquilo) y $-OCONH(C_{1-4}$ alquilo);

R^{11} y R^{15} se seleccionan independientemente del grupo que consiste en: H, C_{1-4} alquilo y halo;

R^{12} y R^{14} se seleccionan independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo y C_{1-4} alcoxi;

R^{13} se selecciona independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo sustituido con 0-1 C_{1-4} alcoxi, C_{1-4} alcoxi, C_{1-4} haloalquilo, C_{1-4} haloalcoxi, $-(CH_2)_m-C_{3-4}$ cicloalquilo, CN, $N(C_{1-4}$ alquilo$)_2$, $NHCO_2(C_{1-4}$ alquilo), $NHSO_2(C_{1-4}$ alquilo), pirazolilo y morfolinilo;

de manera alternativa, R^{12} y R^{13}, junto con los átomos de carbono a los que están unidos, se combinan para formar un anillo carbocíclico de 5 a 6 miembros o un anillo heterocíclico de 5 a 6 miembros, que comprende átomos de carbono y 1 3 heteroátomos seleccionados de N, NR^e, O y S;

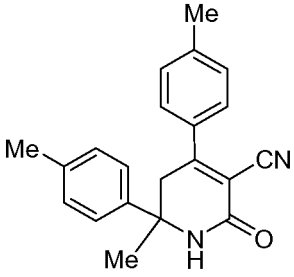
R^b, en cada caso, se selecciona independientemente del grupo que consiste en halo, OH, C_{1-8} alquilo, C_{1-8} alcoxi, C_{1-8} haloalquilo, C_{1-10} haloalcoxi, $O(CH_2)_sO(C_{1-6}$ alquilo), $N(C_{1-4}$ alquilo$)_2$, $-CONH(CH_2)_{6-20}H$, $-(CH_2)_m(C_{3-6}$ cicloalquilo), $(CH_2)_m(C_{4-6}$ cicloalquenilo), $O(CH_2)_m(C_{3-6}$ cicloalquilo), 4-C_{1-4} alcoxi-Ph, $O(CH_2)_m$Ph, morfolinilo, piridilo, 2-C_{1-4} alcoxi-piridin-5-ilo, pirimidinilo, pirazinilo y -O-pirimidinilo;

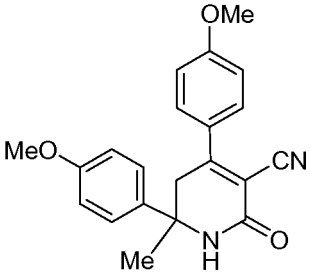
R^g, en cada caso, se selecciona independientemente del grupo que consiste en halo, C_{1-4} alquilo, C_{1-4} alcoxi, C_{1-4} haloalquilo y C_{1-4} haloalcoxi;

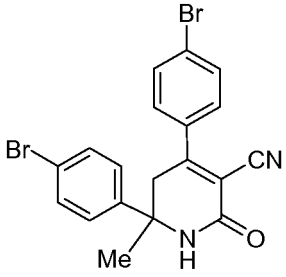
m, en cada caso, es independientemente 0, 1, 2 ó 3; y

s, en cada caso, es independientemente 1, 2 ó 3;

siempre que se excluyan los siguientes compuestos:



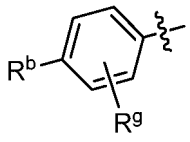
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6. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 5, en donde:

R^1 se selecciona independientemente del grupo que consiste en: C_{1-6} alquilo, $-CONHC_{4-18}$ alquilo, $-CONH(CH_2)_{1-8}Ph$ y



;

R^6 se selecciona independientemente del grupo que consiste en: CN, NH_2, $-CONH(C_{1-6}$ alquilo), $-NHCOCH_2PO(OEt)_2$, $-NHCO(CH_2)SO_2(C_{1-4}$ alquilo), R^c, OR^c, $-CONHR^c$ y $-NHCOR^c$;

R^{12} se selecciona independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo y C_{1-4} alcoxi;

R^{13} se selecciona independientemente del grupo que consiste en: H, halo, C_{1-4} alquilo sustituido con 0-1 C_{1-4} alcoxi, C_{1-4} alcoxi, C_{1-4} haloalquilo, C_{1-4} haloalcoxi, C_{3-4} cicloalquilo, CN, $N(C_{1-4}$ alquilo$)_2$, $NHCO_2(C_{1-4}$ alquilo), $NHSO_2(C_{1-4}$ alquilo), pirazolilo y morfolinilo;

de manera alternativa, R^{12} y R^{13}, junto con los átomos de carbono a los que están unidos, se combinan para

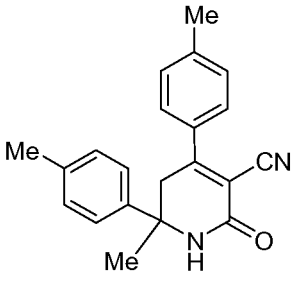
formar un anillo carbocíclico de 5 a 6 miembros o un anillo heterocíclico saturado de 5 a 6 miembros, que comprende átomos de carbono y 1-2 átomos de oxígeno;

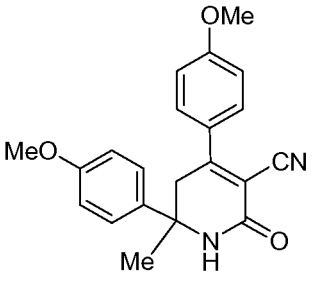
R^{14} se selecciona independientemente del grupo que consiste en: H y C_{1-4} alcoxi;

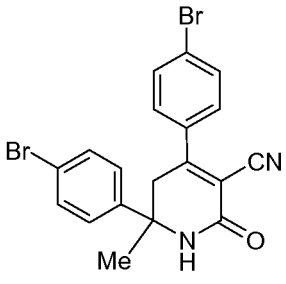
R^b, en cada caso, se selecciona independientemente del grupo que consiste en halo, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} haloalquilo, C_{1-10} haloalcoxi, $O(CH_2)_sO(C_{1-6}$ alquilo), $-CONH(CH_2)_{6-20}H$, $-(CH_2)_m(C_{3-6}$ cicloalquilo), $-(CH_2)_m(C_{4-6}$ cicloalquenilo), $-O(CH_2)_m(C_{3-6}$ cicloalquilo), fenoxi, benzoxi, morfolinilo, 2-C_{1-4} alcoxi-piridin-5-ilo, pirimidin-5-ilo, pirazin-2-ilo y -O-pirimidinilo; y

R^c, en cada caso, se selecciona independientemente del grupo que consiste en: C_{3-6} cicloalquilo sustituido con 0-2 R^d, $-(CH_2)_m$-(fenilo sustituido con 0-3 R^d) y un heteroarilo seleccionado de oxazolilo, isoxazolilo, tiazolilo, pirazolilo, imidazolilo, oxadiazolilo, triazolilo, tetrazolilo, piridilo y pirazinilo; en donde el heteroarilo se sustituye con 0-2 R^d; y

siempre que se excluyan los siguientes compuestos:

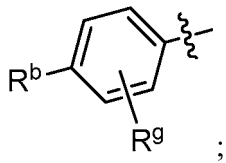


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7. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 6, en donde:

R^1 es  ;

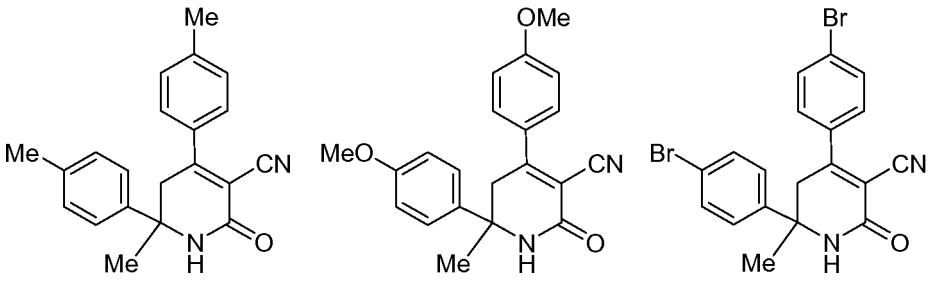
R^6 se selecciona independientemente del grupo que consiste en: NH_2, CN, -CONH(C_{1-4} alquilo), OPh, -CONH(C_{3-6} cicloalquilo), -CONHPh, -CONH-(2-halo-Ph), -CONH(3-halo-Ph), -CONH-(4-halo-Ph), -CONH-(4-C_{1-4} alquil-Ph), -CONH(4-OH-Ph), -CONH-(3-C_{1-4} alcoxi-Ph), -CONH-(4-C_{1-4} alcoxi-Ph), -CONH-(4-C_{1-4} haloalquil-Ph), -CONH-(4-C_{1-4} haloalcoxi-Ph), -CONH-(4-CN-Ph), -CONH-(4-tetrazolil-Ph), -CONH-(3-halo-4 C_{1-4} alquil-Ph), -CONH-(3-halo-4-C_{1-4} alcoxi-Ph), -CONH$(CH_2)_2$Ph, -CONH(4-(4-C_{1-4} alcoxi-Ph)-tiazol-2-ilo), -CONH(1-C_{1-4} alquil-pirazol-3-ilo), -CONH(5-C_{1-4} alcoxi-pirid-2-ilo), -CONH(6-C_{1-4} alcoxi-pirid-3-ilo), -CONH(5-C_{1-4} alcoxi-pirazin-2-ilo), -CONH(6-C_{1-4} alcoxi-piridazin-3-ilo), -NHCO$(CH_2)SO_2$(C_{1-4} alquilo), -NHCOPh, -NHCO(2-C_{1-4} alquil-Ph), -NHCO(3-C_{1-4} alquil-Ph), -NHCO(4-C_{1-4} alquil-Ph), -NHCO(2-halo-Ph), -NHCO(3-halo-Ph), -NHCO(2-C_{1-4} haloalquil-Ph), -NHCO(2-C_{1-4} haloalcoxi-Ph), -NHCO(2-halo-4-halo-Ph), -NHCO(2-halo-5-halo-Ph), -NHCO(oxazolilo), -NHCO(isoxazolilo), -NHCO(3-C_{1-4} alquil-isoxazol-5-ilo), -NHCO(4-C_{1-4} alquil-isoxazol-5-ilo), -NHCO(3-C_{1-4} alcoxi-isoxazol-5-ilo), -NHCO(4-C_{1-4} alcoxi-isoxazol-5-ilo), -NHCO(3-halo-isoxazol-5-ilo), -NHCO(3-OBn-isoxazol-5-ilo), -NHCO(3-

(2-halo-Ph)-isoxazol-5-ilo), -NHCO(3-(3-halo-Ph)-isoxazol-5-ilo), -NHCO(5-C_{1-4} alquil-1*H*-pirazol-3-ilo), imidazolilo, -NHCO(5-C_{1-4} alquil-1,3,4-oxadiazol-2-ilo), -NHCO(1-C_{1-4} alquil-1,2,3-triazol-4-ilo), -NHCO(6-C_{1-4} alcoxi-pirid-3-ilo), -NHCO(pirazinilo), -NHCO(6-halo-piridazin-3-ilo), 5-C_{1-4} haloalquil-1,3,4-oxadiazol-2-ilo, 3-NO_2-1*H*-1,2,4-triazol-1-ilo, tetrazolilo y 5-C_{1-4} alquil-tetrazol-1-ilo;

R^b se selecciona independientemente del grupo que consiste en halo, C_{1-6} alquilo, C_{1-6} alcoxi, C_{1-6} haloalquilo, C_{1-8} haloalcoxi, -CONH$(CH_2)_{6-20}$H, C_{3-6} cicloalquilo, C_{4-6} cicloalquenilo, -O$(CH_2)_m$(C_{3-6} cicloalquilo), fenoxi, benzoxi, pirimidinilo, pirazinilo y -O-pirimidinilo; y

R^g se selecciona independientemente del grupo que consiste en halo y C_{1-4} alquilo;

siempre que se excluyan los siguientes compuestos:



8. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1-7, en donde:

R^2 se selecciona independientemente del grupo que consiste en: CF_3 y Me;

R^3 se selecciona independientemente del grupo que

consiste en: H y F;

R^4 se selecciona independientemente del grupo que consiste en: H y F;

R^6 se selecciona independientemente del grupo que consiste en: NH_2, CN, -CONHMe, OPh, -CONH(ciclopropilo), -CONH(ciclobutilo), -CONH(ciclopentilo), -CONH(ciclohexilo), -CONHPh, -CONH(4-F-Ph), -CONH(2-Cl-Ph), -CONH(4-Cl-Ph), -CONH(4-Me-Ph), -CONH(4-OH-Ph), -CONH(3-OMe-Ph), -CONH(4-OMe-Ph), -CONH(4-CF_3-Ph), -CONH(4-OCF_3-Ph), -CONH(1-Me-pirazol-3-ilo), -CONH(4-(1*H* tetrazol-2-il)Ph), -CONH(4-(2*H*-tetrazol-5-il)-Ph), -CONH(3-F-4-Me-Ph), -CONH(3-F-4-OMe-Ph), -CONH$(CH_2)_2$Ph, -CONH(5-OMe-pirid-2-ilo), -CONH(6-OMe-pirid-3-ilo), -CONH(5-OMe-pirazin-2-ilo), -CONH(6-OMe-piridazin-3-ilo), -NHCO$(CH_2)SO_2$Me, -NHCOPh, -NHCO(2-Me-Ph), -NHCO(3-Me-Ph), -NHCO(4-Me-Ph), -NHCO(2-Cl-Ph), -NHCO(3-Cl-Ph), -NHCO(2-Cl-4-F-Ph), -NHCO(2-Cl-5-F-Ph), -NHCO(isoxazol-5-ilo), -NHCO(3-Me-isoxazol-5-ilo), -NHCO(4-Me-isoxazol-5-ilo), -NHCO(3-OMe-isoxazol-5-ilo), -NHCO(3-Br-isoxazol-5-ilo), -NHCO(3-(2-Cl-Ph)-isoxazol-5-ilo), -NHCO(3-(3-F-Ph)-isoxazol-5-ilo), -NHCO(3-OBn-isoxazol-5-ilo), 1*H*-imidazol-1-ilo, -NHCO(5-Me-1,3,4-oxadiazol-2-ilo), -NHCO(1-Me-1,2,3-triazol-4-ilo), -NHCO(6-OMe-pirid-3-ilo), -NHCO(6-Cl-piridazin-3-ilo), 5-CF3-1,3,4-oxadiazol-2-ilo, 1*H*-tetrazol-1-ilo, 1*H*-tetrazol-3-ilo y 2*H*-tetrazol-5-ilo;

R^{11} y R^{15} se seleccionan independientemente del

grupo que consiste en: H, Me, F y Cl;

R^{12} se selecciona independientemente del grupo que consiste en: H, F, Cl, Me y OMe;

R^{13} se selecciona independientemente del grupo que consiste en: H, F, Cl, Br, Me, OMe, OEt, CH_2OMe, CF_3, CH_2CF_3, $OCHF_2$, OCF_3, CN, $N(Me)_2$ y ciclopropilo;

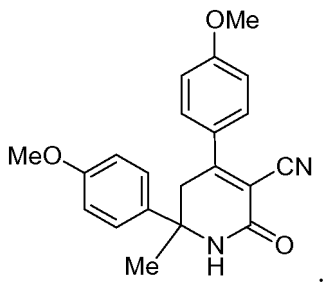
de manera alternativa, R^{12} y R^{13}, junto con los átomos de carbono a los que están unidos, se combinan para formar un anillo carbocíclico de 5 a 6 miembros o un anillo heterocíclico saturado de 5 a 6 miembros, que comprende átomos de carbono y 1-2 átomos de oxígeno;

R^{14} es H;

R^b, en cada caso, se selecciona independientemente del grupo que consiste en n-pentilo, metoxi, n-butoxi, i-butoxi, i-pentoxi, $O(CH_2)_{1-6}CF_3$, $-O(CH_2)_{1-4}CF_2CF_3$, $-CONH(CH_2)_{6-20}H$, ciclopropilo, ciclopent-1-en-1-ilo, ciclohex-1-en-1-ilo, $-O(CH_2)_2$(ciclopentilo), fenoxi, benzoxi, pirimidin-5-ilo, pirazin-2-ilo y -O-pirimidin-2-ilo; y

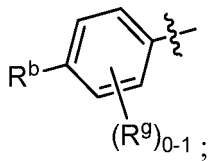
R^g es F;

siempre que se excluya el siguiente compuesto:



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9. Un compuesto de acuerdo con la reivindicación 4 o la reivindicación 5, en donde:

R^1 es  ;

R^2 se selecciona independientemente de CF_3 y CH_3;

R^6 se selecciona independientemente de: CN, R^c, -$CONHR^c$, -$NHCOR^c$ y -$NHCOCH_2SO_2$(C_{1-4} alquilo);

R^b se selecciona independientemente de: -$O(CH_2)_{1-6}CF_3$, $O(CH_2)_{1-4}CF_2CF_3$, -$CONH(CH_2)_{6-20}H$, ciclopent-1-en-1-ilo, ciclohex-1-en-1-ilo, $O(CH_2)_2$(ciclopentilo), fenoxi, benzoxi, pirimidin-5-ilo, pirazin-2-ilo y -O-pirimidin-2-ilo;

R^c, en cada caso, se selecciona independientemente del grupo que consiste en: -$(CH_2)_m$-(fenilo sustituido con 0-3 R^d), y un heteroarilo seleccionado de oxazolilo, isoxazolilo, pirazolilo, imidazolilo, oxadiazolilo, triazolilo, tetrazolilo, piridilo y pirazinilo; en donde el heteroarilo se sustituye con 0-2 R^d; y

R^d, en cada caso, se selecciona independientemente del grupo que consiste en halo, OH, CN, C_{1-4} alquilo, C_{1-4} alcoxi, C_{1-4} haloalquilo, C_{1-4} haloalcoxi, tetrazolilo y OBn.

10. Un compuesto de acuerdo con la reivindicación 1, en donde el compuesto se selecciona de:

(*S*)-3-(1*H*-tetrazol-5-il)-4-(p-tolil)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluoromethil)-5,6-

dihidropiridin-2(1*H*)-ona,

(*S*)-N-(4-metoxifenil)-2-oxo-4-(p-tolil)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carboxamida,

(*S*)-3-(2*H*-tetrazol-5-il)-4-(p-tolil)-6-(4-((6,6,6-trifluorohexil)oxi)fenil)-6-(trifluorometil)-5,6-dihidropiridin-2(1*H*)-ona,

(*S*)-2-oxo-4-(p-tolil)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carbonitrilo,

(*S*)-2-oxo-4-(p-tolil)-6-(4-(4,4,4-trifluorobutoxi)fenil)-N-(4-(trifluorometoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carboxamida,

(*S*)-N-(6-metoxipiridin-3-il)-2-oxo-4-(p-tolil)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carboxamida,

(*S*)-N-ciclopropil-2-oxo-4-(p-tolil)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carboxamida,

(*S*)-N-(4-hidroxifenil)-2-oxo-4-(p-tolil)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carboxamida,

(*S*)-4-(4-(difluorometoxi)fenil)-2-oxo-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carbonitrilo,

(*S*)-2-oxo-4-(p-tolil)-6-(trifluorometil)-6-(4-(3,3,3-trifluoropropoxi)fenil)-1,2,5,6-tetrahidropiridin-3-carbonitrilo,

(*S*)-4-(4-(difluorometoxi)fenil)-3-(1*H*-tetrazol-1-il)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-5,6-dihidropiridin-2(1*H*)-ona,

(*S*)-3-metil-N-(2-oxo-4-(p-tolil)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-il)isoxazol-5-carboxamida,

(*S*)-5-metil-N-(2-oxo-4-(p-tolil)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-il)-1,3,4-oxadiazol-2-carboxamida,

N^2-heptil-N^5-(4-metoxifenil)-2-metil-6-oxo-4-(p-tolil)-1,2,3,6-tetrahidropiridin-2,5-dicarboxamida,

(*S*)-3-(1*H*-tetrazol-1-il)-4-(p-tolil)-6-(4-((6,6,6-trifluorohexil)oxi)fenil)-6-(trifluorometil)-5,6-dihidropiridin-2(1*H*)-ona,

(*S*)-2-oxo-4-(p-tolil)-6-(4-((6,6,6-trifluorohexil)oxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carbonitrilo,

(*S*)-4-(5,6,7,8-tetrahidronaftalen-2-il)-3-(1*H*-tetrazol-5-il)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-5,6-dihidropiridin-2(1*H*)-ona,

(*S*)-2-(metilsulfonil)-N-(2-oxo-4-(p-tolil)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-

tetrahidropiridin-3-il)acetamida,

(*S*)-3-(1*H*-tetrazol-5-il)-6-(4-(4,4,4-trifluorobutoxi)fenil)-4-(4-(2,2,2-trifluoroetil)fenil)-6-(trifluorometil)-5,6-dihidropiridin-2(1*H*)-ona, y

(*S*)-N-(5-metoxipirazin-2-il)-2-oxo-4-(p-tolil)-6-(4-(4,4,4-trifluorobutoxi)fenil)-6-(trifluorometil)-1,2,5,6-tetrahidropiridin-3-carboxamida;

o una sal de aquel aceptable desde el punto de vista farmacéutico.

11. Una composición farmacéutica que comprende un portador aceptable desde el punto de vista farmacéutico y un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 10, o un estereoisómero, un tautómero o una sal de aquel aceptable desde el punto de vista farmacéutico.

12.La composición farmacéutica de acuerdo con la reivindicación 11, que también comprende uno o más de otros agentes terapéuticos adecuados útiles para el tratamiento de los trastornos antes mencionados, que incluyen: agentes antidiabéticos, agentes antihiperglicémicos, agentes antihiperinsulinémicos, agentes antiretinopáticos, agentes antineuropáticos, agentes antinefropáticos, agentes antiateroescleréticos, agentes antiisquémicos, agentes antihipertensores, agentes contra la obesidad, agentes antidislipidémicos, agentes antihiperlipidémicos, agentes antihipertrigliceridémicos, agentes

antihipercolesterolémicos, agentes contra la restenosis, agentes antipancreáticos, hipolipemiantes, anorexígenos, agentes que mejoran la memoria, agentes contra la demencia o agentes promotores del desarrollo cognitivo, supresores del apetito, tratamientos para la insuficiencia cardíaca, tratamientos para la arteriopatía periférica y agentes antiinflamatorios.

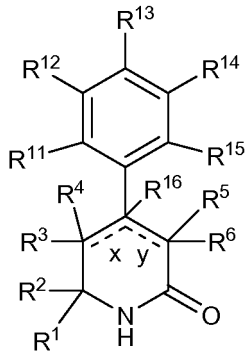
13. La composición farmacéutica de acuerdo con la reivindicación 11, que también comprende un inhibidor de dipeptidil peptidasa-IV.

14. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 10, para usarse en la prevención, la modulación o el tratamiento de diabetes, hiperglucemia, intolerancia a la glucosa, diabetes gestacional, resistencia a la insulina, hiperinsulinemia, hepatopatía grasa no alcohólica (NAFLD), que incluye esteatohepatitis no alcohólica (NASH), retinopatía, neuropatía, nefropatía, cicatrización tardía, aterosclerosis y sus secuelas, actividad cardíaca anormal, isquemia de miocardio, apoplejía, síndrome metabólico, hipertensión, obesidad, dislipidemia, dislipidemia, hiperlipidemia, hipertrigliceridemia, hipercolesterolemia, niveles reducidos de lipoproteínas de alta densidad (HDL), niveles elevados de lipoproteínas de baja densidad (LDL), isquemia no cardíaca, trastornos lipídicos y glaucoma.

15. Un compuesto para usarse de acuerdo con la reivindicación 14, en donde el compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 10, se usa de manera simultánea, separada o secuencial con un agente terapéutico adicional.

RESUMEN

La presente invención provee compuestos de la Fórmula (I):



(I)

o un estereoisómero o una sal de aquel aceptable desde el punto de vista farmacéutico, en donde todas las variables son como se definen en la presente. Estos compuestos son inhibidores de monoacilglicerol aciltransferasa tipo 2 (MGAT2) que se pueden usar como medicamentos.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

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

To:

SUN, Jing G.
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
26 May 2014 (26.05.2014)

Applicant's or agent's file reference
11841 WOPCT

IMPORTANT NOTIFICATION

International application No.
PCT/US2012/067173

International filing date *(day/month/year)*
30 November 2012 (30.11.2012)

1. The following indications appeared on record concerning:

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

Name and Address

State of Nationality | State of Residence

Telephone No.

Facsimile No.

E-mail address

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

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

Name and Address

ZHAO, Guohua
c/o Bristol-Myers Squibb Company
311 Pennington-Rocky Hill Road
Pennington, New Jersey 08534
United States of America

State of Nationality | State of Residence

Telephone No.

Facsimile No.

E-mail address
☐ Notifications by e-mail authorized

3. Further observations, if necessary:
The person identified in Box 2 has been added as inventor only.

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

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

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

Facsimile No. +41 22 338 71 30

Authorized officer
Guadagnino Christine
e-mail pt09.pct@wipo.int
Telephone No. +41 22 338 74 09

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

PODER OTORGADO POR BRISTOL-MYERS SQUIBB COMPANY

APOSTILLA

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA

2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR:
SALLY B. HANSEN

3. QUIEN ACTÚA EN CALIDAD DE NOTARIO PÚBLICO DE NUEVA JERSEY

4. LLEVA EL SELLO DE:
SALLY B. HANSEN, NOTARIO

CERTIFICADO

5. EN TRENTON, NUEVA JERSEY

6. EL 28 DE JUNIO DE 2007

7. POR BRADLEY ABELOW, TESORERO DE NUEVA JERSEY

8. N° A295716

9. SELLO (APARECE ADHERIDO SELLO DORADO)

10. FIRMA (FIRMADO) BRADLEY ABELOW

Texto en inglés y en español mediante el cual **BRISTOL-MYERS SQUIBB COMPANY** domiciliada en Nueva York, Nueva York, otorga poder a **ALVARO CORREA ORDOÑEZ y/o OLGA GEORGETTE OTERO y/o RICARDO METKE y/o JUAN PABLO CONCHA**

Dado y suscrito el 30 de mayo de 2007

(Firmado) Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior)

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
RES. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

1

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

CERTIFICACIÓN NOTARIAL

Texto en inglés y en español mediante el cual el suscrito Notario certifica el 30 de mayo de 2007 la existencia legal de la sociedad **BRISTOL-MYERS SQUIBB COMPANY** así como las funciones y firma de su representante autorizado Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior) para lo cual se basó en los documentos relacionados en inglés en el punto 6 de la certificación los cuales se traducen aquí al español, a saber:

Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.

Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado mayo 24, 2005.

[Firmado] SALLY B. HANSEN, Notario Público

[Sello en tinta que dice: "SALLY B. HANSEN. Notario Público de Nueva Jersey. Mi comisión vence el 6 de junio de 2010"]

[Aparece sello realzado]

La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

Jaime Armando Garavito Burgos
c.c. N° 19.130.702 de Bogotá
Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

BOGDM5 # 82106

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

2

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
SALLY B HANSEN

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
SALLY B HANSEN, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

6. THE 28TH DAY OF JUNE 2007

7. BY: Bradley Abelow, NEW JERSEY TREASURER

8. NO. A295716

9. SEAL/STAMP:



10. SIGNATURE

Bradley Abelow

BAKER & MCKENZIE

Raisbeck, Lara, Rodríguez & Rueda
Av. 82 No. 10 - 62 6th Floor
Bogotá, Colombia

NIT: 860.066.640-3
Tel: +57 1 634 1500
Fax: +57 1 376 2211
www.bakernet.com

POWER OF ATTORNEY

The undersigned.

BRISTOL–MYERS SQUIBB COMPANY

domiciled in

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America

declares that it hereby grants to

ALVARO CORREA-ORDOÑEZ and/or
OLGA GEORGETTE OTERO and/or
RICARDO METKE and/or
JUAN PABLO CONCHA

with domicile at Av. 82 No. 10 – 62, 6Th floor, of Bogotá D. C., Colombia, a full and sufficient power of attorney to obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models, industrial designs, integrated circuits, layout-designs and vegetal varieties; the registration of trademarks, denominations of origin, commercial names, trade emblems, slogans and domain names; its renewal, assignments, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b)Processes of protection to the consumer, unfair competition, oppositions, cancellations, nullity, precautionary injunctions, infringement, granting of licenses, writ mandamus, the protection of trade secrets, and in general the civil, penal, an administrative processes relating to those rights. And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

I hereby ratify all actions previously taken on behalf of this company by the aforementioned attorneys with respect to the mentioned matters.

Done and subscribed in

On the 30 day of May of 2007

Signature of the person issuing the Power

Anastasia P. Winslow
Senior Patent Counsel

PODER DE ABOGADO

La abajo firmada,

BRISTOL–MYERS SQUIBB COMPANY

domiciliada en

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 Estados Unidos de América

declara por el presente que otorga a

ALVARO CORREA-ORDOÑEZ y/o
OLGA GEORGETTE OTERO y/o
RICARDO METKE y/o
JUAN PABLO CONCHA

con domicilio en la Av. 82 No. 10 – 62 Piso 6 en Bogotá D. C., Colombia, poder especial amplio y suficiente, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera autoridades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, diseños industriales, esquemas de trazado de circuitos integrados y variedades vegetales; el registro de marcas, denominaciones de origen, nombres comerciales, enseñas, lemas comerciales y nombres de dominio; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Los procesos para la protección del consumidor, competencia desleal, oposiciones, cancelaciones, nulidades, medidas cautelares, infracciones, concesión de licencias, la tutela, la protección de secretos industriales, y en general procesos civiles, penales, administrativos relacionados con estos derechos. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del caso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

Igualmente, ratifico todo lo actuado hasta el momento en los mismos asuntos, por cualquiera de los mencionados apoderados en representación de ésta sociedad.

Dado y firmado en

A los 30 días del mes de mayo de 2007

Firma de la persona que firma el Poder

BAKER & MCKENZIE

NOTARIAL CERTIFICATION

On this 30 day of May 2007, the undersigned Notary

CERTIFIES

1. That **Name of the person issuing the power**
Anastasia P. Winslow
of legal age and domiciled in
Princeton, NJ USA
Address, city, state, country
set his hand on the foregoing document.

2. That the grantor is to me personally known and that he/she has legal capacity to execute the instrument.

3. That the grantor has executed the foregoing document as
Senior Patent Counsel
Position of the person issuing the Power
of the judicial person **BRISTOL-MYERS SQUIBB COMPANY**

4. That the judicial person **BRISTOL-MYERS SQUIBB COMPANY**
having its home office in
Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America
is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. That the grantor has in fact the referred to authority and that his/her representation is legal.

6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:
(Please indicate here the documents such as the articles of incorporation, by laws or resolution from the Board of Directors and their dates, on which the notary relied to grant the certification)
- Certification executed by Sr. Vice President and General Counsel of Bristol-Myers Squibb Company on April 7, 2007
- Amended and Restated Certificate of Incorporation of Bristol-Myers Squibb Company dated May 24, 2005

Notary Public
SALLY B. HANSEN
Notary Public of New Jersey
My Commission Expires June 6, 2010

CERTIFICACION NOTARIAL

A los 30 días del mes de mayo de 2007, el suscrito Notario

DA FE

1 Que Anastasia P. Winslow
mayor y domiciliado en Princeton, NJ
Estados Unidos de América
suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

3 Que el otorgante ha suscrito el referido documento en su carácter de
Abogados de Patentes Senior
de la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**

4 Que la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**
con sede en
Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 Estados Unidos de América
está legalmente constituída, que tiene existencia legal actual y que el acto para el cual se otorga el poder está comprendido entre los que constituyen su objeto social.

5 Que el otorgante tiene efectivamente la representación que ostenta y que ésta es legítima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:
- Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.
- Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado el 4 de mayo de 2005.

El Notario Público

5

BMS Ref: 11841

NOTARIAL TRUE COPY

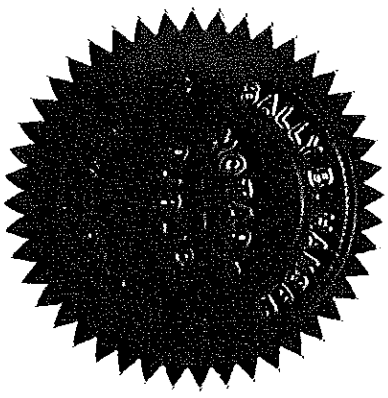
I, Nancy J. Ingram, declare on this 29th day of May, 2014, that the attached Assignments for US Patent Application Numbers 61/566,039 and 13/688,584 are the complete, full, true, and exact copies of the original worldwide Assignments as executed by the named inventors.

Nancy J. Ingram

UNITED STATES OF AMERICA)
STATE OF NEW JERSEY) ss.
COUNTY OF MERCER)

Subscribed and sworn before me in the county of Mercer and state of New Jersey, this 29 day of May 2014.

Sally B. Hansen
Notary Public of New Jersey
My Commission Expires June 6, 2015



Received – BMS IP Dept.
Action Due: ASG
Due Date:
Atty/Agt: SUN, J
By Wendy J. Torres at Jun 13, 2012
WT

UNITED STATES PATENT AND TRADEMARK OFFICE
UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

JUNE 13, 2012

PTAS

JING G. SUN
ROUTE 206 & PROVINCE LINE ROAD
PATENT DEPARTMENT
PRINCETON, NJ 08543-4000

501951761

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT RECORDATION BRANCH OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE ASSIGNMENT RECORDATION BRANCH AT 571-272-3350. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT RECORDATION BRANCH, P.O. BOX 1450, ALEXANDRIA, VA 22313.

RECORDATION DATE: 06/12/2012

REEL/FRAME: 028357/0415
NUMBER OF PAGES: 7

BRIEF: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

DOCKET NUMBER: 11841 USPSP

ASSIGNOR:
TURDI, HUJI

DOC DATE: 06/05/2012

ASSIGNOR:
HANGELAND, JON J.

DOC DATE: 06/05/2012

ASSIGNOR:
LAWRENCE, R. MICHAEL

DOC DATE: 05/16/2012

ASSIGNOR:
CHENG, DONG

DOC DATE: 05/24/2012

ASSIGNEE:
BRISTOL-MYERS SQUIBB COMPANY
ROUTE 206 & PROVINCE LINE ROAD
PATENT DEPARTMENT
PRINCETON, NEW JERSEY 08543-4000

APPLICATION NUMBER: 61566039
FILING DATE: 12/02/2011
PATENT NUMBER:
ISSUE DATE:
TITLE: ARYL DIHYDROPYRIDINONES MGAT2 INHIBITORS

ASSIGNMENT

We,

Huji Turdi, Jon J. Hangeland, R. Michael Lawrence, Dong Cheng

pursuant to contractual obligations heretofore assumed by us and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to **Bristol-Myers Squibb Company**, a Delaware corporation, having a place of business at Rt. 206 & Province Line Road, Princeton, NJ 08543-4000, its successors, assigns and legal representatives, all our right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to me by local laws or by treaty, including any international convention for the protection of industrial property, in and for all countries of the world, including the United States and its territories and possessions, in and to the invention entitled:

ARYL DIHYDROPYRIDINONES MGAT2 INHIBITORS

invented by us and described in the provisional United States patent application

Application Number 61/566039, filed 02 Dec 2011

including said provisional United States patent application and any application claiming priority from said provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

And we hereby agree to communicate to said assignee or its representatives any facts known to us respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents, extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries).

Signed this 5 day of June, 2012 by _____
Huji Turdi

STATE OF NEW JERSEY)
)
COUNTY OF)

On the 5th day of June, 2012, before me came Huji Turdi to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

[SEAL]

SHARON MAY
NOTARY PUBLIC NEW JERSEY
COMM. #2411644 Exp 8/23/16
Mercer County

_____
Notary Public

Signed this 5 day of June, 2012 by _____
Jon J. Hangeland

STATE OF NEW JERSEY)
)
COUNTY OF)

On the 5th day of June, 2012, before me came Jon J. Hangeland to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

[SEAL]

_____
Notary Public

SHARON MAY
NOTARY PUBLIC NEW JERSEY
COMM. #2411644 Exp 8/23/16
Mercer County

Signed this 16 day of May, 2012 by _____
R. Michael Lawrence

STATE OF NEW JERSEY)
)
COUNTY OF Mercer)

On the 16th day of May, 2012, before me came R. Michael Lawrence to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

[SEAL]

_____
Notary Public

SHARON MAY
NOTARY PUBLIC NEW JERSEY
COMM. #2411644 Exp 8/23/16
Mercer County

Signed this 24th day of May, 2012 by _____
Dong Cheng

STATE OF NEW JERSEY)
)
COUNTY OF Mercer)

On the 24th day of May, 2012, before me came Dong Cheng to me known to be the person of that name mentioned In, and who executed the foregoing Assignment and acknowledged that he/she executed it.

[SEAL]

SHARON MAY
NOTARY PUBLIC NEW JERSEY
COMM. #2411644 Exp 8/23/16
Mercer County

_____
Notary Public

Received – BMS IP Dept.
Action Due: ASGC
Due Date: 3/8/2013
Atty/Agt: SUN, J.
By Dawnet Bragg at Jan 15, 2013

UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

JANUARY 14, 2013

PTAS

JING G. SUN
ROUTE 206 & PROVINCE LINE ROAD
PATENT DEPARTMENT
PRINCETON, NJ 08543-4000

502191420

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT RECORDATION BRANCH OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE ASSIGNMENT RECORDATION BRANCH AT 571-272-3350. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT RECORDATION BRANCH, P.O. BOX 1450, ALEXANDRIA, VA 22313.

RECORDATION DATE: 01/11/2013

REEL/FRAME: 029610/0079
NUMBER OF PAGES: 11

BRIEF: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

DOCKET NUMBER: 11841-USNP

ASSIGNOR:
TURDI, HUJI — DOC DATE: 01/04/2013

ASSIGNOR:
HANGELAND, JON J. — DOC DATE: 12/20/2012

ASSIGNOR:
LAWRENCE, R. MICHAEL — DOC DATE: 12/14/2012

ASSIGNOR:
CHENG, DONG — DOC DATE: 01/04/2013

ASSIGNOR:
AHMAD, SALEEM — DOC DATE: 01/09/2013

ASSIGNOR:
MENG, WEI — DOC DATE: 01/04/2013

ASSIGNOR:
BRIGANCE, ROBERT PAUL — DOC DATE: 12/14/2012

ASSIGNOR:
DEVASTHALE, PRATIK DOC DATE: 01/04/2013

ASSIGNEE:
BRISTOL-MYERS SQUIBB COMPANY
ROUTE 206 & PROVINCE LINE ROAD
PATENT DEPARTMENT
PRINCETON, NEW JERSEY 08543-4000

APPLICATION NUMBER: 13688584 FILING DATE: 11/29/2012
PATENT NUMBER: ISSUE DATE:
TITLE: ARYL DIHYDROPYRIDINONE AND PIPERIDINONE MGAT2 INHIBITORS
should be DIHYDROPYRIDINONES

ASSIGNMENT RECORDATION BRANCH
PUBLIC RECORDS DIVISION

ASSIGNMENT

We,

Hujl Turdi, Jon J. Hangeland, R. Michael Lawrence, Dong Cheng, Saleem Ahmad, Wei Meng, Robert Brigance, Pratik Devasthale

pursuant to contractual obligations heretofore assumed by us and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to **Bristol-Myers Squibb Company**, a Delaware corporation, having a place of business at Rt. 206 & Province Line Road, Princeton, NJ 08543-4000, its successors, assigns and legal representatives, all our rights, titles and interests, which includes the right to and full benefit of such priorities as may now or hereafter be granted to us by local laws or by treaty, including any international convention for the protection of industrial property, in and for all countries of the world, including the United States and its territories and possessions, in and to the invention entitled:

ARYL DIHYDROPYRIDINONES AND PIPERIDINONE MGAT2 INHIBITORS

invented by us and described in the non-provisional United States patent application

Application Number 13/688,584, filed November 29, 2012

including said non-provisional United States patent application and any application claiming priority from said non-provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made;

And we hereby agree to communicate to said assignee or its representatives any facts known to us respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents, extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries).

Signed this 4 day of January, 2013, by Huji Turdi
Huji Turdi

STATE OF NEW JERSEY)
)
COUNTY OF Mercer)

On the 4th day of January, 2013, before me came Huji Turdi to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

Sharon May
Notary Public

[SEAL]

SHARON MAY
NOTARY PUBLIC NEW JERSEY
COMM. #2411644 Exp 8/23/16
Mercer County

Signed this 20 day of December, 2012 by _____
Jon J. Hangeland

STATE OF NEW JERSEY)
)
COUNTY OF Mercer)

On the 20th day of December, 2012, before me came Jon J. Hangeland to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

_____
Notary Public

[SEAL]

SHARON MAY
NOTARY PUBLIC NEW JERSEY
COMM. #2411644 Exp 8/23/16
Mercer County

Signed this 14 day of December, 2012 by _____
R. Michael Lawrence

STATE OF NEW JERSEY)
)
COUNTY OF Mercer)

On the 14th day of December, 2012, before me came R. Michael Lawrence to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

_____
Notary Public

[SEAL]

SHARON MAY
NOTARY PUBLIC NEW JERSEY
COMM. #2411644 Exp 8/23/16
Mercer County

Signed this 4th day of Jan, 2013 by _____
Dong Cheng

STATE OF NEW JERSEY)
)
COUNTY OF Mercer)

On the 4th day of January, 2013, before me came Dong Cheng to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

_____
Notary Public

[SEAL]

SHARON MAY
NOTARY PUBLIC NEW JERSEY
COMM. #2411644 Exp 8/23/16
Mercer County

Signed this 9 day of January, 2013 by _____
Saleem Ahmad

STATE OF NEW JERSEY)
)
COUNTY OF Burlington)

On the 9 day of January, 2013, before me came Saleem Ahmad to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

_____
Notary Public

[SEAL]

NELL ANNE E BARTHOLOMEW
Notary Public of New Jersey
My Commission Expires March 23, 2016

Signed this 4th day of January, 2012 2013 by _____
Wei Meng

STATE OF NEW JERSEY)
)
COUNTY OF Mercer)

On the 4th day of January, 2013, before me came Wei Meng to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

[SEAL]

_____
Notary Public

Signed this 14th day of December 2012 by _____
Robert Paul Brigance

STATE OF NEW JERSEY)
)
COUNTY OF Mercer)

On the 14th day of December, 2012, before me came Robert Paul Brigance to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

[SEAL]

_____
Notary Public

SHARON MAY
NOTARY PUBLIC NEW JERSEY
COMM. #2411644 Exp 8/23/16
Mercer County

Signed this 4th day of JAN, 2013 by _____
~~Pratik~~ Devasthale

STATE OF NEW JERSEY)
)
COUNTY OF Mercer)

On the 4th day of January, 2013, before me came Pratik Devasthale to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

[SEAL]

SHARON MAY
NOTARY PUBLIC NEW JERSEY
COMM. #2411644 Exp 8/23/16
Mercer County

_____
Notary Public

Received – BMS IP Dept.
Action Due: ASGR
Due Date:
Atty/Agt: SUN, J

By D. Bragg at Jan 16, 2014

UNITED STATES PATENT AND TRADEMARK OFFICE
UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

JANUARY 16, 2014

PTAS

JING G. SUN
ROUTE 206 & PROVINCE LINE ROAD
PATENT DEPARTMENT
PRINCETON, NJ 08543-4000

502635901

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT RECORDATION BRANCH OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

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RECORDATION DATE: 01/15/2014
REEL/FRAME: 031972/0089
NUMBER OF PAGES: 3

BRIEF: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

DOCKET NUMBER: 11841 USNP

ASSIGNOR:
ZHAO, GUOHUA
DOC DATE: 01/14/2014

ASSIGNEE:
BRISTOL-MYERS SQUIBB COMPANY
ROUTE 206 & PROVINCE LINE ROAD
PATENT DEPARTMENT
PRINCETON, NEW JERSEY 08543-4000

APPLICATION NUMBER: 13688584
FILING DATE: 11/29/2012
PATENT NUMBER:
ISSUE DATE:
TITLE: ARYL DIHYDROPYRIDINONE AND PIPERIDINONE MGAT2 INHIBITORS

ASSIGNMENT RECORDATION BRANCH
PUBLIC RECORDS DIVISION

ASSIGNMENT

I,

Guohua Zhao

pursuant to contractual obligations heretofore assumed by me and/or for good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, do hereby sell and assign to **Bristol-Myers Squibb Company**, a Delaware corporation, having a place of business at Rt. 206 & Province Line Road, Princeton, NJ 08543-4000, its successors, assigns and legal representatives, all my right, title and interest, which includes the right to and full benefit of such priorities as may now or hereafter be granted to me by local laws or by treaty, including any international convention for the protection of industrial property, in and for all countries of the world, including the United States and its territories and possessions, in and to the invention entitled:

ARYL DIHYDROPYRIDINONES AND PIPERIDINONE MGAT2 INHIBITORS

invented by me and described in the non-provisional United States patent application

Application Number 13/688584, filed 29 Nov 2012

including said non-provisional United States patent application and any application claiming priority from said non-provisional application, filed in any country, and any patents which may be issued and/or granted thereon, and all divisions, continuations, reissues, reexamination certificates and extensions thereof in all countries, the said interest being the entire ownership of said invention and all of said applications, patents (including reissue patents), extensions and reexamination certificates to be held and enjoyed by the said Bristol-Myers Squibb Company and its successors and assigns to the full end of the terms to which said patents (including reissue patents), extensions and reexamination certificates may be granted and/or issued, as fully and entirely as the same would have been held and enjoyed by me if this sale, assignment and transfer had not been made;

And I hereby agree to communicate to said assignee or its representatives any facts known to me respecting said invention, to testify in any legal proceedings, to sign and/or execute any further documents and/or instruments which may be necessary, lawful and proper in and/or for the filing and/or prosecution of all applications, including divisional, continuation and reissue applications, extensions and reexamination certificates and/or the granting and/or issuance thereof and/or to otherwise secure title to said invention and all of said applications, patents (including reissue patents, extensions and reexamination certificates in said assignee, and in general to do everything possible to aid said assignee, its successors and assigns to obtain and enforce proper protection for said invention in all countries).

Signed this 14th day of January, 2014 by _____
Guohua Zhao

STATE OF NEW JERSEY)
)
COUNTY OF Mercer)

On the 14th day of January, 2014, before me came Guohua Zhao to me known to be the person of that name mentioned in, and who executed the foregoing Assignment and acknowledged that he/she executed it.

_____
Notary Public

NELL ANNE E BARTHOLOMEW
Notary Public of New Jersey
My Commission Expires March 23, 2016

BSM Ref: 11841

COPIA NOTARIAL VERDADERA

Yo, Nancy J. Ingram, declaro este día 29 de mayo de 2014, que las Cesiones adjuntas para los números de solicitudes de patente Estadounidenses 61/566,039 y 13/688.584 son las copias completas, totales, verdaderas y exactas de las Cesiones mundiales originales tal como fue firmada por los inventores nombrados.

(Firmado)

Nancy J. Ingram

ESTADOS UNIDOS DE AMÉRICA)

ESTADO DE NEW JERSEY) ss.

CONDADO DE MERCER)

Firmado y juramentado ante mí en el Condado de Mercer y el Estado de New Jersey, este día 29 de mayo de 2014.

(firmado)

Sally B. Hansen

(Sello) Notario Público de New Jersey

Mi comisión expira el 6 de junio de 2015

Recibido – BMS IP Dept.

Acción efectuada: ASG

Fecha de firma:

Abogado/Agente: SUN, J

Por Wendy J. Torres el 13 de Jun. De 2012

WT

(Sello)

Oficina de Marcas y Patentes de los Estados Unidos
Bajo la Secretaría de Comercio para la Propiedad Intelectual
Director de la Oficina de Marcas y Patentes de los Estados Unidos

Junio 13, 2012

JING G. SUN

ROUTE 206 & PROVINCE LINE ROAD 501951761

PRINCETON, NJ 08543-4000

OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS
AVISO DE INSCRIPCIÓN DE DOCUMENTO DE CESIÓN

EL DOCUMENTO ADJUNTO HA SIDO INSCRITO POR LA DIVISIÓN DE CESIONES DE LA OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS. UNA COPIA COMPLETA MICROFILMADA ESTÁ DISPONIBLE EN EL SALÓN DE BÚSQUEDAS DE CESIONES EN EL NÚMERO DE ROLLO Y ESTANTE INDICADOS ADELANTE.

POR FAVOR REVISE TODA LA INFORMACIÓN CONTENIDA EN ESTE AVISO. LA INFORMACIÓN CONTENIDA EN ESTE AVISO DE INSCRIPCIÓN REFLEJA LOS DATOS EXISTENTES EN EL SISTEMA DE CESIONES DE MARCAS Y PATENTES. SI USTED ENCUENTRA CUALQUIER ERROR O TIENE PREGUNTAS RESPECTO A ESTE AVISO, POR FAVOR CONTACTE AL EMPLEADO CUYO NOMBRE APARECE EN ESTE AVISO AL TELÉFONO 571-272-3350. POR FAVOR ENVÍE UNA SOLICITUD DE CORRECCIÓN A: OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS, CORREO: ASSIGNMENT SERVICES BRANCH, P.O. BOX 1450, ALEXANDRIA, VA 22313.

FECHA DE INSCRIPCIÓN: 06/12/2012 ROLLO/ESTANTE: 028357/0415

NÚMERO DE PÁGINAS: 7

RESUMEN: CESIÓN DE LOS INTERESES DEL CEDENTE (VER DOCUMENTO PARA LOS DETALLES).

NUMERO DE DOCUMENTO: 11841 USPSP

CEDENTE:

TURDI, HUJI FECHA DOC: 06/05/2012

CEDENTE:

HANGELAND, JON J. FECHA DOC: 06/05/2012

CEDENTE:

LAWRENCE, R. MICHAEL FECHA DOC: 05/16/2012

CEDENTE:

CHENG, DONG FECHA DOC: 05/24/2012

CESIONARIO:

BRISTOL-MYERS SQUIBB COMPANY

ROUTE 206 & PROVINCE LINE ROAD

PATENT DEPARTMENT

PRINCETON, NJ 08543-4000

SOLICITUD No.: 61566039 FECHA DE PRESENTACIÓN: 12/02/2011

NÚMERO DE PATENTE: FECHA DE EMISIÓN:

TÍTULO: INHIBIDORES DE ARIL DIHIDROPIRIDINONAS MGAT2

11841-US-PSP

CESIÓN

Nosotros,

Huji Turdi, jon j. hangeland, r. Michael Lawrence, Dong cheng

De acuerdo con las obligaciones contractuales asumidas aquí por nosotros y/o por la consideración buena y valiosa, cuya recepción y suficiencia reconocemos aquí, vendemos y cedemos a **Bristol-Myers Squibb Company**, una corporación de Delaware, con oficinas en Rt. 206 & Province Line Road, Princeton, NJ 08543-4000, sus sucesores, asignados y representantes legales todo nuestro derecho, título e interés, lo que incluye el derecho a y completo beneficio de cualesquier prioridades que puedan ahora o posteriormente ser otorgadas a nosotros por leyes locales o por tratados, incluyendo cualquier convenio internacional para la protección de la propiedad industrial, en y para todos los países del mundo, incluyendo los Estado Unidos y sus territorios y posesiones, en y para la invención titulada

TITULO

INHIBIDORES DE ARIL DIHIDROPIRIDINONAS MGAT2

Inventada por nosotros y descrita en la Solicitud de Patente Estadounidense

Solicitud No. 61/566039 presentada el 2 de diciembre de 2011

Que incluye dicha Solicitud de Patente Estadounidense provisional y cualquier solicitud que reclame prioridad de dicha Solicitud provisional, que se haya presentado en cualquier país, y cualesquier patentes que se otorguen y/o emitan sobre estas, y todas las divisionales, continuaciones, re-emisiones, certificados de re-exámen y extensiones de las mismas en todos los países, el dicho interés es la propiedad completa de dicha invención y todas las dichas solicitudes, patentes (incluyendo re-emisiones de patentes), extensiones y certificados de reexamen para ser poseídos y disfrutados por la dicha Bristol-Myers Squibb Company y sus sucesores y asignados hasta el final completo de los términos de vigencia otorgados a dichas patentes (incluyendo re-emisiones de patentes), extensiones y certificados de reexamen que puedan ser otorgados y/o emitidos, tan completamente y enteramente como si la misma hubiera sido poseída y disfrutada por nosotros en el caso de que esta venta, cesión y transferencia no se hubiera efectuado;

Y acordamos aquí comunicar a dicho cesionario o sus representantes de cualesquier hechos conocidos por nosotros relacionados con dicha invención, para testificar en cualesquier procesos legales, firmar todas las solicitudes, documentos ó instrumentos necesarios, legales o apropiados en y/o para la presentación y procedimiento de todas las solicitudes, incluyendo divisionales, continuaciones y solicitudes de re-emisión, extensiones y certificados de reexamen y/o el otorgamiento y/o emisión de las mismas y/o para asegurar de otra manera el título a dicha invención y a todas las dichas solicitudes, patentes (incluyendo re-emisiones de patentes), extensiones y certificados de reexamen para el dicho cesionario, y en general hacer todo lo posible para ayudar a dicho cesionario, sus sucesores y asignados para obtener y defender la protección adecuada para dicha invención en todos los países.

Firmado este día 5 de 2012 de 2012 por (Firmado)

Hudi Turdi

ESTADO DE New Jersey)

)

CONDADO DE)

En este día _____5____ de ___junio_____, 2012, se presentó ante mi Hudi Turdi, conocido por mi como la persona con ese nombre, y quien firmó la Cesión anterior y reconoció que la firmó.

[SELLO] ___(Firmado)_____

Notario Público

(sello) SHARON MAY

Notario Público New Jersey

Comisión #2411644 exp. 8/23/16

Condado de Mercer

Firmado este día 5 de junio de 2012 por (Firmado)

Jon J. Hangeland

ESTADO DE New Jersey)

)

CONDADO DE)

En este día _____5____ de ___junio_____, 2012, se presentó ante mi Don J. Hangeland, conocido por mi como la persona con ese nombre, y quien firmó la Cesión anterior y reconoció que la firmó.

[SELLO] ___(Firmado)_____

Notario Público

(sello) SHARON MAY

Notario Público New Jersey

Comisión #2411644 exp. 8/23/16

Condado de Mercer

Firmado este día 16 de mayo de 2012 por (Firmado)

R. Michael Lawrence

ESTADO DE New Jersey)

)

CONDADO DE Mercer)

En este día _____16____ de ___mayo_____, 2012, se presentó ante mi R. Michael Lawrence, conocido por mi como la persona con ese nombre, y quien firmó la Cesión anterior y reconoció que la firmó.

[SELLO] ___(Firmado)_____

Notario Público

(sello) SHARON MAY

Notario Público New Jersey

Comisión #2411644 exp. 8/23/16

Condado de Mercer

Firmado este día 24 de mayo de 2012 por (Firmado)

Dong Cheng

ESTADO DE New Jersey)

)

CONDADO DE Mercer)

En este día _____24__ de ___mayo_____, 2012, se presentó ante mi Dong Cheng, conocido por mi como la persona con ese nombre, y quien firmó la Cesión anterior y reconoció que la firmó.

[SELLO] ___(Firmado)_____

Notario Público

(sello) SHARON MAY

Notario Público New Jersey

Comisión #2411644 exp. 8/23/16

Condado de Mercer

Recibido – BMS IP Dept.

Acción efectuada: ASGC

Fecha de firma: 3/8/2013

Abogado/Agente: SUN, J

Por Dawnet Bragg el 15 de Jun. De 2012

(Sello)

Oficina de Marcas y Patentes de los Estados Unidos
Bajo la Secretaría de Comercio para la Propiedad Intelectual
Director de la Oficina de Marcas y Patentes de los Estados Unidos

Junio 14, 2012

JING G. SUN

ROUTE 206 & PROVINCE LINE ROAD 502191420

PATENT DEPARTMENT

PRINCETON, NJ 08543-4000

OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS
AVISO DE INSCRIPCIÓN DE DOCUMENTO DE CESIÓN

EL DOCUMENTO ADJUNTO HA SIDO INSCRITO POR LA DIVISIÓN DE CESIONES DE LA OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS. UNA COPIA COMPLETA MICROFILMADA ESTÁ DISPONIBLE EN EL SALÓN DE BÚSQUEDAS DE CESIONES EN EL NÚMERO DE ROLLO Y ESTANTE INDICADOS ADELANTE.

POR FAVOR REVISE TODA LA INFORMACIÓN CONTENIDA EN ESTE AVISO. LA INFORMACIÓN CONTENIDA EN ESTE AVISO DE INSCRIPCIÓN REFLEJA LOS DATOS EXISTENTES EN EL SISTEMA DE CESIONES DE MARCAS Y PATENTES. SI USTED ENCUENTRA CUALQUIER ERROR O TIENE PREGUNTAS RESPECTO A ESTE AVISO, POR FAVOR CONTACTE AL EMPLEADO CUYO NOMBRE APARECE EN ESTE AVISO AL TELÉFONO 571-272-3350. POR FAVOR ENVÍE UNA SOLICITUD DE CORRECCIÓN A: OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS, CORREO: ASSIGNMENT SERVICES BRANCH, P.O. BOX 1450, ALEXANDRIA, VA 22313.

FECHA DE INSCRIPCIÓN: 01/11/2013 ROLLO/ESTANTE: 029610/0079

NÚMERO DE PÁGINAS: 11

RESUMEN: CESIÓN DE LOS INTERESES DEL CEDENTE (VER DOCUMENTO PARA LOS DETALLES).

NUMERO DE DOCUMENTO: 11841 USNP

CEDENTE:

TURDI, HUJI FECHA DOC: 01/04/2013

CEDENTE:

HANGELAND, JON J. FECHA DOC: 12/20/2012

CEDENTE:

LAWRENCE, R. MICHAEL FECHA DOC: 12/14/2012

CEDENTE:

CHENG, DONG FECHA DOC: 01/04/2013

CEDENTE:

AHMAD, SALEEM FECHA DOC: 01/09/2013

CEDENTE:

MENG, WEI FECHA DOC: 01/04/2013

CEDENTE:

BRIGANCE, ROBERT PAUL FECHA DOC: 12/14/2012

CEDENTE:

DEVASTHALE, PRATIK FECHA DOC: 01/04/2013

CESIONARIO:

BRISTOL-MYERS SQUIBB COMPANY

ROUTE 206 & PROVINCE LINE ROAD

PATENT DEPARTMENT

PRINCETON, NJ 08543-4000

SOLICITUD No.: 13688584 FECHA DE PRESENTACIÓN: 11/29/2012

NÚMERO DE PATENTE: FECHA DE EMISIÓN:

TÍTULO: INHIBIDORES DE ARIL DIHIDROPIRIDINONA Y PIPERIDINONA MGAT2

Debería decir DIHIDROPIRIDINONAS

SECCIÓN DE REGISTROS DE CESIONES

DIVISION DE REGISTROS PUBLICOS

11841-USNP

CESIÓN

Nosotros,

Huji Turdi, jon j. hangeland, r. Michael Lawrence, Dong cheng, Saleem Ahmad, Wei Meng, Robert Brigance, Pratik Devasthale

De acuerdo con las obligaciones contractuales asumidas aquí por nosotros y/o por la consideración buena y valiosa, cuya recepción y suficiencia reconocemos aquí, vendemos y cedemos a **Bristol-Myers Squibb Company**, una corporación de Delaware, con oficinas en Rt. 206 & Province Line Road, Princeton, NJ 08543-4000, sus sucesores, asignados y representantes legales todo nuestro derecho, título e interés, lo que incluye el derecho a y completo beneficio de cualesquier prioridades que puedan ahora o posteriormente ser otorgadas a nosotros por leyes locales o por tratados, incluyendo cualquier convenio internacional para la protección de la propiedad industrial, en y para todos los países del mundo, incluyendo los Estado Unidos y sus territorios y posesiones, en y para la invención titulada

TITULO

INHIBIDORES DE ARIL DIHIDROPIRIDINONAS Y PIPERIDINONA MGAT2

Inventada por nosotros y descrita en la Solicitud de Patente Estadounidense

Solicitud No. 13/688.584 presentada el 29 de noviembre de 2012

Que incluye dicha Solicitud de Patente Estadounidense provisional y cualquier solicitud que reclame prioridad de dicha Solicitud provisional, que se haya presentado en cualquier país, y cualesquier patentes que se otorguen y/o emitan sobre estas, y todas las divisionales, continuaciones, re-emisiones, certificados de re-exámen y extensiones de las mismas en todos los países, el dicho interés es la propiedad completa de dicha invención y todas las dichas solicitudes, patentes (incluyendo re-emisiones de patentes), extensiones y certificados de reexamen para ser poseídos y disfrutados por la dicha Bristol-Myers Squibb Company y sus sucesores y asignados hasta el final completo de los términos de vigencia otorgados a dichas patentes (incluyendo re-emisiones de patentes), extensiones y certificados de reexamen que puedan ser otorgados y/o emitidos, tan completamente y enteramente como si la misma hubiera sido poseída y disfrutada por nosotros en el caso de que esta venta, cesión y transferencia no se hubiera efectuado;

Y acordamos aquí comunicar a dicho cesionario o sus representantes de cualesquier hechos conocidos por nosotros relacionados con dicha invención, para testificar en cualesquier procesos legales, firmar todas las solicitudes, documentos ó instrumentos necesarios, legales o apropiados en y/o para la presentación y procedimiento de todas las solicitudes, incluyendo divisionales, continuaciones y solicitudes de re-emisión, extensiones y certificados de reexamen y/o el otorgamiento y/o emisión de las mismas y/o para asegurar de otra manera el título a dicha invención y a todas las dichas solicitudes, patentes (incluyendo re-emisiones de patentes, extensiones y certificados de reexamen para el dicho cesionario, y en general hacer todo lo posible para ayudar a dicho cesionario, sus sucesores y asignados para obtener y defender la protección adecuada para dicha invención en todos los países).

Firmado este día 4 de enero de 2013 por (Firmado)

Hudi Turdi

ESTADO DE New Jersey)

)

CONDADO DE Mercer)

En este día _____4____ de ___enero_____, 2013, se presentó ante mi Hudi Turdi, conocido por mi como la persona con ese nombre, y quien firmó la Cesión anterior y reconoció que la firmó.

[SELLO] ___(Firmado)_____

Notario Público

(sello) SHARON MAY

Notario Público New Jersey

Comisión #2411644 exp. 8/23/16

Condado de Mercer

Firmado este día 20 de diciembre de 2012 por (Firmado)

Jon J. Hangeland

ESTADO DE New Jersey)

)

CONDADO DE Mercer)

En este día _____20____ de ___diciembre_____, 2012, se presentó ante mi Don J. Hangeland, conocido por mi como la persona con ese nombre, y quien firmó la Cesión anterior y reconoció que la firmó.

[SELLO] ___(Firmado)_____

Notario Público

(sello) SHARON MAY

Notario Público New Jersey

Comisión #2411644 exp. 8/23/16

Condado de Mercer

Firmado este día 14 de diciembre de 2012 por (Firmado)

R. Michael Lawrence

ESTADO DE New Jersey)

)

CONDADO DE Mercer)

En este día _____14____ de ___diciembre_____, 2012, se presentó ante mi R. Michael Lawrence, conocido por mi como la persona con ese nombre, y quien firmó la Cesión anterior y reconoció que la firmó.

[SELLO] ___(Firmado)_____

Notario Público

(sello) SHARON MAY

Notario Público New Jersey

Comisión #2411644 exp. 8/23/16

Condado de Mercer

Firmado este día 4 de enero de 2013 por (Firmado)

Dong Cheng

ESTADO DE New Jersey)

)

CONDADO DE Mercer)

En este día _____4__ de ___enero_____, 2013, se presentó ante mi Dong Cheng, conocido por mi como la persona con ese nombre, y quien firmó la Cesión anterior y reconoció que la firmó.

[SELLO] ___(Firmado)_____

Notario Público

(sello) SHARON MAY

Notario Público New Jersey

Comisión #2411644 exp. 8/23/16

Condado de Mercer

Firmado este día 9 de enero de 2013 por (Firmado)

Salem Ahmad

ESTADO DE New Jersey)

)

CONDADO DE Burlington)

En este día _____9____ de ___enero_____, 2013, se presentó ante mi Salem Ahmad, conocido por mi como la persona con ese nombre, y quien firmó la Cesión anterior y reconoció que la firmó.

[SELLO] ___(Firmado)_____

Notario Público

(sello) NELL ANNE E BARTHOLOMEW

Notario Público New Jersey

Mi Comisión expira. Marzo 23 de 2016

Firmado este día 4 de enero de 2013 por (Firmado)

Wei Meng

ESTADO DE New Jersey)

)

CONDADO DE Mercer)

En este día _____4____ de ___enero_____, 2013, se presentó ante mi Wei Meng, conocido por mi como la persona con ese nombre, y quien firmó la Cesión anterior y reconoció que la firmó.

[SELLO] ___(Firmado)_____

Notario Público

(sello) SHARON MAY

Notario Público New Jersey

Comisión #2411644 exp. 8/23/16

Condado de Mercer

Firmado este día 14 de diciembre de 2012 por (Firmado)

Robert Paul Brigance

ESTADO DE New Jersey)

)

CONDADO DE Mercer)

En este día _____14____ de ___diciembre_____, 2012, se presentó ante mi Robert Paul Brigance, conocido por mi como la persona con ese nombre, y quien firmó la Cesión anterior y reconoció que la firmó.

[SELLO] ___(Firmado)_____

Notario Público

(sello) SHARON MAY

Notario Público New Jersey

Comisión #2411644 exp. 8/23/16

Condado de Mercer

Firmado este día 4 de enero de 2013 por (Firmado)

Pratik Devasthale

ESTADO DE New Jersey)

)

CONDADO DE Mercer)

En este día _____4____ de ___enero_____, 2013, se presentó ante mi Pratik Devasthale, conocido por mi como la persona con ese nombre, y quien firmó la Cesión anterior y reconoció que la firmó.

[SELLO] ___(Firmado)_____

Notario Público

(sello) SHARON MAY

Notario Público New Jersey

Comisión #2411644 exp. 8/23/16

Condado de Mercer

Recibido – BMS IP Dept.

Acción efectuada: ASGR

Fecha de firma:

Abogado/Agente: SUN, J

Por D. Bragg el 16 de ene. de 2014

(Sello)

Oficina de Marcas y Patentes de los Estados Unidos
Bajo la Secretaría de Comercio para la Propiedad Intelectual
Director de la Oficina de Marcas y Patentes de los Estados Unidos

Enero 16, 2014

JING G. SUN

ROUTE 206 & PROVINCE LINE ROAD **502635901**

PATENT DEPARTMENT

PRINCETON, NJ 08543-4000

OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS
AVISO DE INSCRIPCIÓN DE DOCUMENTO DE CESIÓN

EL DOCUMENTO ADJUNTO HA SIDO INSCRITO POR LA DIVISIÓN DE CESIONES DE LA OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS. UNA COPIA COMPLETA MICROFILMADA ESTÁ DISPONIBLE EN EL SALÓN DE BÚSQUEDAS DE CESIONES EN EL NÚMERO DE ROLLO Y ESTANTE INDICADOS ADELANTE.

POR FAVOR REVISE TODA LA INFORMACIÓN CONTENIDA EN ESTE AVISO. LA INFORMACIÓN CONTENIDA EN ESTE AVISO DE INSCRIPCIÓN REFLEJA LOS DATOS EXISTENTES EN EL SISTEMA DE CESIONES DE MARCAS Y PATENTES. SI USTED ENCUENTRA CUALQUIER ERROR O TIENE PREGUNTAS RESPECTO A ESTE AVISO, POR FAVOR CONTACTE AL EMPLEADO CUYO NOMBRE APARECE EN ESTE AVISO AL TELÉFONO 571-272-3350. POR FAVOR ENVÍE UNA SOLICITUD DE CORRECCIÓN A: OFICINA DE MARCAS Y PATENTES DE LOS ESTADOS UNIDOS, CORREO: ASSIGNMENT SERVICES BRANCH, P.O. BOX 1450, ALEXANDRIA, VA 22313.

FECHA DE INSCRIPCIÓN: 01/15/2014 ROLLO/ESTANTE: 031972/0089

NÚMERO DE PÁGINAS: 3

RESUMEN: CESIÓN DE LOS INTERESES DEL CEDENTE (VER DOCUMENTO PARA LOS DETALLES).

NUMERO DE DOCUMENTO: 11841 USNP

CEDENTE:

ZHAO, GUOHUA FECHA DOC: 01/14/2014

CESIONARIO:

BRISTOL-MYERS SQUIBB COMPANY

ROUTE 206 & PROVINCE LINE ROAD

PATENT DEPARTMENT

PRINCETON, NJ 08543-4000

SOLICITUD No.: 13688584 FECHA DE PRESENTACIÓN: 11/29/2012

NÚMERO DE PATENTE: FECHA DE EMISIÓN:

TÍTULO: INHIBIDORES DE ARIL DIHIDROPIRIDINONA Y PIPERIDINONA MGAT2

SECCION DE REGISTROS DE CESIONES

DIVISION DE REGISTROS PUBLICOS

11841-US-NP

CESIÓN

Yo,

Guohua Zhao

De acuerdo con las obligaciones contractuales asumidas aquí por mi y/o por la consideración buena y valiosa, cuya recepción y suficiencia reconozco aquí, vendemos y cedemos a **Bristol-Myers Squibb Company**, una corporación de Delaware, con oficinas en Rt. 206 & Province Line Road, Princeton, NJ 08543-4000, sus sucesores, asignados y representantes legales todo nuestro derecho, título e interés, lo que incluye el derecho a y completo beneficio de cualesquier prioridades que puedan ahora o posteriormente ser otorgadas a nosotros por leyes locales o por tratados, incluyendo cualquier convenio internacional para la protección de la propiedad industrial, en y para todos los países del mundo, incluyendo los Estado Unidos y sus territorios y posesiones, en y para la invención titulada

TITULO

INHIBIDORES DE ARIL DIHIDROPIRIDINONAS Y PIPERIDINONA MGAT2

Inventada por mi y descrita en la Solicitud de Patente Estadounidense

Solicitud No. 13/688584 presentada el 29 de noviembre de 2012

Que incluye dicha Solicitud de Patente Estadounidense provisional y cualquier solicitud que reclame prioridad de dicha Solicitud provisional, que se haya presentado en cualquier país, y cualesquier patentes que se otorguen y/o emitan sobre estas, y todas las divisionales, continuaciones, re-emisiones, certificados de re-exámen y extensiones de las mismas en todos los países, el dicho interés es la propiedad completa de dicha invención y todas las dichas solicitudes, patentes (incluyendo re-emisiones de patentes), extensiones y certificados de reexamen para ser poseídos y disfrutados por la dicha Bristol-Myers Squibb Company y sus sucesores y asignados hasta el final completo de los términos de vigencia otorgados a dichas patentes (incluyendo re-emisiones de patentes), extensiones y certificados de reexamen que puedan ser otorgados y/o emitidos, tan completamente y enteramente como si la misma hubiera sido poseída y disfrutada por mi en el caso de que esta venta, cesión y transferencia no se hubiera efectuado;

Y yo acuerdo aquí comunicar a dicho cesionario o sus representantes de cualesquier hechos conocidos por mi relacionados con dicha invención, para testificar en cualesquier procesos legales,

firmar todas las solicitudes, documentos ó instrumentos necesarios, legales o apropiados en y/o para la presentación y procedimiento de todas las solicitudes, incluyendo divisionales, continuaciones y solicitudes de re-emisión, extensiones y certificados de reexamen y/o el otorgamiento y/o emisión de las mismas y/o para asegurar de otra manera el título a dicha invención y a todas las dichas solicitudes, patentes (incluyendo re-emisiones de patentes, extensiones y certificados de reexamen para el dicho cesionario, y en general hacer todo lo posible para ayudar a dicho cesionario, sus sucesores y asignados para obtener y defender la protección adecuada para dicha invención en todos los países).

Firmado este día 14 de enero de 2014 por (Firmado)

Guohua Zhao

ESTADO DE New Jersey)

)

CONDADO DE Mercer)

En este día _____14____ de ___enero_____, 2014, se presentó ante mi Guohua Zhao, conocido por mi como la persona con ese nombre, y quien firmó la Cesión anterior y reconoció que la firmó.

[SELLO] ___(Firmado)_____

Notario Público

(sello) NELL ANNE E BARTHOLOMEW

Notario Público New Jersey

Mi Comisión expira el 23 de marzo de 2016