SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SIC

QT

PCT

INVENTARIO

DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

CSA716501

Organizacion y
Digitalizacion CSA Ltda

SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21. **EXPEDIENTE No.** 09-10534

54. **TITULO** TRIAZOLIL FENIL BENCENOSULFONAMIDAS

51. **CLASIFICACION INTERNACIONAL**

71. **SOLICITANTE** CHEMOCENTRYX, INC.

DOMICILIO MOUNTAIN VIEW, CA, ESTADOS UNIDOS DE AMÉRICA

74. **APODERADO** JUAN PABLO CADENA SARMIENTO

22. **SANTAFE DE BOGOTA, D.C.**

PETITORIO

AS: 109.374

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-010534- -00000-0000
Fecha: 2009-02-04 16:31:39 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 470

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☒ Capítulo I. ☐ Capítulo II.

2 SOLICITANTE	Nombre: **CHEMOCENTRYX, INC.** Dirección: 850 Maude Avenue, Mountain View, California 94043, Estados Unidos de América. Nacionalidad o Domicilio: Estados Unidos de América Lugar de Constitución: Estados Unidos de América Teléfono: Fax: E-mail	**IDENTIFICACIÓN** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: JUAN PABLO CADENA SARMIENTO Dirección: Cra. 7 No. 71-21 Torre B – Piso 4, Bogotá, Colombia. Teléfono: 744-2200 Fax: 742-2200 E-mail:	**IDENTIFICACIÓN** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número 80.410.337 TP 57492
4 INVENTOR (ES) (72)	**Nombre:** Trevor T. CHARVAT, Cheng HU, Anita MELIKIAN, Aaron NOVACK, Andrew M.K. PENNELL, Edward J. SULLIVAN, Xuefei TAN, William D. THOMAS, Solomon UNGASHE, Yibin ZENG, Sreenivas PUNNA. **Dirección:** 3320 Parkhaven Drive, San Jose, CA 95132, US; 250 Waverly Street, #6, Menlo Park, CA 94025, US; 4150 17th Street, #25, San Francisco, CA 94114, US; 92 Mirabelli Circle, San Jose, CA 95134, US; 442 Arlington Street, San Francisco, CA 94131, US; 900 Golden Wheel Park Drive, Spc. 94, San Jose, CA 95112, US; 32666 Foxglove Way, Union City, CA 94587, US; 14803 Charmeran Avenue, San Jose, CA 95124, US; 36641 Reynolds Drive, Fremont, CA 94536, US; 144 McLellan Avenue, San Mateo, CA 94403, US; 1240 Vicente Dr, Apt #E, Sunnyvale, CA 94086, US (Respectivamente) **Nacionalidad o Domicilio:** Estados Unidos de América.	

5 PCT (86)

Solicitud Internacional No. PCT/US2007/015808 Fecha 10-07-2007
Publicación Internacional No WO 2008/010934 A3 Fecha 24-01-2008

6 Título (54): TRIAZOLIL FENIL BENCENOSULFONAMIDAS

7 Clasificación Internacional (51): _____

8 Prioridad

SI ☒ NO ☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	14-07-2006	60/831,042
US	22-06-2007	60/945,839

9 Comprobante de pago No. 08-96481; 09-1,114; 08-90,552; 08-87,520; 08-89,073; 08-87,540; 09-1,222
Fecha 04-02-2009

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

10 **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $ 540.000
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [ ] Poderes, si fuere el caso. **Fotocopia autenticada**
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del éxamen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- [ ] Traducción de examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros: Tarjeta de Propietarios
  Documentos PCT
  Comprobante(s) de pago de la tasa por concepto de Reivindicaciones adicionales. $225.000 (9*$25.000)

11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente,

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA:

C.C. 80.410.337 de Usaquén TP 57492 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

4

109 374

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 1,114
FECHA : ENERO 6 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-010534- -00000-0000
Fecha: 2009-02-04 16:31:39 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 470

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	RECIBO DE CAJA			1039	06/01/2009	5,012,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	998	VALOR COMPLEMENTO TARIFA A#O ANTR	39,000.00
			TOTAL : $	39,000.00

SON: TREINTA Y NUEVE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

109 374 5

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-010534- -00000-0000

Fecha: 2009-02-04 16:31:39 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve. 378 FASENACIONALI
Act 411 PRESENTACION Folios: 470

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 08 - 90,552
FECHA : NOVIEMBRE 19 DE 2008

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO DE BOGOTA	062754387	97849986	19/11/2008	25,487,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	100,000.00
		TOTAL : $	100,000.00

SON: CIEN MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 08 - 87,520
FECHA : NOVIEMBRE 6 DE 2008

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO DE BOGOTA	062754387	79585914	06/11/2008	31,842,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	50,000.00
		TOTAL : $	50,000.00

SON: CINCUENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

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109 374

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 08 - 89,073
FECHA : NOVIEMBRE 12 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-010534- -00000-0000

Fecha: 2009-02-04 16:31:39 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 470

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO DE BOGOTA	062754387	3249901	12/11/2008	26,299,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	50,000.00
		TOTAL : $	50,000.00

SON: CINCUENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

109 374

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 87,540
FECHA : NOVIEMBRE 6 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-010534- -00000-0000
Fecha: 2009-02-04 16:31:39 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 470

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO DE BOGOTA	062754387	79585914	06/11/2008	31,842,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	54	INFORMACION DETALLADA DE UN TRAMI	23,000.00
			TOTAL : $	23,000.00

SON: VEINTITRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 1,222
FECHA : ENERO 6 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-010534- -00000-0000

Fecha: 2009-02-04 16:31:39 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 470

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

[redacted]ITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	RECIBO DE CAJA			1039	06/01/2009	5,012,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	998	VALOR COMPLEMENTO TARIFA A#O ANTR	2,000.00
			TOTAL : $	2,000.00

SON: DOS MIL PESOS

[redacted]

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 January 2008 (24.01.2008)

PCT

(10) International Publication Number
WO 2008/010934 A3

(51) International Patent Classification:
C07D 249/08 (2006.01) *C07D 405/12* (2006.01)
C07D 401/04 (2006.01) *C07D 413/04* (2006.01)
C07D 403/04 (2006.01) *A61K 31/41* (2006.01)
C07D 405/04 (2006.01) *A61P 29/00* (2006.01)

(21) International Application Number:
PCT/US2007/015808

(22) International Filing Date: 10 July 2007 (10.07.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/831,042 14 July 2006 (14.07.2006) US
60/945,839 22 June 2007 (22.06.2007) US

(71) Applicant *(for all designated States except US)*: **CHEMOCENTRYX, INC.** [US/US]; 850 Maude Avenue, Mountain View, CA 94043 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CHARVAT, Trevor, T.** [US/US]; 3320 Parkhaven Drive, San Jose, CA 95132 (US). **HU, Cheng** [CN/US]; 250 Waverly Street, #6, Menlo Park, CA 94025 (US). **MELIKIAN, Anita** [FR/US]; 4150 17th Street, #25, San Francisco, CA 94114 (US). **NOVACK, Aaron** [US/US]; 92 Mirabelli Circle, San Jose, CA 95134 (US). **PENNELL, Andrew, M.K.** [IN/US]; 442 Arlington Street, San Francisco, CA 94131 (US). **SULLIVAN, Edward, J.** [US/US]; 900 Golden Wheel Park Drive, Spc. 94, San Jose, CA 95112 (US). **TAN, Xuefei** [CN/US]; 32666 Foxglove Way, Union City, CA 94587 (US). **THOMAS, William, D.** [US/US]; 14803 Charmeran Avenue, San Jose, CA 95124 (US). **UNGASHE, Solomon** [ET/US]; 36641 Reynolds Drive, Fremont, CA 94536 (US). **ZENG, Yibin** [CN/US]; 144 McLellan Avenue, San Mateo, CA 94403 (US). **PUNNA, Sreenivas** [IN/US]; 1240 Vicente Dr, Apt #E, Sunnyvale, CA 94086 (US).

(74) Agent: **SEANEY, Lisa, M.**; Brinks Hofer Gilson & Lione, P.O. Box 10087, Chicago, IL 60610 (US).

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

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

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

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

(88) Date of publication of the international search report:
27 March 2008

(54) Title: TRIAZOLYL PHENYL BENZENESULFONAMIDES

(57) Abstract: Compounds (I) are provided that act as potent antagonists of the CCR2 or CCR9 receptor. Animal testing demonstrates that these compounds are useful for treating inflammation, a hallmark disease for CCR2 and CCR9. The compounds are generally aryl sulfonamide derivatives and are useful in pharmaceutical compositions, methods for the treatment of CCR2 -mediated diseases, CCR9 -mediated diseases, as controls in assays for the identification of CCR2 antagonists and as controls in assays for the identification of CCR9 antagonists.

WO 2008/010934 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/015808

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D249/08 C07D401/04 C07D403/04 C07D405/04 C07D405/12
C07D413/04 A61K31/41 A61P29/00

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/004818 A (IMCLONE SYSTEMS INC [US]; OUYANG XIAOHU [US]; KISELYOV ALEXANDER [US];) 20 January 2005 (2005-01-20) page 130; claim 8; compounds 127,128	1,2
A	WO 2004/058741 A (MERCK & CO INC [US]; WADDELL SHERMAN T [US]; SANTORELLI GINA M [US]; M) 15 July 2004 (2004-07-15) example 54	1-16
A	WO 2005/113513 A (CHEMOCENTRYX [US]; UNGASHE SOLOMON [US]; WRIGHT JOHN JESSEN [US]; PENN) 1 December 2005 (2005-12-01) paragraph [0001]; claim 1	1-24

-/—

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 January 2008	30/01/2008

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gettins, Marc

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/015808

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2004/171654 A1 (UGASHE SOLOMON [US] ET AL UNGASHE SOLOMON [US] ET AL) 2 September 2004 (2004-09-02) cited in the application paragraph [0002]; claim 1	1-24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/015808

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17-24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/015808

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005004818 A	20-01-2005	NONE	
WO 2004058741 A	15-07-2004	AT 375336 T	15-10-2007
		AU 2003297231 A1	22-07-2004
		AU 2003302255 A1	22-07-2004
		BR 0317451 A	16-11-2005
		CA 2510540 A1	15-07-2004
		EP 1581515 A1	05-10-2005
		HR 20050575 A2	28-02-2006
		IS 7876 A	31-05-2005
		JP 2006513266 T	20-04-2006
		KR 20050085790 A	29-08-2005
		MA 27579 A1	03-10-2005
		MX PA05006726 A	08-09-2005
		NZ 540465 A	22-12-2006
		WO 2004058730 A2	15-07-2004
		US 2005154038 A1	14-07-2005
		US 2004133011 A1	08-07-2004
WO 2005113513 A	01-12-2005	AU 2005245401 A1	01-12-2005
		CA 2566387 A1	01-12-2005
		EP 1748989 A2	07-02-2007
US 2004171654 A1	02-09-2004	US 2005165067 A1	28-07-2005
		US 2005137193 A1	23-06-2005

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 January 2008 (24.01.2008)

PCT

(10) International Publication Number
WO 2008/010934 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/US2007/015808

(22) International Filing Date: 10 July 2007 (10.07.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/831,042 14 July 2006 (14.07.2006) US
60/945,839 22 June 2007 (22.06.2007) US

(71) Applicant *(for all designated States except US)*: CHEMOCENTRYX, INC. [US/US]; 850 Maude Avenue, Mountain View, CA 94043 (US).

(72) Inventors; and

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(54) Title: TRIAZOLYL PHENYL BENZENESULFONAMIDES

(57) Abstract: Compounds are provided that act as potent antagonists of the CCR2 or CCR9 receptor. Animal testing demonstrates that these compounds are useful for treating inflammation, a hallmark disease for CCR2 and CCR9. The compounds are generally aryl sulfonamide derivatives and are useful in pharmaceutical compositions, methods for the treatment of CCR2-mediated diseases, CCR9-mediated diseases, as controls in assays for the identification of CCR2 antagonists and as controls in assays for the identification of CCR9 antagonists.

WO 2008/010934 A2

TRIAZOLYL PHENYL BENZENESULFONAMIDES

RELATED APPLICATIONS

[0001] This application claims priority to U.S. provisional application Serial No. 60/831,042 filed July 14, 2006. The disclosure of this priority application is incorporated herein in its entirety.

FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] The present invention described herein was supported at least in part by NIH (U19-AI056690-01). The government may have certain rights in the invention.

BACKGROUND

[0003] The present invention provides compounds, pharmaceutical compositions containing one or more of those compounds or their pharmaceutically acceptable salts, which are effective in inhibiting the binding or function of various chemokines to chemokine receptors. As antagonists or modulators of chemokine receptors, the compounds and compositions have utility in treating various immune disorder conditions and diseases.

[0004] Chemokines, also known as chemotactic cytokines, are a group of small molecular-weight proteins that are released by a wide variety of cells and have a variety of biological activities. Chemokines attract various types of cells of the immune system, such as macrophages, T cells, eosinophils, basophils and neutrophils, and cause them to migrate from the blood to various lymphoid and none-lymphoid tissues. They mediate infiltration of inflammatory cells to sites of inflammation, and are responsible for the initiation and perpetuation of many inflammation diseases (reviewed in Schall, *Cytokine*, 3:165-183 (1991), Schall et al., *Curr. Opin. Immunol.*, 6:865-873 (1994)).

[0005] In addition to stimulating chemotaxis, chemokines can induce other changes in responsive cells, including changes in cell shape, granule exocytosis, integrin up-regulation, formation of bioactive lipids (e.g., leukotrienes), respiratory burst associated with leukocyte activation, cell

proliferation, resistance to induction of apoptosis and angiogenesis. Thus, chemokines are early triggers of the inflammatory response, causing inflammatory mediator release, chemotaxis and extravasation to sites of infection or inflammation. They are also stimulators of a multitude of cellular processes that bear important physiological functions as well as pathological consequences.

[0006] Chemokines exert their effects by activating chemokine receptors expressed by responsive cells. Chemokine receptors are a class of G-protein coupled receptors, also known as seven-transmembrane receptors, found on the surface of a wide variety of cell types such as leukocytes, endothelial cells, smooth muscle cells and tumor cells.

[0007] Chemokines and chemokine receptors are expressed by intrinsic renal cells and infiltrating cells during renal inflammation (Segerer et al., *J. Am. Soc. Nephrol.*, 11:152-76 (2000); Morii et al., *J. Diabetes Complications*, 17:11-5 (2003); Lloyd et al. *J. Exp. Med.*, 185:1371-80 (1997); Gonzalez-Cuadrado et al. *Clin. Exp. Immunol.*, 106:518-22 (1996); Eddy & Giachelli, *Kidney Int.*, 47:1546-57 (1995); Diamond et al., *Am. J. Physiol.*, 266:F926-33 (1994)). In humans, CCR2 and ligand MCP-1 are among the proteins expressed in renal fibrosis, and are correlated with the extent of macrophage infiltration into the interstitium (Yang et al., *Zhonghua Yi Xue Za Zhi*, 81:73-7 (2001); Stephan et al., *J. Urol.*, 167:1497-502 (2002); Amann et al., *Diabetes Care*, 26:2421-5 (2003); Dai et al., *Chin. Med. J. (Engl)*, 114:864-8 (2001)). In animal models of renal fibrosis, blockade of CCR2 or MCP-1 leads to a marked reduction in severity of renal inflammation (Kitagawa et al., *Am. J. Pathol.*, 165:237-46 (2004); Wada et al., *Am. J. Pathol.*, 165:237-46 (2004); Shimizu et al., *J. Am. Soc. Nephrol.*, 14:1496-505 (2003)).

[0008] Rheumatoid arthritis is a chronic disease of the joints characterized by synovial inflammation that leads to the destruction of cartilage and bone. Although the underlying causes of the disease are unknown, it is believed that macrophages and Th-1 type T cells play a key role in the initiation and perpetuation of the chronic inflammatory process (Vervoordeldonk et al., *Curr. Rheumatol. Rep.*, 4:208-17 (2002)).

[0009] MCP-1 is among the several chemokines, including MIP-1α and IL-8, identified in rheumatoid synovium (Villiger et al., *J. Immunol.*, 149:722-7 (1992); Scaife et al., Rheumatology (Oxford), 43:1346-52 (2004); Shadidi et al., Scand. *J. Immunol.*, 57:192-8 (2003); Taylor et al., *Arthritis Rheum.*, 43:38-47 (2000); Tucci et al., *Biomed. Sci. Instrum.*, 34:169-74 (1997)). Chemokine receptors CCR1, CCR2, CCR3 and CCR5 are up-regulated in the joints from arthritic mice (Plater-Zyberk et al., *Immunol. Lett.*, 57:117-20 (1997). Blockade of MCP-1 activity using a CCR2 antagonist or an antibody against MCP-1 have been shown efficacious in reducing joint inflammation in experimental models of rheumatoid arthritis (Gong et al., *J. Exp. Med.*, 186:131-7 (1997); Ogata et al., *J. Pathol.*, 182:106-14 (1997)).

[0010] Chemokine receptor-mediated infiltration of macrophages in the fat tissues may also contribute to the complications arising from obesity, a condition resulting from excessive storage of fat in the body. Obesity predisposes the affected individuals to many disorders, such as non-insulin-dependent diabetes, hypertension, stroke, and coronary artery disease. In obesity, adipose tissues have altered metabolic and endocrine functions that lead to an increased release of fatty acids, hormones, and pro-inflammatory molecules. Adipose tissue macrophages are believed to be a key source of pro-inflammatory cytokines including TNF-alpha, iNOS and IL-6 (Weisberg et al., *J. Clin. Invest.*, 112:1796-808 (2003)). Recruitment of macrophages to the adipose tissue is likely mediated by MCP-1 produced by adipocytes (Christiansen T, et al., *Int. J. Obes.* (Lond). 2005 Jan;29(1):146-50; Sartipy et al., *Proc. Natl. Acad. Sci. U.S.A.*, 100:7265-70 (2003)).

[0011] Elevated MCP-1 may induce adipocyte differentiation and insulin resistance, and contribute to pathologies associated with hyper-insulinemia and obesity. MCP-1 is over-expressed in plasma in obese mice compared to lean controls and white adipose is a major source. MCP-1 has also been shown to accelerate wound healing, and has a direct angiogenic effect on epithelial cells, and may play a direct role in the remodeling of adipose tissue in obesity. (Sartipy P, Loskutoff DJ., *Proc. Natl. Acad. Sci. U.S.A.*,100:7265 (2003)).

[0012] MCP-1 plasma levels are substantially increased in Diet Induce Obesity (DIO) mice, and a strong correlation between plasma MCP-1 levels and body weight has been identified. Furthermore, elevation of MCP-1 induced by high fat diet causes changes in the CD11b positive monocyte population in DIO mice. (Takahashi K, et al., *J. Biol. Chem.*, 46654 (2003)).

[0013] Furthermore, chronic inflammation in fat is thought to play a crucial role in the development of obesity-related insulin resistance (Xu H, et al., *J Clin Invest.* 2003 Dec;112(12):1821-30). It has been proposed that obesity related insulin resistance is, at least in part, a chronic inflammatory disease initiated in adipose tissue. Many inflammation and macrophage specific genes are dramatically upregulated in white adipose tissue in mouse models of genetic and high fat diet-induced obesity (DIO), and this upregulation precedes a dramatic increase in circulating insulin.

[0014] Increased expression levels of monocyte CCR2 and monocyte chemoattractant protein-1 in patients with diabetes mellitus (*Biochemical and Biophysical Research Communications*, 344(3):780-5 (2006)) were found in a study involving diabetic patients. Serum MCP-1 concentrations and surface expression of CCR2 on monocytes in diabetic patients were significantly higher than in non-diabetics, and the serum MCP-1 levels correlated with HbA1c, triglycerides, BMI, hs-CRP. Surface expression levels of CD36 and CD68 on monocytes were significantly increased in diabetic patients and more unregulated by MCP-1 in diabetics, augmenting uptake of ox-LDL, and hence potentially foam cell transformation. Elevated serum MCP-1 and increased monocyte CCR2, CD36, CD68 expression correlated with poor blood glucose control and potentially correlate with increased vessel wall monocyte recruitment.

[0015] MCP-1 is a potential player in negative cross talk between adipose tissue and skeletal muscle (Bianco JJ, et al., *Endocrinology*, 2458 (2006)). MCP-1 can significantly reduce insulin-stimulated glucose uptake, and is a prominent inducer of insulin resistance in human skeletal muscle cell. Adipose tissue is a major secretory and endocrine active organ producing bioactive proteins regulating energy metabolism and insulin sensitivity.

[0016] CCR2 modulates inflammatory and metabolic effects of high-fat feeding (Weisberg SP, et al., *J. Clin. Invest.*, 115 (2006)). Genetic deficiency in CCR2 reduced food intake and attenuated the development of obesity in mice fed a high fat diet. In obese mice matched for adiposity, CCR2 deficiency reduced macrophage content and inflammatory profile of adipose tissue, increased adiponectin expression, and improved glucose homeostatis and insulin sensitivity. In lean animals, no effect of CCR2 genotype on metabolic trait was found. In high-fat diet mice, CCR2 genotype modulated feeding, the development of obesity and adipose tissue inflammation. Once established, short term antagonism was shown to attenuate macrophage accumulation in adipose tissue and insulin resistance.

[0017] Chemokine and chemokine receptors are the key regulators of immune cell trafficking. MCP-1 is a potent chemoattractant of monocytes and T cells; its expression is induced under inflammatory conditions including proinflammatory cytokine stimulations and hypoxia. The interaction between MCP-1 and CCR2 mediates migration of monocytes, macrophage as well as activated T cells and play a key role in the pathogenesis of many inflammatory diseases. Inhibition of CCR2 functions using small molecule antagonists described in this invention represents a new approach for the treatments of inflammatory disorders.

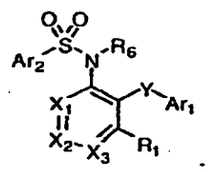
[0018] Psoriasis is a chronic inflammatory disease characterized by hyperproliferation of keratinocytes and pronounced leukocyte infiltration. It is known that keratinocytes from psoriasis lesion express abundant CCR2 ligand MCP-1, particularly when stimulated by proinflammatory cytokines such as TNF-α (Vestergaard et al., *Acta. Derm. Venereol.*, 84(5):353-8 (2004); Gillitzer et al., *J. Invest. Dermatol.*, 101(2):127-31 (1993); Deleuran et al., *J. Dermatol. Sci.*, 13(3):228-36 (1996)). Since MCP-1 can attract migration of both macrophages and dendritic cells expressing CCR2 to the skin, this receptor and ligand pair is believed to be important in regulating the interaction between proliferating keratinocytes and dermal macrophage during the development of psoriasis. A small molecule antagonist may thus be useful in the treatment of psoriasis.

[0019] In addition to inflammatory diseases, chemokines and chemokine receptors have also been implicated in cancers (Broek et al., *Br. J. Cancer*, 88(6):855-62 (2003)). Tumor cells stimulate the formation of stroma that secretes various mediators pivotal for tumor growth, including growth factors, cytokines, and proteases. It is known that the level of MCP-1 is associated significantly with tumor-associated macrophage accumulation, and prognostic analysis reveals that high expression of MCP-1 is a significant indicator of early relapse in breast cancer (Ueno et al., *Clin. Cancer Res.*, 6(8):3282-9 (2001)). A small molecule antagonist of a chemokine may thus be able to reduce the release of growth-stimulating cytokines by blocking accumulation of macrophages at sites of tumor formation.

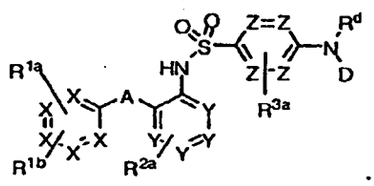
[0020] T lymphocyte (T cell) infiltration into the small intestine and colon has been linked to the pathogenesis of Coeliac diseases, food allergies, rheumatoid arthritis, human inflammatory bowel diseases (IBD) which include Crohn's disease and ulcerative colitis. Blocking trafficking of relevant T cell populations to the intestine can lead to an effective approach to treat human IBD. More recently, chemokine receptor 9 (CCR9) has been noted to be expressed on gut-homing T cells in peripheral blood, elevated in patients with small bowel inflammation such as Crohn's disease and celiac disease. The only CCR9 ligand identified to date, TECK (thymus-expressed chemokine) is expressed in the small intestine and the ligand receptor pair is now thought to play a pivotal role in the development of IBD. In particular, this pair mediates the migration of disease causing T cells to the intestine. See for example, Zaballos et al., *J. Immunol.*, 162(10):5671 5675 (1999); Kunkel et al., J. Exp. Med., 192(5):761-768 (2000); Papadakis et al., *J. Immunol.*, 165(9):5069-5076 (2000); Papadakis et al., *Gastroenterology*, 121(2):246-254 (2001); Campbell et al., *J. Exp. Med.*, 195(1):135-141 (2002); Wurbel et al., *Blood*, 98(9):2626-2632 (2001); and Uehara et al., *J. Immunol.*, 168(6):2811-2819 (2002). Rivera-Nieves, et al., *Gastroenterology*, 2006 Nov;131(5):1518-29; and Kontoyiannis et al., *J. Exp. Med.*, Vol. 196, Number 12, Dec. 16, 2002. In addition CCR9 bearing lymphocytes have been show to mediate the pathology of filariasis (lymphatic filarial disease) and inhibition of CCR9 has been correlated with reduction of the pathology associated with such

conditions. See for example Babu et al., Journal of Infectious Diseases, 191: 1018-26, 2005.

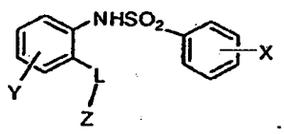
[0021] PCT Published Application WO 2003/099773 (Millennium Pharmaceuticals, Inc.) discloses compounds which can bind to CCR9 receptors of the formula



[0022] PCT Published Application WO 2005/004810 (Merck & Co., Inc.) discloses brandykinin B1 antagonists or inverse agonists of the formula



[0023] US Published Patent Application 2005/137193 A1 (ChemoCentryx, Inc.) discloses CCR9 modulators of the formula



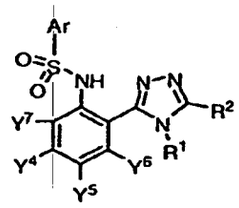
BRIEF SUMMARY

[0024] The present invention is directed to compounds and pharmaceutically acceptable salts thereof, compositions, and methods useful in modulating chemokine activity. The compounds and salts thereof, compositions, and methods described herein are useful in treating or preventing chemokine-mediated conditions or diseases, including certain inflammatory and immunoregulatory disorders and diseases.

[0025] The compounds of the present invention have been shown to modulate one or more of CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR3, CXCR4, CXCR5, and CX3CR1. In particular,

various compounds of the present invention modulate CCR2 and CCR9 as shown in the examples.

[0026] In one embodiment, the present compound may be represented by formula (I) or salts thereof:



(I)

where Ar, Y^4, Y^5, Y^6, Y^7, R^1 and R^2 are as defined below.

[0027] In another aspect, the present invention provides compositions useful in modulating chemokine activity. In one embodiment, a composition according to the present invention comprises a compound according to the invention and a pharmaceutically acceptable carrier or excipient.

[0028] In yet another aspect, the present invention provides a method of modulating chemokine function in a cell, comprising contacting the cell with a therapeutically effective amount of a compound or composition according to the invention.

[0029] In still another aspect, the present invention provides a method for modulating chemokine function, comprising contacting a chemokine receptor with a therapeutically effective amount of a compound or composition according to the invention.

[0030] In still another aspect, the present invention provides a method for treating a chemokine-mediated condition or disease, comprising administering to a subject a safe and effective amount of a compound or composition according to the invention.

[0031] In addition to the compounds provided herein, the present invention further provides pharmaceutical compositions containing one or more of these compounds, as well as methods for the use of these compounds in therapeutic methods, primarily to treat diseases associated with chemokine signaling activity.

DETAILED DESCRIPTION

[0032] General

[0033] The present invention is directed to compounds and salts thereof, compositions and methods useful in the modulation of chemokine receptor function, particularly CCR2 or CCR9 function. Modulation of chemokine receptor activity, as used herein in its various forms, is intended to encompass antagonism, agonism, partial antagonism, inverse agonism and/or partial agonism of the activity associated with a particular chemokine receptor, preferably the CCR2 or CCR9 receptor. Accordingly, the compounds of the present invention are compounds which modulate at least one function or characteristic of mammalian CCR2 or CCR9, for example, a human CCR2 or CCR9 protein. The ability of a compound to modulate the function of CCR2 or CCR9, can be demonstrated in a binding assay (*e.g.*, ligand binding or agonist binding), a migration assay, a signaling assay (*e.g.*, activation of a mammalian G protein, induction of rapid and transient increase in the concentration of cytosolic free calcium), and/or cellular response assay (*e.g.*, stimulation of chemotaxis, exocytosis or inflammatory mediator release by leukocytes).

[0034] Abbreviations and Definitions

[0035] When describing the compounds, compositions, methods and processes of this invention, the following terms have the following meanings, unless otherwise indicated.

[0036] "Alkyl" by itself or as part of another substituent refers to a hydrocarbon group which may be linear, cyclic, or branched or a combination thereof having the number of carbon atoms designated (i.e., C_{1-8} means one to eight carbon atoms). Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, cyclopentyl, (cyclohexyl)methyl, cyclopropylmethyl, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, etc. Alkyl groups can be substituted or unsubstituted, unless otherwise indicated. Examples of substituted alkyl include haloalkyl, thioalkyl, aminoalkyl, and the like.

[0037] "Alkoxy" refers to –O-alkyl. Examples of an alkoxy group include methoxy, ethoxy, n-propoxy etc.

[0038] "Alkenyl" refers to an unsaturated hydrocarbon group which may be linear, cyclic or branched or a combination thereof. Alkenyl groups with 2-8 carbon atoms are preferred. The alkenyl group may contain 1, 2 or 3 carbon-carbon double bonds. Examples of alkenyl groups include ethenyl, n-propenyl, isopropenyl, n-but-2-enyl, n-hex-3-enyl, cyclohexenyl, cyclopentenyl and the like. Alkenyl groups can be substituted or unsubstituted, unless otherwise indicated.

[0039] "Alkynyl" refers to an unsaturated hydrocarbon group which may be linear, cyclic or branched or a combination thereof. Alkynyl groups with 2-8 carbon atoms are preferred. The alkynyl group may contain 1, 2 or 3 carbon-carbon triple bonds. Examples of alkynyl groups include ethynyl, n-propynyl, n-but-2-ynyl, n-hex-3-ynyl and the like. Alkynyl groups can be substituted or unsubstituted, unless otherwise indicated.

[0040] "Aryl" refers to a polyunsaturated, aromatic hydrocarbon group having a single ring (monocyclic) or multiple rings (bicyclic), which can be fused together or linked covalently. Aryl groups with 6-10 carbon atoms are preferred, where this number of carbon atoms can be designated by C_{6-10}, for example. Examples of aryl groups include phenyl and naphthalene-1-yl, naphthalene-2-yl, biphenyl and the like. Aryl groups can be substituted or unsubstituted, unless otherwise indicated.

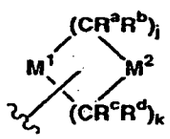
[0041] "Halo" or "halogen", by itself or as part of a substituent refers to a chlorine, bromine, iodine, or fluorine atom.

[0042] "Haloalkyl", as a substituted alkyl group, refers to a monohaloalkyl or polyhaloalkyl group, most typically substituted with from 1-3 halogen atoms. Examples include 1-chloroethyl, 3-bromopropyl, trifluoromethyl and the like.

[0043] "Heterocyclyl" refers to a saturated or unsaturated non-aromatic ring containing at least one heteroatom (typically 1 to 5 heteroatoms) selected from nitrogen, oxygen or sulfur. The heterocyclyl ring may be monocyclic or bicyclic. Preferably, these groups contain 0-5 nitrogen atoms, 0-2 sulfur atoms and 0-2 oxygen atoms. More preferably, these groups contain 0-3 nitrogen atoms, 0-1 sulfur atoms and 0-1 oxygen atoms. Examples of

heterocycle groups include pyrrolidine, piperidine, imidazolidine, pyrazolidine, butyrolactam, valerolactam, imidazolidinone, hydantoin, dioxolane, phthalimide, piperidine, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine-S-oxide, thiomorpholine-S,S-dioxide, piperazine, pyran, pyridone, 3-pyrroline, thiopyran, pyrone, tetrahydrofuran, tetrahydrothiophene, quinuclidine and the like. Preferred heterocyclic groups are monocyclic, though they may be fused or linked covalently to an aryl or heteroaryl ring system.

[0044] In one preferred embodiment, heterocyclic groups may be represented by formula (AA) below:



AA

[0045] where formula (AA) is attached via a free valence on either M^1 or M^2; M^1 represents O, NR^e, or $S(O)_l$; M^2 represents CR^fR^g, O, $S(O)_l$, or NR^e; l is 0, 1 or 2; j is 1, 2 or 3 and k is 1, 2 or 3, with the proviso that j + k is 3, 4, or 5; and R^a, R^b, R^c, R^d, R^e, R^f, and R^g are independently selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, $-COR^h$, $-CO_2R^h$, $-CONR^hR^i$, $-NR^hCOR^i$, $-SO_2R^h$, $-SO_2NR^hR^i$, $-NSO_2R^hR^i$ $-NR^hR^i$, $-OR^h$, $-Q^1COR^h$, $-Q^1CO_2R^h$, $-Q^1CONR^hR^i$, $-Q^1NR^hCOR^i$, $-Q^1SO_2R^{28}$, $-Q^1SO_2NR^hR^i$, $-Q^1NSO_2R^hR^i$, $-Q^1NR^hR^i$, $-Q^1OR^h$, wherein Q^1 is a member selected from the group consisting of C_{1-4} alkylene, C_{2-4} alkenylene and C_{2-4} alkynylene, and R^h and R^i are independently selected from the group consisting of hydrogen and C_{1-8} alkyl, and wherein the aliphatic portions of each of the R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h and R^i substituents are optionally substituted with from one to three members selected from the group consisting of halogen, -OH, $-OR^n$, $-OC(O)NHR^n$, $-OC(O)NR^nR^o$, -SH, $-SR^n$, $-S(O)R^n$, $-S(O)_2R^n$, $-SO_2NH_2$, $-S(O)_2NHR^n$, $-S(O)_2NR^nR^o$, $-NHS(O)_2R^n$, $-NR^nS(O)_2R^o$, $-C(O)NH_2$, $-C(O)NHR^n$, $-C(O)NR^nR^o$, $-C(O)R^n$, $-NHC(O)R^o$, $-NR^nC(O)R^o$, $-NHC(O)NH_2$, $-NR^nC(O)NH_2$, $-NR^nC(O)NHR^o$, $-NHC(O)NHR^n$, $-NR^nC(O)NR^oR^p$, $-NHC(O)NR^nR^o$, $-CO_2H$, $-CO_2R^n$, $-NHCO_2R^n$, $-NR^nCO_2R^o$,

-CN, -NO_2, -NH_2, -NHR^n, -NR^nR^o, -$NR^nS(O)NH_2$ and –$NR^nS(O)_2NHR^o$, wherein R^n, R^o and R^p are independently an unsubstituted C_{1-8} alkyl. Additionally, any two of R^a, R^b, R^c, R^d, R^e, R^f and R^g may be combined to form a bridged or spirocyclic ring system.

[0046] In one preferred embodiment, the number of $R^a + R^b + R^c + R^d$ groups that are other than hydrogen is 0, 1 or 2. In a more preferred embodiment, R^a, R^b, R^c, R^d, R^e, R^f, and R^g are independently selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C_{1-8} alkyl, -COR^h, -CO_2R^h, -$CONR^hR^h$, -NR^hCOR^h, -SO_2R^h, -$SO_2NR^hR^i$, -$NSO_2R^hR^i$, -NR^hR^i, and –OR^h, wherein R^h and R^i are independently selected from the group consisting of hydrogen and unsubstituted C_{1-8} alkyl and wherein the aliphatic portions of each of the R^a, R^b, R^c, R^d, R^e, R^f and R^g substituents are optionally substituted with from one to three members selected from the group consisting of halogen, -OH, -OR^n, -$OC(O)NHR^n$, -$OC(O)NR^nR^o$, -SH, -SR^n, -$S(O)R^o$, -$S(O)_2R^n$, -SO_2NH_2, -$S(O)_2NHR^n$, -$S(O)_2NR^nR^o$, -$NHS(O)_2R^n$, -$NR^nS(O)_2R^o$, -$C(O)NH_2$, -$C(O)NHR^n$, -$C(O)NR^nR^o$, -$C(O)R^n$, -$NHC(O)R^n$, -$NR^nC(O)R^o$, -$NHC(O)NH_2$, -$NR^nC(O)NH_2$, -$NR^nC(O)NHR^o$, -$NHC(O)NHR^n$, -$NR^nC(O)NR^oR^p$, -$NHC(O)NR^nR^o$, -CO_2H, -CO_2R^n, -$NHCO_2R^n$, -$NR^nCO_2R^o$, -CN, -NO_2, -NH_2, -NHR^n, -NR^nR^o, -$NR^nS(O)NH_2$ and –$NR^nS(O)_2NHR^o$, wherein R^n, R^o and R^p are independently an unsubstituted C_{1-8} alkyl.

[0047] In a more preferred embodiment, R^a, R^b, R^c, R^d, R^e, R^f, and R^g are independently hydrogen or C_{1-4} alkyl. In another preferred embodiment, at least three of R^a, R^b, R^c, R^d, R^e, R^f, and R^g are hydrogen.

[0048] "Heteroaryl" refers to an aromatic group containing at least one heteroatom, where the heteroaryl group may be monocyclic or bicyclic. Examples include pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, quinolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, benzotriazinyl, purinyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, benzisoxazolyl, isobenzofuryl, isoindolyl, indolizinyl, benzotriazinyl, thienopyridinyl, thienopyrimidinyl, pyrazolopyrimidinyl, imidazopyridines, benzothiazolyl, benzofuranyl, benzothienyl, indolyl, azaindolyl, azaindazolyl, quinolyl, isoquinolyl, isothiazolyl, pyrazolyl, indazolyl, pteridinyl, imidazolyl, triazolyl,

tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, thiazolyl, furyl or thienyl. Preferred heteroaryl groups are those having at least one aryl ring nitrogen atom, such as quinolinyl, quinoxalinyl, purinyl, benzimidazolyl, benzopyrazolyl, benzotriazolyl, benzothiazolyl, indolyl, quinolyl, isoquinolyl and the like. Preferred 6-ring heteroaryl systems include pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl and the like. Preferred 5-ring heteroaryl systems include isothiazolyl, pyrazolyl, imidazolyl, thienyl, furyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, thiazolyl and the like.

[0049] Heterocyclyl and heteroaryl can be attached at any available ring carbon or heteroatom. Each heterocyclyl and heteroaryl may have one or more rings. When multiple rings are present, they can be fused together or linked covalently. Each heterocyclyl and heteroaryl must contain at least one heteroatom (typically 1 to 5 heteroatoms) selected from nitrogen, oxygen or sulfur. Preferably, these groups contain 0-5 nitrogen atoms, 0-2 sulfur atoms and 0-2 oxygen atoms. More preferably, these groups contain 0-3 nitrogen atoms, 0-1 sulfur atoms and 0-1 oxygen atoms. Heterocyclyl and heteroaryl groups can be substituted or unsubstituted, unless otherwise indicated. For substituted groups, the substitution may be on a carbon or heteroatom. For example, when the substitution is oxo (=O or $-O^-$), the resulting group may have either a carbonyl (-C(O)-) or a N-oxide ($-N^+-O^-$).

[0050] Suitable substituents for substituted alkyl, substituted alkenyl, and substituted alkynyl include halogen, -CN, $-CO_2R'$, -C(O)R', -C(O)NR'R", oxo (=O or $-O^-$), –OR', -OC(O)R', -OC(O)NR'R" $-NO_2$, -NR'C(O)R', -NR"'C(O)NR'R", -NR'R", -NR'CO_2R", -NR'S(O)R", -NR'$S(O)_2$R"', -NR"'S(O)NR'R", -NR"'$S(O)_2$NR'R", -SR', -S(O)R', $-S(O)_2$R', $-S(O)_2$NR'R", -NR'-C(NHR")=NR"', -SiR'R"R"',$-N_3$, substituted or unsubstituted $C_{6\text{-}10}$ aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl. The number of possible substituents range from zero to (2m'+1), where m' is the total number of carbon atoms in such radical.

[0051] Suitable substituents for substituted aryl, substituted heteroaryl and substituted heterocyclyl include halogen, -CN, $-CO_2R'$, -C(O)R', -C(O)NR'R",

oxo (=O or –O⁻), –OR', -OC(O)R', -OC(O)NR'R", $-NO_2$, -NR'C(O)R", -NR"'C(O)NR'R", -NR'R", $-NR'CO_2R"$, -NR'S(O)R", $-NR'S(O)_2R"$, -NR"'S(O)NR'R", $-NR"'S(O)_2NR'R"$, -SR', -S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, -NR'-C(NHR")=NR"', -SiR'R"R"', $-N_3$, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10 membered heterocyclyl. The number of possible substituents range from zero to the total number of open valences on the aromatic ring system.

[0052] As used above, R', R" and R"' each independently refer to a variety of groups including hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryloxyalkyl. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 3-, 4-, 5-, 6-, or 7-membered ring (for example, -NR'R" includes 1-pyrrolidinyl and 4-morpholinyl). Furthermore, R' and R", R" and R"', or R' and R"' may together with the atom(s) to which they are attached, form a substituted or unsubstituted 5- ,6- or 7-membered ring.

[0053] Two of the substituents on adjacent atoms of an aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-$(CH_2)_q$-U-, wherein T and U are independently –NR""-, -O-, $-CH_2-$ or a single bond, and q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula –A'-$(CH_2)_r$-B'-, wherein A' and B' are independently $-CH_2-$, -O-, -NR""-, -S-, -S(O)-, $-S(O)_2-$, $-S(O)_2NR""-$ or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -$(CH_2)_s$-X-$(CH_2)_t$-, where s and t are independently integers of from 0 to 3, and X is -O-, -NR""-, -

S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2NR'$-. R'''' in is selected from hydrogen or unsubstituted C_{1-8} alkyl.

[0054] "Heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

[0055] "Pharmaceutically acceptable" carrier, diluent, or excipient is a carrier, diluent, or excipient compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0056] "Pharmaceutically-acceptable salt" refers to a salt which is acceptable for administration to a patient, such as a mammal (e.g., salts having acceptable mammalian safety for a given dosage regime). Such salts can be derived from pharmaceutically-acceptable inorganic or organic bases and from pharmaceutically-acceptable inorganic or organic acids, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary, tertiary and quaternary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Salts derived from pharmaceutically-acceptable acids include acetic,

ascorbic, benzenesulfonic, benzoic, camphosulfonic, citric, ethanesulfonic, fumaric, gluconic, glucoronic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, lactobionic, maleic, malic, mandelic, methanesulfonic, mucic, naphthalenesulfonic, nicotinic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic and the like.

[0057] Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M. et al, "Pharmaceutical Salts", J. Pharmaceutical Science, 1977, 66:1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0058] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

[0059] "Salt thereof" refers to a compound formed when the hydrogen of an acid is replaced by a cation, such as a metal cation or an organic cation and the like. Preferably, the salt is a pharmaceutically-acceptable salt, although this is not required for salts of intermediate compounds which are not intended for administration to a patient.

[0060] In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0061] Prodrugs may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in

routine manipulation or in vivo, to the parent compounds. Prodrugs include compounds wherein hydroxyl, amino, sulfhydryl, or carboxyl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, sulfhydryl, or carboxyl group respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the invention. Preparation, selection, and use of prodrugs is discussed in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series; "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985; and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, each of which are hereby incorporated by reference in their entirety.

[0062] The compounds of the invention may be present in the form of pharmaceutically acceptable metabolites thereof. The term "metabolite" means a pharmaceutically acceptable form of a metabolic derivative of a compound of the invention (or a salt thereof). In some aspects, the metabolite may be a functional derivative of a compound that is readily convertible in vivo into an active compound. In other aspects, the metabolite may be an active compound.

[0063] "Therapeutically effective amount" refers to an amount sufficient to effect treatment when administered to a patient in need of treatment.

[0064] "Treating" or "treatment" as used herein refers to the treating or treatment of a disease or medical condition (such as a viral, bacterial or fungal infection or other infectious diseases, as well as autoimmune or inflammatory conditions) in a patient, such as a mammal (particularly a human or a companion animal) which includes ameliorating the disease or medical condition, i.e., eliminating or causing regression of the disease or medical condition in a patient; suppressing the disease or medical condition, i.e., slowing or arresting the development of the disease or medical condition in a patient; or alleviating the symptoms of the disease or medical condition in a patient.

[0065] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, both solvated forms and unsolvated forms are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms (i.e., as polymorphs). In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0066] It will be apparent to one skilled in the art that certain compounds of the present invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention. Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers (e.g., separate enantiomers) are all intended to be encompassed within the scope of the present invention. The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

[0067] The compounds of the present invention may include a detectable label. A detectable label is a group that is detectable at low concentrations, usually less than micromolar, possibly less than nanomolar, and that can be readily distinguished from other molecules, due to differences in a molecular property (e. g. molecular weight, mass to charge ratio, radioactivity, redox potential, luminescence, fluorescence, electromagnetic properties, binding properties, and the like). Detectable labels may be detected by spectroscopic, photochemical, biochemical, immunochemical, electrical, magnetic, electromagnetic, optical or chemical means and the like.

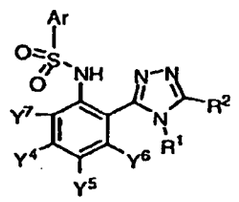
[0068] A wide variety of detectable labels are within the scope of the present invention, including hapten labels (e.g. biotin, or labels used in

conjunction with detectable antibodies such as horse radish peroxidase antibodies); mass tag labels (e.g. stable isotope labels); radioisotopic labels (including ^{3}H, ^{125}I, ^{35}S, ^{14}C, or ^{32}P); metal chelate labels; luminescent labels including fluorescent labels (such as fluorescein, isothiocyanate, Texas red, rhodamine, green fluorescent protein, and the like), phosphorescent labels, and chemiluminescent labels, typically having quantum yield greater than 0.1; electroactive and electron transfer labels; enzyme modulator labels including coenzymes, organometallic catalysts horse radish peroxidase, alkaline phosphatase and others commonly used in an ELISA;photosensitizer labels; magnetic bead labels including Dynabeads; colorimetric labels such as colloidal gold, silver, selenium, or other metals and metal sol labels (see U. S. Patent No. 5,120,643, which is herein incorporated by reference in its entirety for all purposes), or colored glass or plastic (e.g., polystyrene, polypropylene, latex, etc.) bead labels; and carbon black labels. Patents teaching the use of such detectable labels include U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; 4,366,241; 6,312,914; 5,990,479; 6,207,392; 6,423,551; 6,251,303; 6,306,610; 6,322,901; 6,319,426; 6,326,144; and 6,444,143, which are herein incorporated by reference in their entirety for all purposes.

[0069] Detectable labels are commercially available or may be prepared as known to one skilled in the art. Detectable labels may be covalently attached to the compounds using a reactive functional group, which can be located at any appropriate position. Methods for attaching a detectable label are known to one skilled in the art. When the reactive group is attached to an alkyl, or substituted alkyl chain tethered to an aryl nucleus, the reactive group may be located at a terminal position of an alkyl chain.

[0070] Compounds

[0071] In one embodiment, the compounds of the present invention are represented by formula (I), or salts thereof:



(I)

[0072] Ar is selected from the group consisting of substituted or unsubstituted C_{6-10} aryl and substituted or unsubstituted 5- to 10-membered heteroaryl;

[0073] Y^4, Y^5, Y^6, and Y^7 are each independently selected from the group consisting of hydrogen, halogen, -CN, $-C(O)R^{15}$, $-CO_2R^{15}$, $-C(O)NR^{15}R^{16}$, $-OR^{15}$, $-OC(O)R^{15}$, $-OC(O)NR^{15}R^{16}$, $-SR^{15}$, $-S(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2NR^{15}R^{16}$, $-NO_2$, $-NR^{15}R^{16}$, $-NR^{15}C(O)R^{16}$, $-NR^{15}C(O)OR^{16}$, $-NR^{15}S(O)_2R^{16}$, $-NR^{15}C(O)NR^{16}R^{17}$, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl;

[0074] R^{15}, R^{16} and R^{17} are each independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl; and

[0075] R^{15} and R^{16}, R^{16} and R^{17} or R^{15} and R^{17} may, together with the atoms to which they are attached, form a substituted or unsubstituted 5-, 6-, or 7-membered ring;

[0076] R^1 is selected from the group consisting of hydrogen, $-C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2NR^7R^8$, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl;

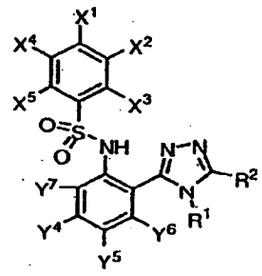
[0077] R^2 is selected from the group consisting of hydrogen, halogen, -CN, $-C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$, $-OR^7$, $-OC(O)R^7$, $-OC(O)NR^7R^8$, $-SR^7$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2NR^7R^8$, $-NO_2$, $-NR^7R^8$, $-NR^7C(O)R^8$, $-NR^7C(O)OR^8$, $-NR^7S(O)_2R^8$, $-NR^7C(O)NR^8R^9$, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl;

[0078] R^7, R^8, and R^9 are each independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl;

[0079] R^7 and R^8, R^8 and R^9 or R^7 and R^9 may, together with the atoms to which they are attached, form a substituted or unsubstituted 5-, 6-, or 7-membered ring; and

[0080] where R^1 and R^2 may, together with the atoms to which they are attached, form a substituted or unsubstituted 5-, 6-, or 7-membered ring.

[0081] In one embodiment, the compounds of the present invention are represented by formula (II), or salts thereof:



(II)

[0082] where Y^4, Y^5, Y^6, Y^7, R^1 and R^2 are as defined for formula (I);

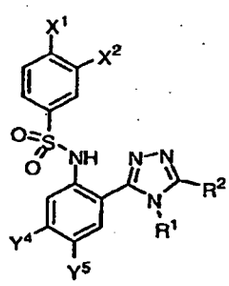
[0083] X^1, X^2, X^3, X^4, and X^5 are each independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, -CN, $-NO_2$, $-C(O)R^{18}$, $-CO_2R^{18}$, $-C(O)NR^{18}R^{19}$, $-OR^{18}$, $-OC(O)R^{19}$, $-OC(O)NR^{18}R^{19}$, $-NO_2$, $-NR^{18}C(O)R^{19}$, $-NR^{18}C(O)NR^{19}R^{20}$, $-NR^{18}R^{19}$,

$-NR^{18}CO_2R^{19}$, $-NR^{18}S(O)_2R^{19}$, $-SR^{18}$, $-S(O)R^{18}$, $-S(O)_2R^{18}$, $-S(O)_2NR^{18}R^{19}$, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl;

[0084] R^{18}, R^{19} and R^{20} are each independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl; and

[0085] R^{18} and R^{19}, R^{19} and R^{20} or R^{18} and R^{20} may, together with the atoms to which they are attached, form a substituted or unsubstituted 5-, 6-, or 7-membered ring.

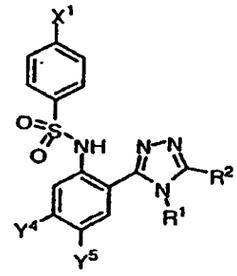
[0086] In another embodiment, the compounds are represented by formula (III), or salts thereof:



(III)

[0087] where Y^4, Y^5, R^1 and R^2 are as defined for formula (I); and X^1 and X^2 are as defined for formula (II); with the proviso that at least one of X^1 and X^2 is other than hydrogen and at least one of Y^4 and Y^5 is other than hydrogen.

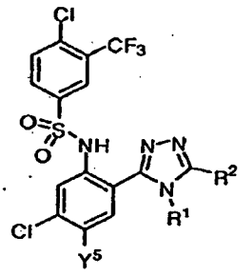
[0088] In another embodiment, the compounds are represented by formula (IV), or salts thereof:



(IV)

[0089] where Y^4, Y^5, R^1 and R^2 are as defined for formula (I); and X^1 is as defined for formula (II), with the proviso that X^1 is other than hydrogen and at least one of Y^4 and Y^5 is other than hydrogen.

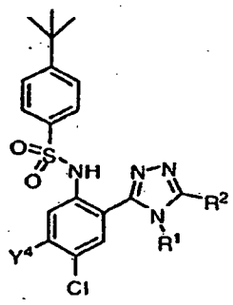
[0090] In another embodiment, the compounds of the present invention are represented by formula (V), or salts thereof:



(V)

[0091] where Y^5 is halogen or hydrogen; and R^1 and R^2 are as defined for formula (I).

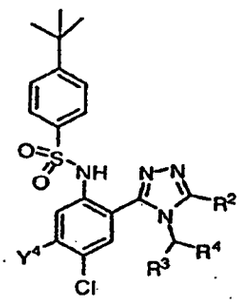
[0092] In another embodiment, the compounds of the present invention are represented by formula (VI), or salts thereof:



(VI)

[0093] where Y^4 is hydrogen or fluoro; R^1 and R^2 is as defined in formula (I).

[0094] In another embodiment, the compounds of the present invention are represented by formula (VIIa), or salts thereof:

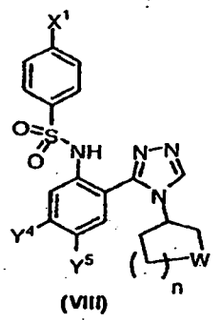


(VIIa)

[0095] where Y^4 is hydrogen or fluoro; R^2 is as defined in formula (I); and

[0096] R^3 and R^4 are each independently hydrogen, unsubstituted or substituted C_{1-8} alkyl, or R^3 and R^4 together with the carbon which they substitute form a 3-10 member carbocyclic, 4 -10 member heterocyclic, 5-10 member heteroaryl ring or 6-10 membered aryl ring.

[0097] In another embodiment, the compounds of the present invention are represented by formula (VIII), or salts thereof:



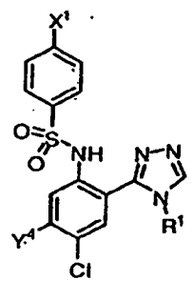
(VIII)

[0098] where Y^4 and Y^5 are as defined for formula (I); X^1 is as defined for formula (II), with the proviso that X^1 and Y^5 are other than hydrogen;

[0099] W is NH or O; and

[00100] n is 0, 1, or 2.

[00101] In another embodiment, the compounds of the present invention are represented by formula (IXa), or salts thereof:

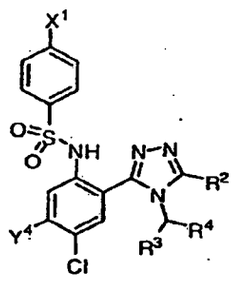


(IXa)

[00102] where Y^4 is hydrogen or fluoro; R^1 is as defined in formula (I); and

[00103] X^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, $-OR^{18}$, $-NR^{18}R^{19}$, and substituted or unsubstituted 3- to 10-membered heterocyclyl.

[00104] In another embodiment, the compounds of the present invention are represented by formula (IXb), or salts thereof:



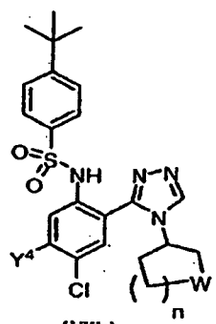
(IXb)

[00105] where Y^4 is hydrogen or fluoro; R^2 is as defined in formula (I);

[00106] X^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, $-OR^{18}$, $-NR^{18}R^{19}$, and substituted or unsubstituted 3- to 10-membered heterocyclyl; and

[00107] R^3 and R^4 are each independently hydrogen, unsubstituted or substituted C_{1-8} alkyl, or R^3 and R^4 together with the carbon which they substitute form a 3-10 member carbocyclic, 4 -10 member heterocyclic, 5-10 member heteroaryl ring or 6-10 membered aryl ring.

[00108] In another embodiment, the compounds of the present invention are represented by formula (VIIb), or salts thereof:



(VIIb)

[00109] Y^4 is hydrogen or fluoro;

[00110] W is NH or O; and

[00111] n is 0, 1, or 2.

[00112] **Compounds that Modulate CCR2 or CCR9 Activity**

[00113] The present invention provides compounds that modulate at least one of CCR2 or CCR9 activity. Chemokine receptors are integral membrane proteins which interact with an extracellular ligand, such as a chemokine, and mediate a cellular response to the ligand, *e.g.*, chemotaxis, increased intracellular calcium ion concentration, etc. Therefore, modulation of a chemokine receptor function, *e.g.*, interference with a chemokine receptor ligand interaction, will modulate a chemokine receptor mediated response, and treat or prevent a chemokine receptor mediated condition or disease. Modulation of a chemokine receptor function includes both inducement and inhibition of the function. The type of modulation accomplished will depend on the characteristics of the compound, i.e., antagonist or full, partial or inverse agonist.

[00114] Without intending to be bound by any particular theory, it is believed that the compounds provided herein interfere with the interaction between a chemokine receptor and one or more cognate ligands. In particular, it is believed that the compounds interfere with the interaction between CCR2 and a CCR2 ligand, such as MCP-1. Compounds contemplated by the invention include, but are not limited to, the exemplary compounds provided herein and salts thereof.

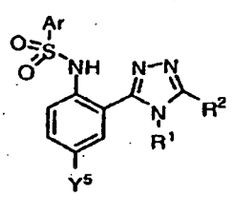
[00115] For example, compounds of this invention act as potent CCR2 antagonists, and this antagonistic activity has been further confirmed in animal testing for inflammation, one of the hallmark disease states for CCR2. Accordingly, the compounds provided herein are useful in pharmaceutical compositions, methods for the treatment of CCR2-mediated diseases, and as controls in assays for the identification of competitive CCR2 antagonists.

[00116] The compounds of the invention are thought to interfere with inappropriate T-cell trafficking by specifically modulating or inhibiting a chemokine receptor function. Without intending to be bound by any particular theory, it is believed that the compounds provided herein interfere with the interaction between a chemokine receptor and one or more cognate ligands. In particular, it is believed that the compounds interfere with the interaction between CCR9 and a CCR9 ligand, such as TECK. Compounds contemplated by the invention include, but are not limited to, the exemplary compounds provided herein and salts thereof.

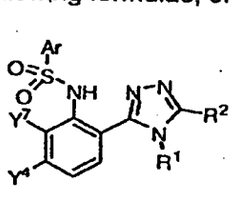
[00117] For example, compounds of this invention act as potent CCR9 antagonists, and this antagonistic activity has been further confirmed in animal testing for inflammation, one of the hallmark disease states for CCR9. Accordingly, the compounds provided herein are useful in pharmaceutical compositions, methods for the treatment of CCR9-mediated diseases, and as controls in assays for the identification of competitive CCR9 antagonists.

[00118] **Preferred Compounds**

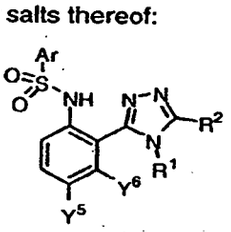
[00119] In several preferred embodiments, the compounds may be represented by the following formulae, or salts thereof:



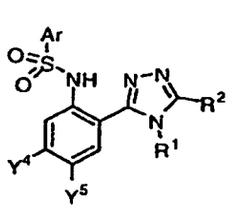
(X)



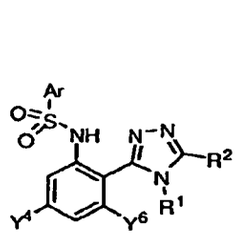
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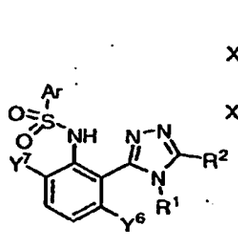
(XII)



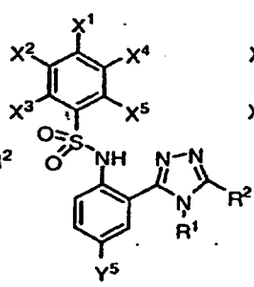
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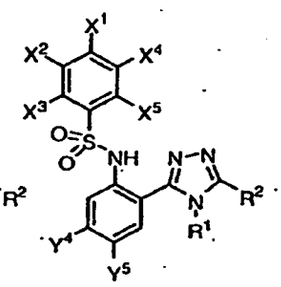
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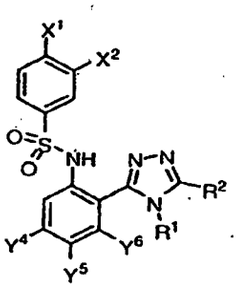
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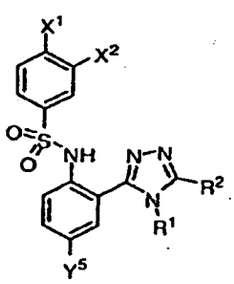
(XVI)



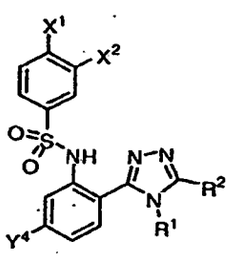
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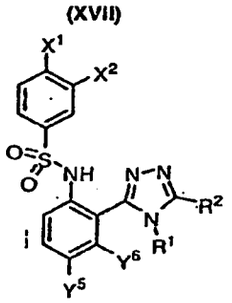
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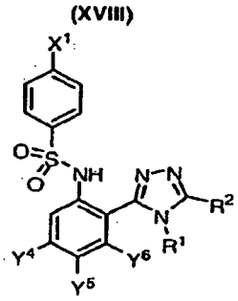
(XIX)



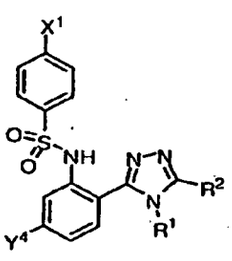
(XX)



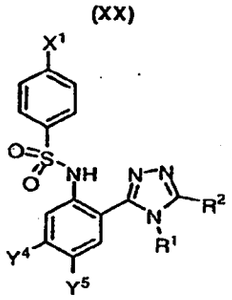
(XXI)



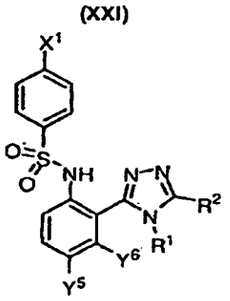
(XXII)



(XXIII)



(XXIV)



(XXV)

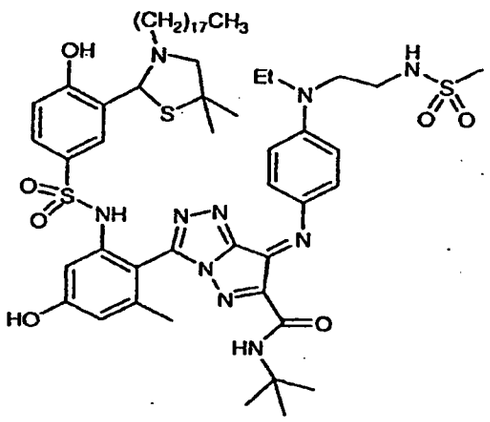
[00120] Formulae X to XXV are examples of Formula I.

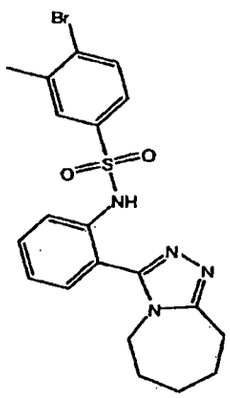
[00121] In the following descriptions and embodiments, references to specific substituents only correspond to formula numbers in which those specific substituents are present or appear.

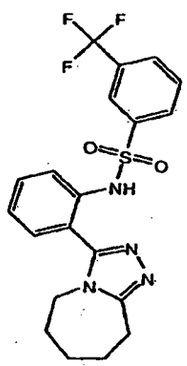
[00122] In each of the formulae (X to XXV), Ar, X^1, X^2, X^3, X^4, X^5, Y^4, Y^5, Y^6, Y^7, R^1 and R^2 are as defined above.

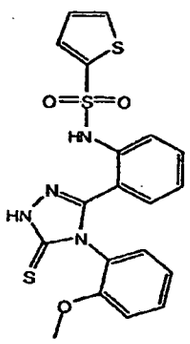
Known Compound

[00123] The compound shown below:









[00124] also referred to as

[00125] N-(1,1-dimethylethyl)-3-[2-{[[3-(5,5-dimethyl-3-octadecyl-2-thiazolidinyl)-4-hydroxyphenyl]sulfonyl]amino]-4-hydroxy-6-methylphenyl]-7-[[4-[ethyl[2-[(methylsulfonyl)amino]ethyl]amino]phenyl]imino]-7H-pyrazolo[5,1-c]-1,2,4-triazole-6-carboxamide;

[00126] Benzenesulfonamide, 4-bromo-3-methyl-N-[2-(6,7,8,9-tetrahydro-5H-1,2,4-triazolo[4,3-a]azepin-3-yl)phenyl];

[00127] Benzenesulfonamide, N-[2-(6,7,8,9-tetrahydro-5H-1,2,4-triazolo[4,3-a]azepin-3-yl)phenyl]-3-(trifluoromethyl); and

[00128] 2-Thiophenesulfonamide, N-[2-[4,5-dihydro-4-(2-methoxyphenyl)-5-thioxo-1H-1,2,4-triazol-3-yl]phenyl];

[00129] are known, but not as CCR9 or CCR2 antagonists

[00130] **Preferred Embodiments**

[00131] In one embodiment of formula (II), X^1 is selected from the group consisting of halogen, substituted or unsubstituted C_{1-8} alkyl, $-OR^{18}$, $-NR^{18}R^{19}$, and substituted or unsubstituted 3- to 10-membered heterocyclyl; Y^7 is hydrogen; Y^4, Y^5, and Y^6 are each independently selected from the group consisting of hydrogen, halogen, -CN, $-CO_2R^{15}$, $-C(O)NR^{15}R^{16}$; R^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl; and R^2 is selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl.

[00132] In one embodiment of formula (III) X^1 is halogen; X^2 is halogen or $-CF_3$; Y^4 is halogen; Y^5 is hydrogen or halogen; R^1 is aryl or heteroaryl; and R^2 is hydrogen or substituted or unsubstituted C_{1-8} alkyl.

[00133] In one embodiment of formula (V), Y^5 is halogen or hydrogen; R^1 is substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl; and R^2 is as defined for formula (I).

[00134] In one embodiment of formula (III), X^2 and Y^4 are each independently hydrogen or halogen; X^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, $-OR^{18}$, $-NR^{18}R^{19}$, and substituted or unsubstituted 3- to 10-membered heterocyclyl; Y^5 is selected from the group consisting of hydrogen, halogen, -CN, $-CO_2R^{15}$, $-C(O)NR^{15}R^{16}$; R^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl; R^2 is selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl.

[00135] In one embodiment of formula (IV), Y^4 is hydrogen or halogen; X^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, $-OR^{18}$, $-NR^{18}R^{19}$, and substituted or unsubstituted 3- to 10-membered

heterocyclyl; Y^5 is selected from the group consisting of hydrogen, halogen, -CN, $-CO_2R^{15}$, $-C(O)NR^{15}R^{16}$; R^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl; R^2 is selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl.

[00136] In one embodiment of formula (V), Y^5 is halogen or hydrogen; R^1 is substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl; and R^2 is selected from the group consisting of hydrogen, $C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$, and substituted or unsubstituted C_{1-8} alkyl.

[00137] In one embodiment of formula (VI), Y^4 is hydrogen or fluoro; R^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl; and R^2 is selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl.

[00138] In one embodiment of formula (VII), Y^4 is hydrogen or fluoro; R^2 is selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl; and R^3 and R^4 are each independently hydrogen, unsubstituted or substituted C_{1-8} alkyl, or R^3 and R^4 together with the carbon which they substitute form a 3-10 member carbocyclic, 4-10 member heterocyclic, 5-10 member heteroaryl ring or 6-10 membered aryl ring.

[00139] In one embodiment of formula (VIII), X^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, $-OR^{18}$, $-NR^{18}R^{19}$,

and substituted or unsubstituted 3- to 10-membered heterocyclyl; Y^4 is hydrogen or fluoro; Y^5 is chloro; W is NH or O; and n is 0, 1, or 2.

[00140] In one embodiment of formula (VIII), Y^4 and Y^5 are as defined for formula (I); X^1 is tert-butyl, with the proviso that at least one of Y^4 and Y^5 is other than hydrogen; W is NH or O; and n is 0, 1, or 2.

[00141] In one embodiment of formula (VIII), X^1 is tert-butyl; Y^4 is hydrogen or fluoro; Y^5 is chloro; W is NH or O; and n is 0, 1, or 2.

[00142] In one embodiment of formula (XXIV), X^1 is tert-butyl, Y^4 and Y^5 are halogen; and R^1 and R^2 are as defined for formula (I).

[00143] In one embodiment of formula (XXIV), X^1 is tert-butyl, Y^4 is hydrogen and Y^5 is -CN; and R^1 and R^2 are as defined for formula (I).

[00144] In one embodiment of formula (XXIV), X^1 is tert-butyl, Y^4 is fluoro and Y^5 is chloro; and R^1 and R^2 are as defined for formula (I).

[00145] In one embodiment of formula (XXIV), X^1 is tert-butyl, Y^4 and Y^5 are halogen, and R^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl and substituted or unsubstituted 3- to 10-membered heterocyclyl; and R^2 is as defined for formula (I).

[00146] In one embodiment of formula (XXIV), X^1 is tert-butyl, Y^4 and Y^5 are halogen, and R^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl and substituted or unsubstituted 3- to 10-membered heterocyclyl; and R^2 is substituted or unsubstituted C_{2-8} alkyl and substituted or unsubstituted 3- to 10-membered heterocyclyl.

[00147] In one embodiment of formula (VI), R^1 is heterocyclyl, and R^2 is hydrogen or substituted or unsubstituted C_{1-8} alkyl.

[00148] In one embodiment of formula (XXV), X^1 is t-butyl, Y^5 is chloro, Y^6 is fluoro.

[00149] In one embodiment of formula (XXIV), X^1 is t-butyl, Y^4 is fluoro, and Y^5 is fluoro.

[00150] In one embodiment of formula (XXIV), X^1 is t-butyl, Y^4 is fluoro, and Y^5 is chloro.

[00151] In one embodiment of formulae (IV and XXII-XXV), X^1 is *t*-Bu or –OiPr; X^2, Y^4, Y^5, and Y^6 are each independently hydrogen or halogen,

wherein at least one of Y^4, Y^5, and Y^6 is halogen; and R^1 and R^2 are defined as in formula (I).

[00152] In one embodiment of formulae (IV and XXII-XXV), X^1 is substituted or unsubstituted C_{1-8} alkyl, $-NR^{18}R^{19}$, or $-OR^{18}$; X^2, Y^4, Y^5, and Y^6 are each independently hydrogen or halogen, wherein at least one of Y^4, Y^5, and Y^6 is halogen; and R^1 and R^2 are defined as in formula (I).

[00153] In one embodiment of formulae (IV and XXII-XXV), X^1 is substituted or unsubstituted C_{1-8} alkyl, $-NR^{18}R^{19}$, or $-OR^{18}$; X^2, Y^4, Y^5, and Y^6 are each independently halogen or hydrogen, wherein at least one of Y^4, Y^5, and Y^6 is halogen; R^1 is hydrogen, Me, Et, *i*-Bu, *i*-Pr, cyclopropyl, cyclobutyl, cyclopentyl,
$-CH(CH_3)CH_2OH$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)CH_3$, phenyl, 2-pyridyl, 4-pyridyl, 1H-pyrazol-3-yl, tetrahydrofuran-3-yl, tetrahydro-2H-pyran-3-yl, tetrahydro-2H-pyran-4-yl, azetidin-3-yl, pyrrolidin-3-yl, 1-isopropylpyrrolidin-3-yl, 1-(methylsulfonyl)pyrrolidin-3-yl, 1-(carboxamido)pyrrolidin-3-yl piperidin-3-yl, piperidin-4-yl, 1-carboxamido-piperidin-4-yl, 1-methylsulfonyl-piperidin-4-yl, 1-acetyl-piperidin-4-yl, 1-methyl-piperidin-4-yl, or 3-pyrrolidin-2-only; R^2 is hydrogen, Me, Et, *i*-Pr, $-NH_2$, $-CH_2OH$, $-C(CH_3)_2OH$, $-CH(OH)CH_3$, $-CH_2C(CH_3)_2OH$, $-CH_2C(O)OCH_2CH_3$, $-CH_2OCH_3$, $-CH_2OCH(CH_3)_2$, $-CH_2CH_2OCH_3$, $-CH_2N(CH_3)_2$, $-CH_2NHCH_3$, $-CH_2NHCH_2CH_3$, $-CH_2NHCH(CH_2CH_2)$, $-CH_2NHCH(CH_3)_2$, $-CH_2SO_2CH_3$, $-CH_2CH_2SO_2CH_3$, $-C(O)CH_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, 2-pyridyl, oxazol-4-yl, 5-methyloxazol-4-yl, tetrahydro-2H-pyran-3-yl, tetrahydro-2H-pyran-4-yl, tetrahydro-4-methyl-2H-pyran-4-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, morpholinomethyl, piperidin-4-yl, (pyrrolidin-1-yl)methyl, or (azetidin-1-yl)methyl)

[00154] In one embodiment of formulae (III, and XVIII-XXI), X^2, Y^4, Y^5, and Y^6 are halogen, and X^1, R^1 and R^2 are defined as in formula (I).

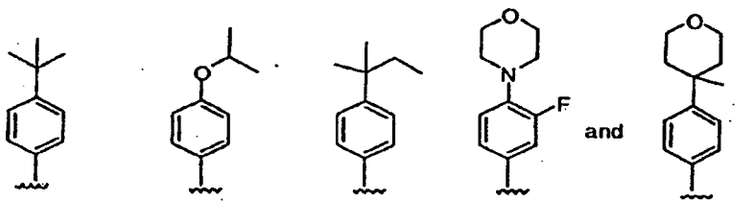
[00155] *Preferred Ar Groups*

[00156] In one embodiment of any the formulae (I and X-XV), Ar is selected from the group consisting of substituted or unsubstituted C_{6-10} aryl and substituted or unsubstituted 5- to 10-membered heteroaryl.

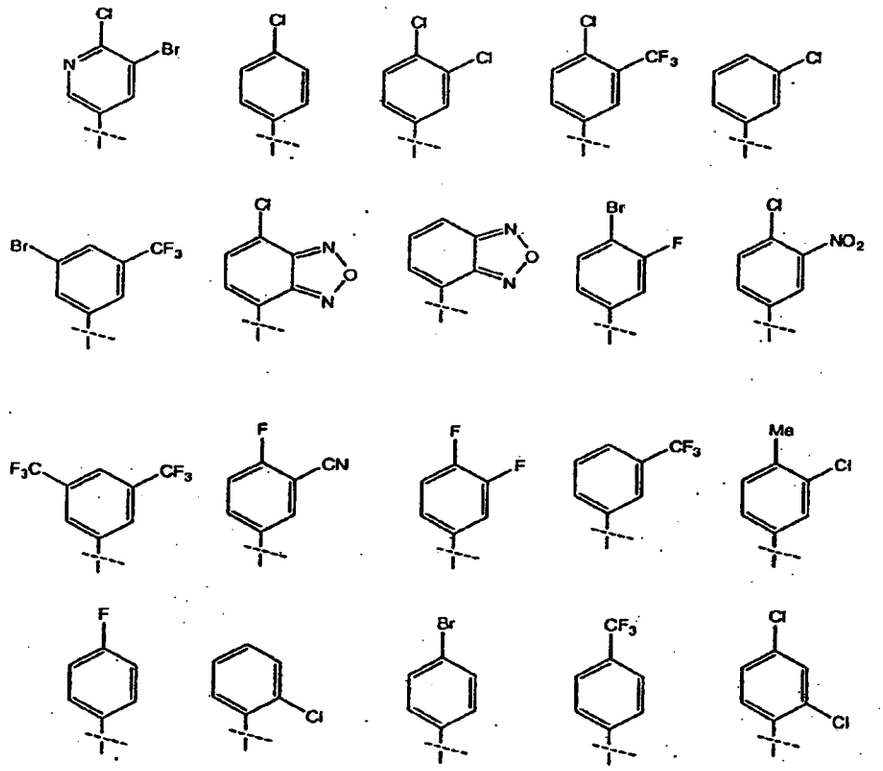
[00157] In one embodiment of any the formulae (I and X-XV), Ar is a C_{6-10} aryl with at least 2 substituents other than hydrogen.

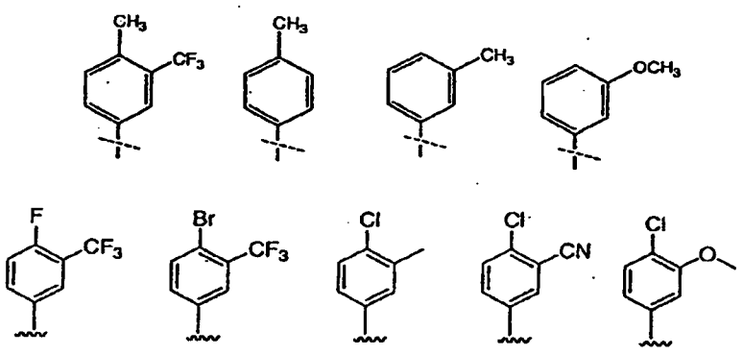
[00158] In one embodiment of any the formulae (I and X-XV), Ar is a substituted or unsubstituted bicyclic aryl or substituted or unsubstituted bicyclic heteroaryl.

[00159] In one embodiment of any the formulae (I and X-XV), Ar is selected from the group consisting of:



[00160] In one embodiment of any the formulae (I and X-XV), Ar is selected from the group consisting of:





[00161] *Preferred X Groups*

[00162] In one embodiment of formulae (II-IV, and XX-XV), at least one of X^1, X^2, X^3, X^4, and X^5 is other than hydrogen;

[00163] In one embodiment of formulae (II, III, XVI-XXI), at least two of X^1, X^2, X^3, X^4, and X^5 is other than hydrogen.

[00164] In one embodiment of formula (II, III, XVI-XXI), X^1 and X^2 are other than hydrogen.

[00165] In one embodiment of formula (II-IV, VIII, IX and XX-XV), X^1, X^2, X^3, X^4, and X^5 are each independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, $-OR^{18}$, $-C(O)R^{18}$, $-SO_2R^{18}$, $-NR^{18}R^{19}$, unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted 5- or 6-membered heteroaryl, and unsubstituted or substituted 5- or 6-membered heterocyclyl.

[00166] In one embodiment of formula (II-IV, VIII, IX and XX-XV), X^1, X^2, X^3, X^4, and X^5 are each independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, $-OR^{18}$, $-C(O)R^{18}$, $-SO_2R^{18}$, $-NR^{18}R^{19}$, unsubstituted C_{2-8} alkyl, substituted C_{1-8} alkyl; unsubstituted or substituted phenyl, unsubstituted or substituted 5- or 6-membered heteroaryl, and unsubstituted or substituted 5- or 6-membered heterocyclyl.

[00167] In another embodiment of formula (II-IV, VIII, IX and XX-XV), X^1, X^2, X^3, X^4, and X^5 are each independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, $-OR^{18}$, $-C(O)R^{18}$, $-SO_2R^{18}$, $-NR^{18}R^{19}$, unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted phenyl,

unsubstituted or substituted 5- or 6-membered heteroaryl, and unsubstituted or substituted 5- or 6-membered heterocyclyl; with the proviso that at least two of X^1, X^2, X^3, X^4, and X^5 are other than hydrogen; or with the proviso that at least one of X^1, X^2, X^3, X^4, and X^5 is other than hydrogen.

[00168] In another embodiment of formula (II-IV, VIII, IX and XX-XV), X^1, X^2, X^3, X^4, and X^5 are each independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, $-OR^{18}$, $-C(O)R^{18}$, $-SO_2R^{18}$, $-NR^{18}R^{19}$, unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted 5- or 6-membered heteroaryl, and unsubstituted or substituted 5- or 6-membered heterocyclyl; with the proviso that at least two of X^1, X^2 and X^4 are other than hydrogen; or with the proviso at least one of X^1, X^2 and X^4 is other than hydrogen.

[00169] In a further embodiment of formula (II-IV, VIII, IX and XX-XV), X^1, X^2, X^3, X^4, and X^5 are each independently selected from the group consisting of hydrogen, halogen, -CN, $-NO_2$, $-OR^{18}$, $-C(O)R^{18}$, $-SO_2R^{18}$, and $-NR^{18}R^{19}$; with the proviso that at least three of X^1, X^2, X^3, X^4, and X^5 are other than hydrogen; or with the proviso that at least two of X^1, X^2, X^3, X^4, and X^5 is other than hydrogen; or with the proviso that at least one of X^1, X^2, X^3, X^4, and X^5 is other than hydrogen.

[00170] In a further embodiment of formula (II-IV, VIII, IX and XX-XV), X^1, X^2, X^3, X^4, and X^5 are each independently selected from the group consisting of: hydrogen, halogen, unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted 5- or 6-membered heteroaryl, and unsubstituted or substituted 5- or 6-membered heterocyclyl; with the proviso that at least three of X^1, X^2, X^3, X^4, and X^5 are other than hydrogen; or with the proviso that at least two of X^1, X^2, X^3, X^4, and X^5 is other than hydrogen; or with the proviso that at least one of X^1, X^2, X^3, X^4, and X^5 is other than hydrogen.

[00171] In one embodiment of formulae (II-IV, VIII, IX and XX-XV), any two occurrences of X^1, X^2, X^3, X^4, and X^5 that are located adjacently to each other, can be joined to form a substituted 5- or 6-membered substituted or unsubstituted heterocyclyl or substituted or unsubstituted heteroaryl.

[00172] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is other than hydrogen.

[00173] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is other than methyl.

[00174] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, -CN, $-C(O)R^{18}$, $-CO_2R^{18}$, $-C(O)NR^{18}R^{19}$, $-OC(O)R^{19}$, $-OC(O)NR^{18}R^{19}$, $-NO_2$, $-NR^{18}C(O)NR^{19}R^{20}$, $-NR^{18}R^{19}$, $-NR^{18}CO_2R^{19}$, $-NR^{18}S(O)_2R^{19}$, $-SR^{18}$, $-S(O)R^{18}$, $-S(O)_2R^{18}$, $-S(O)_2NR^{18}R^{19}$, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl.

[00175] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is selected from the group consisting of -CN, $-NO_2$, $-C(O)R^{18}$, $-CO_2R^{18}$, $-C(O)NR^{18}R^{19}$, $-OR^{18}$, $-OC(O)R^{19}$, $-OC(O)NR^{18}R^{19}$, $-NO_2$, $-NR^{18}C(O)R^{19}$, $-NR^{18}C(O)NR^{19}R^{20}$, $-NR^{18}R^{19}$, $-NR^{18}CO_2R^{19}$, $-NR^{18}S(O)_2R^{19}$, $-SR^{18}$, $-S(O)R^{18}$, $-S(O)_2R^{18}$, and $-S(O)_2NR^{18}R^{19}$.

[00176] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is $-OR^{18}$.

[00177] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is $-NR^{18}R^{19}$.

[00178] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, and substituted or unsubstituted C_{2-8} alkynyl.

[00179] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is selected from the group consisting of substituted C_{1-8} alkyl or unsubstituted C_{2-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, and substituted or unsubstituted C_{2-8} alkynyl.

[00180] In one embodiment of formulae (II-IV, VIII, IX and XVI-XXV), X^1 is an unsubstituted C_{2-8} alkyl.

[00181] In one embodiment of formulae (II-IV, VIII, IX and XVI-XXV), X^1 is tert-butyl.

[00182] In one embodiment of formulae (II-IV, VIII, IX and XVI-XXV), X^1 is iso-propoxy.

[00183] In one embodiment of formulae (II-IV, VIII, IX and XVI-XXV), X^1 is morpholinyl.

[00184] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is selected from the group consisting of substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl.

[00185] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is selected from the group consisting of substituted or unsubstituted phenyl, substituted or unsubstituted 5- to 6-membered heteroaryl, and substituted or unsubstituted 5- to 6-membered heterocyclyl.

[00186] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is substituted or unsubstituted phenyl.

[00187] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is substituted or unsubstituted 5- to 6-membered heteroaryl.

[00188] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), X^1 is substituted or unsubstituted 5- to 6-membered heterocyclyl.

[00189] In one embodiment of formula (II-IV, VIII, IX and XVI-XXV), when X^2, X^3, X^4 and X^5 are hydrogen, X^1 is other than –Cl, $-NO_2$, $-OCH_3$, $-CH_3$, $-NHC(O)CH_3$, or $-CH_2CH_2$-(phenyl).

[00190] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), X^1 is a substituted or unsubstituted 5- or 6- membered heterocyclic ring, and the heterocycle is selected from the group consisting of pyrrolidine, piperidine, imidazolidine, pyrazolidine, butyrolactam, valerolactam, imidazolidinone, hydantoin, dioxolane, phthalimide, piperidine, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine-S-oxide, thiomorpholine-S,S-dioxide, piperazine, pyran, pyridone, 3-pyrroline, thiopyran, pyrone, tetrahydrofuran, and tetrahydrothiophene.

[00191] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), X^1 is a substituted or unsubstituted 5- or 6-membered heteroaryl

ring selected from the group consisting of pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, isothiazolyl, pyrazolyl, imidazolyl, thienyl, furyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, and thiazolyl.

[00192] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), X^1 is substituted or unsubstituted heterocyclic group selected from the group consisting of pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, 1,3-dioxalanyl, thiomorpholinyl, thiomorpholinyl-S,S-dioxide, piperazinyl and pyranyl.

[00193] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), X^1 is a substituted C_{1-8} alkyl. Preferably, the substituent is a substituted or unsubstituted heterocyclic group of the formula (AA) as defined in paragraph [0044], [0045] and [0046]. More preferably, the substituent is selected from the group including pyrrolidine, piperidine, imidazolidine, pyrazolidine, butyrolactam, valerolactam, imidazolidinone, hydantoin, dioxolane, phthalimide, piperidine, 1,4-dioxane, morpholine, thiomorpholine, thiomorpholine-S-oxide, thiomorpholine-S,S-dioxide, piperazine, pyran, pyridone, 3-pyrroline, thiopyran, pyrone, tetrahydrofuran, and tetrahydrothiophene.

[00194] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), a suitable substituent for substituted C_{1-8} alkyl (X^1, X^2, X^3, X^4, or X^5) can be selected from the group consisting of –CN, $-OR^{18}$, $-C(O)R^{18}$, $-CO_2R^{18}$, $-O(CO)R^{18}$, $-SO_2R^{18}$ and halogen. In one embodiment, X^2, X^3, X^4, and X^5 are hydrogen.

[00195] In one embodiment of each of the (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is halogen, particularly chlorine.

[00196] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is an unsubstituted C_{1-8} alkyl.

[00197] In one embodiment of each of the formulae (II-IV, VIII and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is an unsubstituted C_{2-8} alkyl.

[00198] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is t-butyl.

[00199] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is oxazolyl.

[00200] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is trifluoromethoxy.

[00201] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is $-SO_2R^{18}$. In one particular embodiment, R^{18} is methyl.

[00202] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV, at least one of X^1, X^2, X^3, X^4, or X^5 is $-OR^{18}$. In one particular embodiment, R^{18} is methyl.

[00203] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is $-SR^{18}$. In one particular embodiment, R^{18} is methyl.

[00204] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is unsubstituted C_{1-6} alkyl (in particular methyl) or C_{1-6} haloalkyl (in particular $-CF_3$).

[00205] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is substituted C_{1-6} alkyl (preferably not C_{1-6} haloalkyl).

[00206] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is isopropyl.

[00207] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is a cyano.

[00208] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is a cyano, halogen or trifluoromethyl group.

[00209] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is $-C(Me)_2CH_2OH$.

[00210] In one embodiment of each of the formulae ((II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is -C(O)Me.

[00211] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is $-(CH_2)_2CO_2Me$.

[00212] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is isoamyl.

[00213] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, X^5 is 1,3-dioxalanyl.

[00214] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is furyl.

[00215] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is pyrazolyl.

[00216] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), at least one of X^1, X^2, X^3, X^4, or X^5 is thienyl.

[00217] In one embodiment of each of the formulae (II-IV, VIII, IX and XVI-XXV), X^1 is a substituted C_{1-8} alkyl, where suitable substituents are as defined for formula (II). In one preferred embodiment, the substituted C_{1-8} alkyl is substituted with a 5- or 6-membered heteroaryl selected from the group consisting of pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, isothiazolyl, pyrazolyl, imidazolyl, thienyl, furyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl, and thiazolyl. More preferably, the substituted C_{1-8} alkyl is substituted with oxazolyl.

[00218] In one embodiment of formula (II-IV, VIII and XVI-XXV), X^1 and X^2 are other than hydrogen.

[00219] In one embodiment of formula (II-IV, VIII and XVI-XXV), X^1 and X^2 are selected from the group consisting of halogen, substituted or unsubstituted C_{1-8} alkyl, OR^{18}, $-NO_2$, -CN, and $-CO_2R^{18}$.

[00220] In one embodiment of formulae (II, III, XVI-XXI), at least one of X^1 and X^2 is selected from the group consisting of halogen, -CN, and $-CF_3$.

[00221] In one embodiment of formulae (II, III, XVI-XXI), both X^1 and X^2 are selected from the group consisting of halogen, -CN, and $-CF_3$.

[00222] In an additional embodiment of formulae (II, III, XVI-XXI), one of X^1 and X^2 is halogen and one of X^1 and X^2 is selected from the group consisting of halogen, -CN, and $-CF_3$.

[00223] In an additional embodiment of formulae (II, III, XVI-XXI), one of X^1 and X^2 is halogen and one of X^1 and X^2 is selected from the group consisting of halogen, -CN, $-CH_3$ and $-CF_3$.

[00224] In an additional embodiment of formulae (II, III, XVI-XXI), X^1 is selected from the group consisting of halogen and $-CH_3$, and X^2 is selected from the group consisting of halogen, $-CN$, $-CH_3$, $-OCH_3$, $-OCF_3$ and $-CF_3$.

[00225] In one embodiment of formula (II, III, XVI-XXI), X^1 is selected from the group consisting of halogen and $-CH_3$, and X^2 is selected from the group consisting of halogen, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCF_3$, $-CF_2H$, and CF_2R^{10}, where R^{10} is substituted or unsubstituted C_{1-8} alkyl.

[00226] In one embodiment of formula (II, III, XVI-XXI), X^1 and X^2 are selected from the group consisting of -Cl, -F, -Br, $-CF_3$, $-CONHCH_3$, $-OCF_3$, $-CH_3$, $-OCH_3$, $-NO_2$, -CN, and $-CO_2H$.

[00227] In one embodiment of formula (II, III, XVI-XXI), X^1 is selected from the group consisting of halogen and $-CH_3$, and X^2 is selected from the group consisting of halogen, $-CH_3$, $-CF_3$, $-OCH_3$, and $-OCF_3$.

[00228] In one embodiment of formula (II, III, XVI-XXI), X^1 is chloro and X^2 is $-CF_3$.

[00229] In one embodiment of formula (II, III, XVI-XXI), X^2 is other than hydrogen.

[00230] In one embodiment of formulae (II, III, XVI-XXI), X^2 is other than hydrogen.

[00231] In one embodiment of formula (II, III, XVI-XXI), X^2 is selected from the group consisting of halogen, substituted or unsubstituted C_{1-8} alkyl, OR^{18}, $-NO_2$, -CN, and $-CO_2R^{18}$.

[00232] In one embodiment of formula (II, III, XVI-XXI), X^2 is selected from the group consisting of -Cl, -F, -Br, $-CF_3$, $-CONHCH_3$, $-OCF_3$, $-CH_3$, $-OCH_3$, $-NO_2$, -CN, and $-CO_2H$.

[00233] In one embodiment of formulae (II, III, XVI-XXI), X^2 is fluoro.

[00234] *Preferred Y Groups*

[00235] In one embodiment of any of formula (I-IX and X-XXV), Y^4, Y^5, Y^6, and Y^7 are each independently selected from the group consisting of hydrogen, halogen, -CN, $-CO_2R^{15}$, $-OR^{15}$, and substituted or unsubstituted C_{1-8} alkyl, where 1 to 2 of Y^4, Y^5, Y^6, and Y^7 are other than hydrogen.

[00236] In one embodiment of any of formulae (I-IX and X-XXV), Y^4, Y^5, Y^6, and Y^7 are each independently selected from the group consisting of hydrogen, -CN, fluorine, chlorine, and bromine, where 1 to 2 of Y^4, Y^5, Y^6, and Y^7 are other than hydrogen.

[00237] In another embodiment of any of formulae (I-IX and X-XXV), at least one of Y^4, Y^5, Y^6, and Y^7 is other than hydrogen; preferably Y^4 is halogen.

[00238] In another embodiment of any of formula (I-VIII and X-XXV), at least one of Y^4, Y^5, Y^6, and Y^7 is other than hydrogen; preferably Y^5 is halogen.

[00239] In another embodiment of any of formulae (I-VIII and X-XXV)), Y^5 and Y^7 are hydrogen and Y^4 is halogen.

[00240] In another embodiment of any of formulae (I-VIII and X-XXV)), Y^5 and Y^7 are hydrogen and Y^4 is chloro.

[00241] In one embodiment of any of formulae (I, II and X-XXV)), Y^7 and Y^6 are hydrogen, and Y^4 and Y^5 are fluoro.

[00242] In one embodiment of any of formulae (I, II and X-XXV)), Y^7 and Y^6 are hydrogen, and Y^4 is chloro and Y^5 is $-CH_3$.

[00243] In one embodiment of any of formulae (I-IX and X-XXV)), Y^4 and Y^5 are selected from the group consisting of halogen, -CN, $-OR^{15}$, and substituted or unsubstituted C_{1-8} alkyl.

[00244] In one embodiment of any of formulae (I-IX and X-XXV)), Y^4 and Y^5 are selected from the group consisting of –Cl, -Br, -F, $-OCH_3$, $-CH_3$, $-CF_3$, and -CN

[00245] In one embodiment of any of formulae (I-IV, VI-IX and X-XXV)), Y^4 is selected from the group consisting of –Cl, -Br, -F, and $-OCH_3$.

[00246] In one embodiment of any of formulae ((I-IV, VI-IX, XI, XIII, XIV, XVII, XVIII, XX, XXII-XXIV), Y^4 is halogen.

[00247] In one embodiment of any of formulae ((I-IV, VI-IX, XI, XIII, XIV, XVII, XVIII, XX, XXII-XXIV), Y^4 is fluoro.

[00248] In one embodiment of any of formulae ((I-IV, VI-IX, XI, XIII, XIV, XVII, XVIII, XX, XXII-XXIV), Y^4 is chloro.

[00249] In one embodiment of any of formulae (I-V, VIII, X, XII, XIII, XVI-XIX, XXI, XXII, XXIV, XXV), Y^5 is selected from the group consisting of -Cl, -Br, -F, $-CH_3$, $-CF_3$, and -CN.

[00250] In one embodiment of any of formulae (I-V, VIII, X, XII, XIII, XVI-XIX, XXI, XXII, XXIV, XXV), Y^5 is halogen.

[00251] In one embodiment of any of formulae (I-V, VIII, X, XII, XIII, XVI-XIX, XXI, XXII, XXIV, XXV), Y^5 is chloro.

[00252] In one embodiment of any of formulae (I-V, VIII, X, XII, XIII, XVI-XIX, XXI, XXII, XXIV, XXV), Y^5 is fluoro.

[00253] In one embodiment of any of formulae (I-V, VIII, X, XII, XIII, XVI-XIX, XXI, XXII, XXIV, XXV), Y^5 is -CN.

[00254] In one embodiment of any of formulae (I, II, XII, XIV, XV, XVIII, XXI, XXII, XXV), Y^6 is fluoro.

[00255] In one embodiment of any of formula (I, II, XII, XVIII, XXI, XXII, XXV), Y^5 is chloro and Y^6 is fluoro.

[00256] In one embodiment of any of formulae(I-IV, VIII, XIII, XVII, XVIII, XXII, XXIV), Y^5 is chloro and Y^4 is fluoro.

[00257] In one embodiment of any of formulae (I-IV, VIII, XIII, XVII, XVIII, XXII, XXIV), Y^5 and Y^4 are fluoro.

[00258] In one embodiment of any of formulae(I-IV, VIII, XIII, XVII, XVIII, XXII, XXIV), Y^5 is -CN and Y^4 is fluoro.

[00259] In one embodiment of any of formulae(I-IV, VIII, XIII, XVII, XVIII, XXII, XXIV), Y^5 is -CN and Y^4 is hydrogen.

[00260] *Preferred R^1 and R^2 Groups*

[00261] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is other than hydrogen.

[00262] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is selected from the group consisting of $-C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$, $-S(O)R^7$, $-S(O)_2R^7$, and $-S(O)_2NR^7R^8$.

[00263] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 and R^2 together with the atoms which they substitute form a carbocyclic or heterocyclic ring.

[00264] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl.

[00265] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 5- to 6-membered heterocyclyl, substituted or unsubstituted phenyl, and substituted or unsubstituted 5- to 6-membered heteroaryl.

[00266] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is substituted or unsubstituted C_{1-8} alkyl.

[00267] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is substituted or unsubstituted phenyl.

[00268] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is substituted or unsubstituted 5- to 6-membered heteroaryl.

[00269] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is substituted or unsubstituted 5- to 6-membered heterocyclyl.

[00270] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is methyl, ethyl or isopropyl.

[00271] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is selected from the group consisting of unsubstituted or substituted phenyl, unsubstituted or substituted pyridyl, and unsubstituted or substituted pyrazolyl.

[00272] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is methyl, ethyl, isopropyl or isobutyl.

[00273] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is cyclopropyl, cyclobutyl, or cyclopentyl.

[00274] In one embodiment of formulae (I-VI, IXa and X-XXV), R^1 is heterocyclyl.

[00275] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is hydrogen.

[00276] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is other than hydrogen.

[00277] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is selected from the group consisting of halogen, -CN, $-C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$, $-OR^7$, $-OC(O)R^7$, $-OC(O)NR^7R^8$, $-SR^7$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2NR^7R^8$, $-NO_2$, $-NR^7R^8$, $-NR^7C(O)R^8$, $-NR^7C(O)OR^8$, $-NR^7S(O)_2R^8$, and $-NR^7C(O)NR^8R^9$.

[00278] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl.

[00279] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 5- to 6-membered heterocyclyl, substituted or unsubstituted phenyl, and substituted or unsubstituted 5- to 6-membered heteroaryl.

[00280] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is substituted or unsubstituted C_{1-8} alkyl.

[00281] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is substituted or unsubstituted phenyl.

[00282] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is substituted or unsubstituted 5- to 6-membered heterocyclyl.

[00283] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is substituted or unsubstituted 5- to-6-membered heteroaryl.

[00284] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is methyl.

[00285] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is selected from the group consisting of methyl, ethyl, isopropyl, and 4-tetrahydro-2H-pyranyl.

[00286] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is methyl, ethyl, or isopropyl.

[00287] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is substituted C_{1-8} alkyl.

[00288] In one embodiment of formulae (I-VII, IXb and X-XXV), R^2 is $-CH_2OR^7$ or $-CH_2NR^7R^8$.

[00289] In one embodiment of formulae (I-VII and X-XXV), R^1 and R^2 combine to form a 6-membered ring.

[00290] *Preferred R^3 and R^4 Groups*

[00291] In one embodiment of formula (VII and IXb), R^3 and R^4 are each hydrogen.

[00292] In one embodiment of formula (VII and IXb), one of R^3 and R^4 is hydrogen and the other is unsubstituted or substituted C_{1-8} alkyl.

[00293] In one embodiment of formula (VII and IXb), both of R^3 and R^4 are unsubstituted or substituted C_{1-8} alkyl.

[00294] In one embodiment of formula (VII and IXb), R^3 and R^4 together with the carbon which they substitute form a 3-10 member carboxylic ring.

[00295] In one embodiment of formula (VII and IXb), R^3 and R^4 together with the carbon which they substitute form a 4 -10 member heterocyclic ring.

[00296] In one embodiment of formula (VII and IXb), R^3 and R^4 together with the carbon which they substitute form a 5-10 member heteroaryl ring.

[00297] *Preferred W Groups*

[00298] In one embodiment of formula (VIII and VIIb), W is NH.

[00299] In one embodiment of formula (VIII and VIIb), W is O.

[00300] **Exemplary Compounds**

[00301] The following compounds are within the scope of the formula (I):

[00302] 4-tert-butyl-N-(4-chloro-2-(4,5-diisopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00303] 4-tert-butyl-N-(4-chloro-2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00304] 4-tert-butyl-N-(4-chloro-2-(4-cyclopentyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00305] 4-tert-butyl-N-(4-chloro-2-(4-cyclopropyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00306] 4-tert-butyl-N-(4-chloro-2-(4-ethyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00307] 4-tert-butyl-N-(4-chloro-2-(4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00308] 4-tert-butyl-N-(4-chloro-2-(4-isopropyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00309] 4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(tetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00310] 4-tert-butyl-N-(4-chloro-2-(4-phenyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00311] 4-tert-butyl-N-(4-chloro-2-(5-(methoxymethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00312] 4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00313] 4-tert-butyl-N-(4-chloro-2-(5-isopropyl-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00314] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(1H-pyrazol-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00315] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(pyridin-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00316] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00317] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(tetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00318] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-phenyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00319] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00320] N-(4-chloro-2-(4-isopropyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)-4-isopropoxybenzenesulfonamide;

[00321] N-(2-(3-(2-(4-tert-butylphenylsulfonamido)-5-chlorophenyl)-5-methyl-4H-1,2,4-triazol-4-yl)ethyl)acetamide;

[00322] (R)-4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(tetrahydrofuran-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00323] (S)-4-tert-butyl-N-(4,5-difluoro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00324] (S)-4-tert-butyl-N-(4-chloro-2-(4-(1-hydroxypropan-2-yl)-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00325] (S)-4-tert-butyl-N-(4-chloro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00326] (S)-4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(tetrahydrofuran-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00327] 4-tert-butyl-N-(2-(4-ethyl-4H-1,2,4-triazol-3-yl)-4,5-difluorophenyl)benzenesulfonamide;

[00328] 4-tert-butyl-N-(2-(4-ethyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00329] 4-tert-butyl-N-(4,5-difluoro-2-(4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00330] 4-tert-butyl-N-(4-chloro-2-(4,5-diethyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00331] 4-tert-butyl-N-(4-chloro-2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)-3-fluorophenyl)benzenesulfonamide;

[00332] 4-tert-butyl-N-(4-chloro-2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00333] 4-tert-butyl-N-(4-chloro-2-(4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00334] 4-tert-butyl-N-(4-chloro-2-(4-ethyl-4H-1,2,4-triazol-3-yl)-3-fluorophenyl)benzenesulfonamide;

[00335] 4-tert-butyl-N-(4-chloro-2-(4-ethyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00336] 4-tert-butyl-N-(4-chloro-2-(4-ethyl-5-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00337] 4-tert-butyl-N-(4-chloro-2-(4-ethyl-5-methyl-4H-1,2,4-triazol-3-yl)-3-fluorophenyl)benzenesulfonamide;

[00338] 4-tert-butyl-N-(4-chloro-2-(4-isobutyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00339] 4-tert-butyl-N-(4-chloro-2-(4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00340] 4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(oxazol-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00341] 4-tert-butyl-N-(4-chloro-2-(5-((dimethylamino)methyl)-4-methyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00342] 4-tert-butyl-N-(4-chloro-2-(5-(2-methoxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00343] 4-tert-butyl-N-(4-chloro-2-(5-(methoxymethyl)-4-(tetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00344] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(piperidin-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00345] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(piperidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00346] 4-tert-butyl-N-(5-chloro-2-(4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00347] 4-tert-butyl-N-(5-chloro-2-(4-isopropyl-5-(4-methyltetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00348] 4-tert-butyl-N-(5-fluoro-2-(4-isopropyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00349] N-(4-chloro-2-(4-ethyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)-4-isopropoxybenzenesulfonamide;

[00350] ethyl 2-(5-(2-(4-tert-butylphenylsulfonamido)-5-chloro-4-fluorophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)acetate;

[00351] 5-(2-(4-tert-butylphenylsulfonamido)-5-chloro-4-fluorophenyl)-4-methyl-4H-1,2,4-triazole-3-carboxamide;

[00352] 5-(2-(4-tert-butylphenylsulfonamido)-5-chloro-4-fluorophenyl)-N,4-dimethyl-4H-1,2,4-triazole-3-carboxamide;

[00353] (R)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(1-hydroxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00354] (S)-4-tert-butyl-N-(4-chloro-2-(4-(piperidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00355] (S)-4-tert-butyl-N-(4-chloro-2-(4-(tetrahydro-2H-pyran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00356] (S)-4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(piperidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00357] (S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(piperidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00358] (S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00359] (S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00360] (S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(1-hydroxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00361] (S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-methyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00362] (S)-N-(4-chloro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)-4-isopropoxybenzenesulfonamide;

[00363] 4-tert-butyl-N-(4-chloro-2-(4-isopropyl-5-(tetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00364] 4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(5-methyloxazol-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00365] 4-tert-butyl-N-(4-chloro-2-(5-((cyclopropylamino)methyl)-4-methyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00366] 4-tert-butyl-N-(4-chloro-2-(5-((ethylamino)methyl)-4-methyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00367] 4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00368] 4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00369] 4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00370] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(tetrahydro-2H-pyran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00371] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00372] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-isopropyl-5-(methoxymethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00373] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-((methylamino)methyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00374] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(methylsulfonylmethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00375] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(morpholinomethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00376] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(oxazol-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00377] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(pyrrolidin-1-ylmethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00378] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(tetrahydro-2H-pyran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00379] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(tetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00380] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00381] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-((isopropylamino)methyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00382] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(1-hydroxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00383] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(2-hydroxy-2-methylpropyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00384] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(2-hydroxypropan-2-yl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00385] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(2-methoxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00386] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(hydroxymethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00387] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(methoxymethyl)-4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00388] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(methoxymethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00389] N-(2-(5-(azetidin-1-ylmethyl)-4-methyl-4H-1,2,4-triazol-3-yl)-4-chloro-5-fluorophenyl)-4-tert-butylbenzenesulfonamide;

[00390] N-(2-(5-acetyl-4-methyl-4H-1,2,4-triazol-3-yl)-4-chloro-5-fluorophenyl)-4-tert-butylbenzenesulfonamide;

[00391] (S)-4-tert-butyl-N-(4,5-difluoro-2-(5-methyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00392] (S)-4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00393] (S)-4-tert-butyl-N-(4-chloro-2-(5-isopropyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00394] (S)-4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00395] 4-tert-butyl-N-(2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00396] 4-tert-butyl-N-(2-(4-ethyl-5-methyl-4H-1,2,4-triazol-3-yl)-4,5-difluorophenyl)benzenesulfonamide;

[00397] 4-tert-butyl-N-(2-(4-ethyl-5-methyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00398] 4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(piperidin-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00399] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00400] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-isopropyl-5-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00401] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00402] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(5-methyloxazol-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00403] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-isopropyl-4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00404] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-methyl-4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00405] N-(4-chloro-2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)phenyl)-4-isopropoxybenzenesulfonamide;

[00406] N-(4-chloro-2-(4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)-4-isopropoxybenzenesulfonamide;

[00407] (S)-4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00408] (S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(2-oxopyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00409] (S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-isopropyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00410] (S)-N-(4-chloro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)-4-(4-methyltetrahydro-2H-pyran-4-yl)benzenesulfonamide;

[00411] 4-tert-butyl-N-(4-chloro-2-(4-cyclobutyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00412] 4-tert-butyl-N-(4-chloro-2-(4-ethyl-5-isopropyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

[00413] 4-tert-butyl-N-(4-chloro-2-(4-isopropyl-5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00414] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(1-methylpiperidin-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00415] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(2-(methylsulfonyl)ethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00416] N-(2-(4-(1-acetylpiperidin-4-yl)-5-methyl-4H-1,2,4-triazol-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide;

[00417] N-(2-(4-(2-aminoethyl)-5-methyl-4H-1,2,4-triazol-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide;

[00418] N-(2-(4-(azetidin-3-yl)-4H-1,2,4-triazol-3-yl)-4-chloro-5-fluorophenyl)-4-tert-butylbenzenesulfonamide;

[00419] (R)-4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00420] 4-tert-butyl-N-(2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)-4,5-difluorophenyl)benzenesulfonamide;

[00421] 4-tert-butyl-N-(4-chloro-2-(4-isopropyl-5-(methoxymethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00422] 4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(pyridin-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00423] 4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(tetrahydrofuran-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00424] 4-tert-butyl-N-(4-chloro-2-(5-((dimethylamino)methyl)-4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00425] 4-tert-butyl-N-(4-chloro-2-(5-(isopropoxymethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00426] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00427] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00428] 4-(3-(2-(4-tert-butylphenylsulfonamido)-5-chlorophenyl)-5-methyl-4H-1,2,4-triazol-4-yl)piperidine-1-carboxamide;

[00429] 4-tert-butyl-N-(4-chloro-2-(4-(2-(dimethylamino)ethyl)-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00430] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00431] 4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(2-(methylamino)ethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00432] 4-tert-butyl-N-(5-chloro-2-(4-isopropyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00433] N-(2-(4-(1-acetylpyrrolidin-3-yl)-5-methyl-4H-1,2,4-triazol-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide;

[00434] N-(2-(5-amino-4-isopropyl-4H-1,2,4-triazol-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide;

[00435] (R)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00436] (R)-4-tert-butyl-N-(4-chloro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00437] 4-tert-butyl-N-(4-cyano-2-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00438] 4-(4-tert-butylphenylsulfonamido)-3-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)benzamide;

[00439] 4-(4-tert-butylphenylsulfonamido)-3-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)benzoic acid;

[00440] N-(2-(4-(azetidin-3-yl)-4H-1,2,4-triazol-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide;

[00441] 4-tert-butyl-N-(4-chloro-2-(4-methyl-5-((methylamino)methyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00442] methyl 4-(4-tert-butylphenylsulfonamido)-3-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)benzoate;

[00443] N-(4-chloro-2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)phenyl)-3-fluoro-4-morpholinobenzenesulfonamide;

[00444] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00445] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(2-hydroxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00446] 4-tert-butyl-N-(4-chloro-2-(5-((isopropylamino)methyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00447] (S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(1-methoxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00448] (R)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(pyrrolidin-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00449] (S)-4-tert-butyl-N-(4-chloro-2-(4-(1-isopropylpyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00450] (S)-3-(3-(2-(4-tert-butylphenylsulfonamido)-5-chlorophenyl)-4H-1,2,4-triazol-4-yl)pyrrolidine-1-carboxamide;

[00451] 4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(morpholinomethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00452] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(piperidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00453] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(piperazin-1-ylmethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00454] (S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-((tetrahydrofuran-3-ylamino)methyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00455] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(((2-methoxyethyl)(methyl)amino)methyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00456] 4-tert-butyl-N-(4-chloro-2-(4-isopropyl-5-(4-methyltetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00457] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-((4-methylpiperazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00458] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-((tetrahydro-2H-pyran-4-ylamino)methyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00459] (S)-4-tert-butyl-N-(4-chloro-2-(4-(1-(methylsulfonyl)pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00460] 4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-isopropyl-5-(morpholinomethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

[00461] N-(2-(4-(1H-pyrazol-3-yl)-4H-1,2,4-triazol-3-yl)-5-chlorophenyl)-4-chloro-3-(trifluoromethyl)benzenesulfonamide;

[00462] 4-chloro-N-(5-chloro-2-(5-methyl-4-(1H-pyrazol-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)-3-(trifluoromethyl)benzenesulfonamide;

[00463] 4-chloro-N-(5-chloro-2-(4-phenyl-4H-1,2,4-triazol-3-yl)phenyl)-3-(trifluoromethyl)benzenesulfonamide;

[00464] N-(2-(4-(1H-pyrazol-3-yl)-4H-1,2,4-triazol-3-yl)-5-chloro-4-fluorophenyl)-4-chloro-3-(trifluoromethyl)benzenesulfonamide;

[00465] 5-(4-chloro-2-(4-chloro-3-(trifluoromethyl)phenylsulfonamido)-5-fluorophenyl)-4-(1H-pyrazol-3-yl)-4H-1,2,4-triazole-3-carboxamide; and

[00466] N-(2-([1,2,4]triazolo[4,3-a]pyrimidin-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide.

[00467] **Compositions that Modulate Chemokine activity**

[00468] In another aspect, the present invention provides compositions that modulate chemokine activity, specifically CCR2 activity or CCR9 activity. Generally, the compositions for modulating chemokine receptor activity in humans and animals will comprise a pharmaceutically acceptable excipient or diluent and a compound having the formula provided above as formula (I).

[00469] The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[00470] The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory

ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases.

[00471] The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions and self emulsifications as described in U.S. Pat. No. 6,451,339, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with other non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents such as cellulose, silicon dioxide, aluminum oxide, calcium carbonate, sodium carbonate, glucose, mannitol, sorbitol, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example PVP, cellulose, PEG, starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated enterically or otherwise by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

[00472] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for

example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil. Additionally, emulsions can be prepared with a non-water miscible ingredient such as oils and stabilized with surfactants such as mono-diglycerides, PEG esters and the like.

[00473] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[00474] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti oxidant such as ascorbic acid.

[00475] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or

more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[00476] The pharmaceutical compositions of the invention may also be in the form of oil in water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[00477] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative. and flavoring and coloring agents. Oral solutions can be prepared in combination with, for example, cyclodextrin, PEG and surfactants.

[00478] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, axed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[00479] The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols. Additionally, the compounds can be administered via ocular delivery by means of solutions or ointments. Still further, transdermal delivery of the subject compounds can be accomplished by means of iontophoretic patches and the like.

[00480] For topical use, creams, ointments, jellies, solutions or suspensions containing the compounds of the present invention are employed. As used herein, topical application is also meant to include the use of mouth washes and gargles.

[00481] The pharmaceutical compositions and methods of the present invention may further comprise other therapeutically active compounds as noted herein, such as those applied in the treatment of the above mentioned pathological conditions.

[00482] In one embodiment, the present invention provides a composition consisting of a pharmaceutically acceptable carrier and a compound of the invention.

[00483] **Methods of Treatment**

[00484] Depending on the disease to be treated and the subject's condition, the compounds and compositions of the present invention may be administered by oral, parenteral (*e.g.*, intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each rouse of administration. The present invention also contemplates administration of the compounds and compositions of the present invention in a depot formulation.

[00485] In the treatment or prevention of conditions which require chemokine receptor modulation an appropriate dosage level will generally be about 0.001 to 100 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.01 to about 25 mg/kg per day; more preferably about 0.05 to about 10 mg/kg per day. A suitable dosage level may be about 0.01 to 25 mg/kg per day, about 0.05 to 10 mg/kg per day, or about 0.1 to 5 mg/kg per day. Within this range the dosage may be 0.005 to 0.05, 0.05 to 0.5, 0.5 to 5.0, or 5.0 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

[00486] It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, hereditary characteristics, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[00487] In still other embodiments, the present methods are directed to the treatment of allergic diseases, wherein a compound or composition of the invention is administered either alone or in combination with a second therapeutic agent, wherein said second therapeutic agent is an antihistamine. When used in combination, the practitioner can administer a combination of the compound or composition of the present invention and a second therapeutic agent. Also, the compound or composition and the second therapeutic agent can be administered sequentially, in any order.

[00488] The compounds and compositions of the present invention can be combined with other compounds and compositions having related utilities

to prevent and treat the condition or disease of interest, such as inflammatory conditions and diseases, including inflammatory bowel disease, allergic diseases, psoriasis, atopic dermatitis and asthma, and those pathologies noted above. Selection of the appropriate agents for use in combination therapies can be made one of ordinary skill in the art. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

[00489] In treating, preventing, ameliorating, controlling or reducing the risk of inflammation, the compounds of the present invention may be used in conjunction with an anti-inflammatory or analgesic agent such as an opiate agonist, a lipoxygenase inhibitor, such as an inhibitor of 5-lipoxygenase, a cyclooxygenase inhibitor, such as a cyclooxygenase-2 inhibitor, an interleukin inhibitor, such as an interleukin-1 inhibitor, an NMDA antagonist, an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide, a non-steroidal anti-inflammatory agent, or a cytokine-suppressing anti-inflammatory agent, for example with a compound such as acetaminophen, aspirin, codeine, biological TNF sequestrants, fentanyl, ibuprofen, indomethacin, ketorolac, morphine, naproxen, phenacetin, piroxicam, a steroidal analgesic, sufentanyl, sunlindac, tenidap, and the like.

[00490] Similarly, the compounds of the present invention may be administered with a pain reliever; a potentiator such as caffeine, an H2-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as pseudophedrine; an antitussive such as codeine; a diuretic; a sedating or non-sedating antihistamine; a very late antigen (VLA-4) antagonist; an immunosuppressant such as cyclosporin, tacrolimus, rapamycin, EDG receptor agonists, or other FK-506 type immunosuppressants; a steroid; a non-steroidal anti-asthmatic agent such as a β2-agonist, leukotriene antagonist, or leukotriene biosynthesis inhibitor; an inhibitor of phosphodiesterase type IV (PDE-IV); a cholesterol lowering agent such as a HMG-CoA reductase inhibitor, sequestrant, or cholesterol

absorption inhibitor; and an anti-diabetic agent such as insulin, α-glucosidase inhibitors or glitazones.

[00491] The weight ratio of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with an NSAID the weight ratio of the compound of the present invention to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

[00492] **Methods of Treating or Preventing CCR2-mediated Conditions or Diseases**

[00493] In yet another aspect, the present invention provides methods of treating or preventing a CCR2-mediated condition or disease by administering to a subject having such a condition or disease a therapeutically effective amount of any compound of formula (I) above. Compounds for use in the present methods include those compounds according to formula (I), those provided above as embodiments, those specifically exemplified in the Examples below, and those provided with specific structures herein. The "subject" is defined herein to include animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In preferred embodiments, the subject is a human.

[00494] As used herein, the phrase "CCR2-mediated condition or disease" and related phrases and terms refer to a condition or disease characterized by inappropriate, i.e., less than or greater than normal, CCR2 functional activity. Inappropriate CCR2 functional activity might arise as the result of CCR2 expression in cells which normally do not express CCR2, increased CCR2 expression (leading to, e.g., inflammatory and immunoregulatory disorders and diseases) or decreased CCR2 expression.

Inappropriate CCR2 functional activity might also arise as the result of MCP-1 secretion by cells which normally do not secrete MCP-1, increased MCP-1 expression (leading to, e.g., inflammatory and immunoregulatory disorders and diseases) or decreased MCP-1 expression. A CCR2-mediated condition or disease may be completely or partially mediated by inappropriate CCR2 functional activity. However, a CCR2-mediated condition or disease is one in which modulation of CCR2 results in some effect on the underlying condition or disease (e.g., a CCR2 antagonist results in some improvement in patient well being in at least some patients). Furthermore, MCP-2, 3 and 4 are also CCR2 ligands.

[00495] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention.

[00496] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention, where the CCR2-mediated condition or disease is atherosclerosis.

[00497] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention, where the CCR2-mediated condition or disease is restenosis.

[00498] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention, where the CCR2-mediated condition or disease is multiple sclerosis.

[00499] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention, where the CCR2-mediated condition or disease is selected from the group consisting of inflammatory bowel disease, renal fibrosis, rheumatoid arthritis, obesity and non-insulin-dependent diabetes.

[00500] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention, where the CCR2-mediated condition or disease is type 2 diabetes.

[00501] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention, where the CCR2-mediated condition or disease is selected from the group consisting of chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis and idiopathic pneumonia syndrome.

[00502] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention, where the administering is oral, parenteral, rectal, transdermal, sublingual, nasal or topical.

[00503] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention, where the compound is administered in combination with an anti-inflammatory or analgesic agent.

[00504] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention, where an anti-inflammatory or analgesic agent is also administered.

[00505] In one embodiment, the present invention provides a method of modulating CCR2 function in a cell, where the CCR2 function in the cell is modulated by contacting the cell with a CCR2 modulating amount of the compound of the present invention.

[00506] In one embodiment, the present invention provides a method of treating a CCR2-mediated condition or disease involving administering to a subject a safe and effective amount of the compound or composition of the invention, where the disease is selected from the group consisting of

pulmonary fibrosis, transplantation rejection, graft-versus-host disease and cancer.

[00507] In yet other embodiments, the present methods are directed to the treatment of psoriasis wherein a compound or composition of the invention is used alone or in combination with a second therapeutic agent such as a corticosteroid, a lubricant, a keratolytic agent, a vitamin D_3 derivative, PUVA and anthralin.

[00508] In other embodiments, the present methods are directed to the treatment of atopic dermatitis using a compound or composition of the invention either alone or in combination with a second therapeutic agent such as a lubricant and a corticosteroid.

[00509] In further embodiments, the present methods are directed to the treatment of asthma using a compound or composition of the invention either alone or in combination with a second therapeutic agent such as a β2-agonist and a corticosteroid.

[00510] Methods of Treating or Preventing CCR9-mediated Conditions or Diseases

[00511] In yet another aspect, the present invention provides methods of treating or preventing a CCR9-mediated condition or disease by administering to a subject having such a condition or disease a therapeutically effective amount of any compound of formula (I) above. Compounds for use in the present methods include those compounds according to formula (I), those provided above as embodiments, those specifically exemplified in the Examples below, and those provided with specific structures herein. The "subject" is defined herein to include animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In preferred embodiments, the subject is a human.

[00512] As used herein, the phrase "CCR9-mediated condition or disease" and related phrases and terms refer to a condition or disease characterized by inappropriate, i.e., less than or greater than normal, CCR9 functional activity. Inappropriate CCR9 functional activity might arise as the

result of CCR9 expression in cells which normally do not express CCR9, increased CCR9 expression (leading to, e.g., inflammatory and immunoregulatory disorders and diseases) or decreased CCR9 expression. Inappropriate CCR9 functional activity might also arise as the result of TECK secretion by cells which normally do not secrete TECK, increased TECK expression (leading to, e.g., inflammatory and immunoregulatory disorders and diseases) or decreased TECK expression. A CCR9-mediated condition or disease may be completely or partially mediated by inappropriate CCR9 functional activity. However, a CCR9-mediated condition or disease is one in which modulation of CCR9 results in some effect on the underlying condition or disease (e.g., a CCR9 antagonist results in some improvement in patient well being in at least some patients).

[00513] The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a cell, tissue, system, or animal, such as a human, that is being sought by the researcher, veterinarian, medical doctor or other treatment provider.

[00514] Diseases and conditions associated with inflammation, immune disorders, infection and cancer can be treated or prevented with the present compounds, compositions, and methods. In one group of embodiments, diseases or conditions, including chronic diseases, of humans or other species can be treated with inhibitors of CCR9 function. These diseases or conditions include: (1) allergic diseases such as systemic anaphylaxis or hypersensitivity responses, drug allergies, insect sting allergies and food allergies, (2) inflammatory bowel diseases, such as Crohn's disease, ulcerative colitis, ileitis and enteritis, (3) vaginitis, (4) psoriasis and inflammatory dermatoses such as dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria and pruritus, (5) vasculitis, (6) spondyloarthropathies, (7) scleroderma, (8) asthma and respiratory allergic diseases such as allergic asthma, allergic rhinitis, hypersensitivity lung diseases and the like, (9) autoimmune diseases, such as fibromyalagia, scleroderma, ankylosing spondylitis, juvenile RA, Still's disease, polyarticular juvenile RA, pauciarticular juvenile RA, polymyalgia rheumatica, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, polyarticular arthritis, multiple

sclerosis, systemic lupus erythematosus, type I diabetes, type II diabetes, glomerulonephritis, and the like, (10) graft rejection (including allograft rejection), (11) graft-v-host disease (including both acute and chronic), (12) other diseases in which undesired inflammatory responses are to be inhibited, such as atherosclerosis, myositis, neurodegenerative diseases (e.g., Alzheimer's disease), encephalitis, meningitis, hepatitis, nephritis, sepsis, sarcoidosis, allergic conjunctivitis, otitis, chronic obstructive pulmonary disease, sinusitis, Behcet's syndrome and gout, (13) immune mediated food allergies such as Coeliac (Celiac) disease (14) pulmonary fibrosis and other fibrotic diseases, and (15) irritable bowel syndrome.

[00515] In another group of embodiments, diseases or conditions can be treated with modulators and agonists of CCR9 function. Examples of diseases to be treated by modulating CCR9 function include cancers, cardiovascular diseases, diseases in which angiogenesis or neovascularization play a role (neoplastic diseases, retinopathy and macular degeneration), infectious diseases (viral infections, e.g., HIV infection, and bacterial infections) and immunosuppressive diseases such as organ transplant conditions and skin transplant conditions. The term "organ transplant conditions" is means to include bone marrow transplant conditions and solid organ (e.g., kidney, liver, lung, heart, pancreas or combination thereof) transplant conditions.

[00516] Preferably, the present methods are directed to the treatment of diseases or conditions selected from inflammatory bowel disease including Crohn's disease and Ulcerative Colitis, allergic diseases, psoriasis, atopic dermatitis and asthma, autoimmune disease such as rheumatoid arthritis and immune-mediated food allergies such as Coelaic disease.

[00517] In yet other embodiments, the present methods are directed to the treatment of psoriasis where a compound or composition of the invention is used alone or in combination with a second therapeutic agent such as a corticosteroid, a lubricant, a keratolytic agent, a vitamin D_3 derivative, PUVA and anthralin.

[00518] In other embodiments, the present methods are directed to the treatment of atopic dermatitis using a compound or composition of the

invention either alone or in combination with a second therapeutic agent such as a lubricant and a corticosteroid.

[00519] In further embodiments, the present methods are directed to the treatment of asthma using a compound or composition of the invention either alone or in combination with a second therapeutic agent such as a β2-agonist and a corticosteroid.

[00520] **Preparation of modulators**

[00521] The following examples are offered to illustrate, but not to limit, the claimed invention.

[00522] Additionally, those skilled in the art will recognize that the molecules claimed in this patent may be synthesized using a variety of standard organic chemistry transformations.

[00523] Certain general reaction types employed widely to synthesize target compounds in this invention are summarized in the examples. Specifically, generic procedures for sulfonamide formation, pyridine N-oxide formation and 2-aminophenyl-arylmethanone synthesis via Friedel-Crafts type approaches are given, but numerous other standard chemistries are described within and were employed routinely.

[00524] While not intended to be exhaustive, representative synthetic organic transformations which can be used to prepare compounds of the invention are included below.

[00525] These representative transformations include; standard functional group manipulations; reductions such as nitro to amino; oxidations of functional groups including alcohols and pyridines; aryl substitutions via *IPSO* or other mechanisms for the introduction of a variety of groups including nitrile, methyl and halogen; protecting group introductions and removals; Grignard formation and reaction with an electrophile; metal-mediated cross couplings including but not limited to Buckwald, Suzuki and Sonigashira reactions; halogenations and other electrophilic aromatic substitution reactions; diazonium salt formations and reactions of these species; etherifications; cyclative condensations, dehydrations, oxidations and reductions leading to heteroaryl groups; aryl metallations and

transmetallations and reaction of the ensuing aryl-metal species with an electrophile such as an acid chloride or Weinreb amide; amidations; esterifications; nucleophilic substitution reactions; alkylations; acylations; sulfonamide formation; chlorosulfonylations; ester and related hydrolyses, and the like.

[00526] Certain molecules claimed in this patent can exist in different enantiomeric and diastereomeric forms and all such variants of these compounds are within the scope of the invention.

[00527] In the descriptions of the syntheses that follow, some precursors were obtained from commercial sources. These commercial sources include Aldrich Chemical.Co., Acros Organics, Ryan Scientific Incorporated, Oakwood Products Incorporated, Lancaster Chemicals, Sigma Chemical Co., Lancaster Chemical Co., TCI-America, Alfa Aesar, Davos Chemicals, and GFS Chemicals.

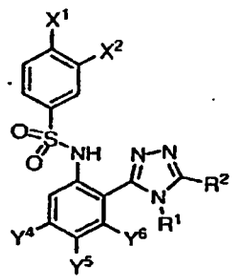
[00528] Compounds of the invention, including those listed in the table of activities, can be made by the methods and approaches described in the following experimental section, and by the use of standard organic chemistry transformations that are well known to those skilled in the art.

[00529] **Examples**

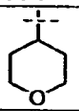
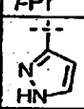
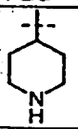
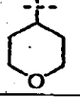
[00530] The above compounds and others within the scope of this invention can be made and tested for activity using the following procedures.

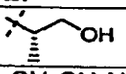
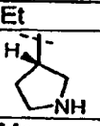
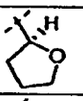
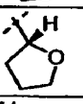
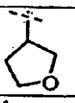
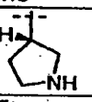
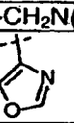
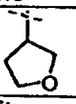
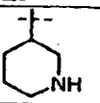
[00531] Exemplary compounds used in the method of the invention and in pharmaceutical compositions of the invention include but are not limited to the compounds listed in Table 1. Pharmaceutically acceptable salts of the compounds listed in Table 1 are also useful in the method of the invention and in pharmaceutical compositions of the invention.

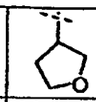
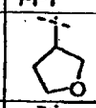
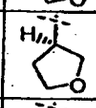
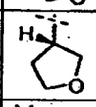
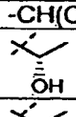
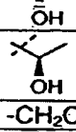
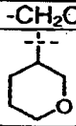
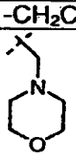
Table 1: Exemplary compounds

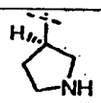
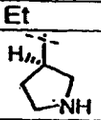
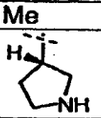
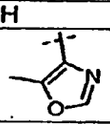
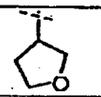
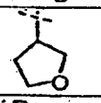
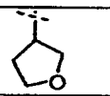
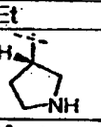
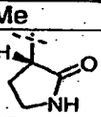
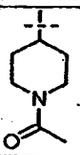


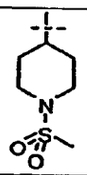
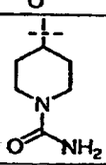
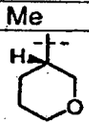
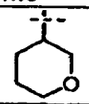
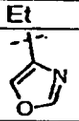
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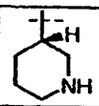
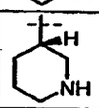
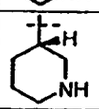
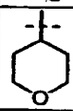
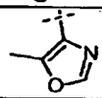
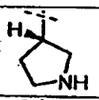
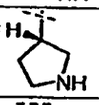
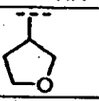
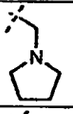
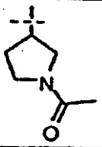
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1	*t*-Bu	H	H	Cl	H	*i*-Pr	H
2	*t*-Bu	H	H	Cl	H	Ph	H
3	*t*-Bu	H	H	Cl	H	*i*-Pr	Me
4	*t*-Bu	H	H	Cl	H	Ph	Me
5	*t*-Bu	H	H	Cl	H	Et	Me
6	*t*-Bu	H	H	Cl	H	Me	Me
7	*t*-Bu	H	H	Cl	H	cyclopropyl	Me
8	*t*-Bu	H	H	Cl	H	Me	*i*-Pr
9	*t*-Bu	H	H	Cl	H	Me	
10	*t*-Bu	H	H	Cl	H	Me	$-CH_2OCH_3$
11	*t*-Bu	H	H	Cl	H	*i*-Pr	*i*-Pr
12	*t*-Bu	H	H	Cl	H		Me
13	*t*-Bu	H	H	Cl	H	*i*-Pr	Et
14	*t*-Bu	H	H	Cl	H	cyclopentyl	Me
15	O*i*-Pr	H	H	Cl	H	*i*-Pr	Me
16	*t*-Bu	H	H	Cl	H		Me
17	O*i*-Pr	H	H	Cl	H	Et	Me
18	*t*-Bu	H	Cl	H	H	*i*-Pr	H
19	*t*-Bu	H	H	Cl	H	*i*-Bu	Me
20	*t*-Bu	H	H	Cl	H		Me
21	*t*-Bu	H	H	Cl	H		$-CH_2OCH_3$

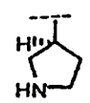
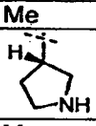
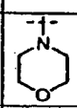
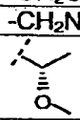
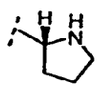
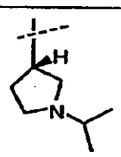
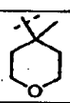
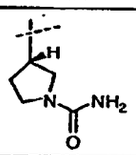
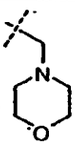
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23	*t*-Bu	H	F	H	H	Et	H
24	*t*-Bu	H	F	H	H	*i*-Pr	Me
25	*t*-Bu	H	H	Cl	F	Et	H
26	*t*-Bu	H	H	Cl	H		Me
27	*t*-Bu	H	H	Cl	H	$-CH_2CH_2NHC(O)CH_3$	Me
28	*t*-Bu	H	H	Cl	F	Me	Me
29	*t*-Bu	H	H	Cl	F	Et	Me
30	*t*-Bu	H	H	Cl	H	Me	H
31	*t*-Bu	H	H	Cl	H	Et	H
32	*t*-Bu	H	H	Cl	H		H
33	*t*-Bu	H	H	Cl	H	Me	
34	*t*-Bu	H	H	Cl	H	Me	
35	*t*-Bu	H	H	Cl	H		H
36	*t*-Bu	H	F	Cl	H	Me	Me
37	*t*-Bu	H	F	F	H		H
38	*t*-Bu	H	H	Cl	H	Et	Et
39	*t*-Bu	H	F	Cl	H	Me	$-CH_2N(CH_3)_2$
40	*t*-Bu	H	H	Cl	H	Me	
41	*t*-Bu	H	H	Cl	H	Me	$-CH_2CH_2OCH_3$
42	*t*-Bu	H	F	F	H		H
43	*t*-Bu	H	H	Cl	H	Et	*i*-Pr
44	*t*-Bu	H	F	Cl	H		H
45	*t*-Bu	H	F	Cl	H	Me	$-CH_2NHCH_3$
46	*t*-Bu	H	H	Cl	H	*i*-Pr	

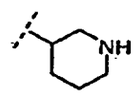
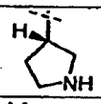
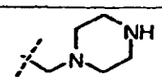
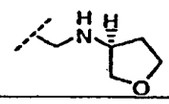
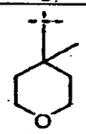
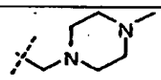
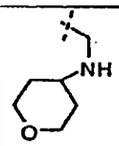
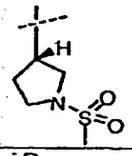
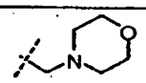
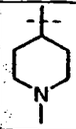
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49	*t*-Bu	H	F	Cl	H	Me	$-CH_2NHCH(CH_3)_2$
50	*t*-Bu	H	F	Cl	H	Me	$-CH_2NHCH(CH_2CH_2)$
51	*t*-Bu	H	F	Cl	H	*i*-Pr	$-CH_2OCH_3$
52	*t*-Bu	H	F	Cl	H		$-CH_2OCH_3$
53	*t*-Bu	H	F	Cl	H		H
54	*t*-Bu	H	F	Cl	H		H
55	*t*-Bu	H	F	Cl	H	Me	$-C(O)NH_2$
56	*t*-Bu	H	F	Cl	H	Me	$-C(O)NHCH_3$
57	*t*-Bu	H	F	Cl	H	Me	$-C(CH_3)_2OH$
58	*t*-Bu	H	F	Cl	H	Me	$-C(O)CH_3$
59	*t*-Bu	H	F	Cl	H	Me	$-CH(OH)CH_3$
60	*t*-Bu	H	F	Cl	H	Me	
61	*t*-Bu	H	F	Cl	H	Me	
62	*t*-Bu	H	F	Cl	H	Me	$-CH_2CH_2OCH_3$
63	*t*-Bu	H	F	Cl	H	Me	
64	*t*-Bu	H	F	Cl	H	Me	$-CH_2C(O)OCH_2CH_3$
65	*t*-Bu	H	F	Cl	H	Me	$-CH_2C(CH_3)_2OH$
66	*t*-Bu	H	F	Cl	H	Me	
67	*t*-Bu	H	F	Cl	H	Me	$-CH_2SO_2CH_3$
68	O*i*-Pr	H	H	Cl	H	Me	Me
69	O*i*-Pr	H	H	Cl	H	*i*-Pr	H
70	*t*-Bu	H	H	Cl	H	Me	
71	*t*-Bu	H	F	F	H	Et	Me
72	*t*-Bu	H	F	H	H	Me	Me

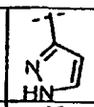
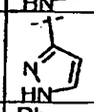
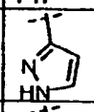
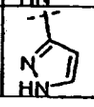
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74	*t*-Bu	H	F	H	H	Et	Me
75	*t*-Bu	H	H	Cl	H		H
76	*t*-Bu	H	F	Cl	H	Me	H
77	*t*-Bu	H	F	F	H		Me
78	*t*-Bu	H	F	Cl	H	*i*-Pr	H
79	*t*-Bu	H	F	Cl	H	Me	
80	*t*-Bu	H	F	Cl	H		Me
81	*t*-Bu	H	F	Cl	H		*i*-Pr
82	*t*-Bu	H	F	Cl	H	*i*-Pr	
83	*t*-Bu	H	H	Cl	H	$-CH_2H_2NH_2$	Me
84	*t*-Bu	H	H	Cl	H	cyclobutyl	Me
85	*t*-Bu	H	F	Cl	H		H
86	*t*-Bu	H	H	Cl	H	*i*-Pr	$-CF_3$
87	*t*-Bu	H	F	Cl	H	Et	*i*-Pr
88	*t*-Bu	H	F	Cl	H		Et
89	*t*-Bu	H	F	Cl	H	Me	$-CH_2CH_2SO_2CH_3$
90	*t*-Bu	H	F	Cl	H		H
91	*t*-Bu	H	H	Cl	H		Me
92	*t*-Bu	H	H	Cl	H	*i*-Pr	NH_2

93	*t*-Bu	H	H	Cl	H		Me
94	*t*-Bu	H	H	Cl	H		Me
95	*t*-Bu	H	Cl	H	H	*i*-Pr	Me
96	*t*-Bu	H	H	Cl	H	*i*-Pr	$-CH_2OCH_3$
97	*t*-Bu	H	H	Cl	H	Me	2-pyridyl
98	*t*-Bu	H	H	Cl	H	*i*-Pr	$-CH_2N(CH_3)_2$
99	*t*-Bu	H	H	Cl	H		Me
100	*t*-Bu	H	F	F	H	Me	Me
101	*t*-Bu	H	H	Cl	H		Me
102	*t*-Bu	H	H	Cl	H	Me	
103	*t*-Bu	H	H	Cl	H	Me	$-CH_2OCH(CH_3)_2$
104	*t*-Bu	H	H	Cl	H		H
105	*t*-Bu	H	H	Cl	H	Me	Et
106	*t*-Bu	H	F	Cl	H		Me
107	*t*-Bu	H	F	Cl	H	Me	$-CH_2OCH_3$
108	*t*-Bu	H	F	Cl	H		H
109	*t*-Bu	H	F	Cl	H		H
110	*t*-Bu	H	F	Cl	H	Me	Et
111	*t*-Bu	H	F	Cl	H	Me	

112	*t*-Bu	H	F	Cl	H		H
113	*t*-Bu	H	H	Cl	H		H
114	*t*-Bu	H	H	Cl	H		Me
115	*t*-Bu	H	F	Cl	H	Me	
116	*t*-Bu	H	F	Cl	H	Me	
117	*t*-Bu	H	H	Cl	H	Me	
118	*t*-Bu	H	H	Cl	H		*i*-Pr
119	*t*-Bu	H	H	Cl	H		Et
120	*t*-Bu	H	F	Cl	H		H
121	*t*-Bu	H	F	Cl	H	Me	
122	*t*-Bu	H	F	Cl	H	Me	
123	*t*-Bu	H	F	Cl	H	Me	$-CH_2OH$
124	*t*-Bu	H	H	Cl	H		Me
125	*t*-Bu	H	H	Cl	H	$-CH_2CH_2N(CH_3)_2$	Me
126	*t*-Bu	H	H	Cl	H	$-CH_2CH_2NHCH_3$	Me

127	*t*-Bu	H	H	Cl	H		Me
128	*t*-Bu	H	H	CN	H	Me	Et
129	*t*-Bu	H	H	$-C(O)NH_2$	H	Me	Et
130	*t*-Bu	H	H	$-CO_2H$	H	Me	Et
131	*t*-Bu	H	H	Cl	H		H
132	*t*-Bu	H	H	Cl	H	Me	$-CH_2NHCH_3$
133	*t*-Bu	H	H	$-CO_2Me$	H	Me	Et
134	O-*i*Pr	H	H	Cl	H		H
135		F	H	Cl	H	Me	Me
136	*t*-Bu	H	F	Cl	H	$-CH_2CH_2OCH_3$	H
137	*t*-Bu	H	F	Cl	H	Me	$-CH_2CH_2OH$
138	*t*-Bu	H	H	Cl	H	Me	$-CH_2NHCH(CH_3)_2$
139	*t*-Bu	H	F	Cl	H	Me	
140	*t*-Bu	H	F	Cl	H	Me	
141	*t*-Bu	H	H	Cl	H		H
142		H	H	Cl	H		H
143	*t*-Bu	H	H	Cl	H		H
144	*t*-Bu	H	H	Cl	H	Me	

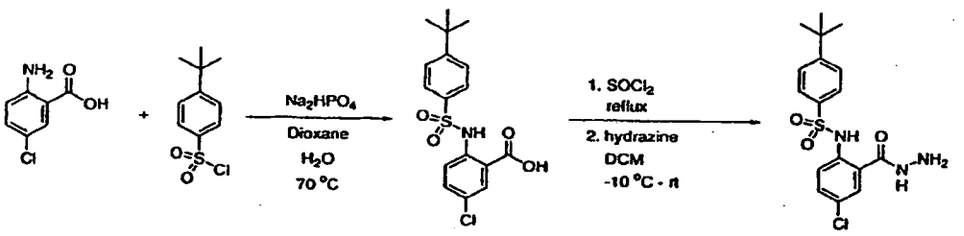
145	*t*-Bu	H	F	Cl	H	Me	
146	*t*-Bu	H	F	Cl	H		*i*-Pr
147	*t*-Bu	H	F	Cl	H	Me	
148	*t*-Bu	H	F	Cl	H	Me	
149	*t*-Bu	H	F	Cl	H	Me	- $CH_2N(CH_3)CH_2CH_2OCH_3$
150	*t*-Bu	H	F	Cl	H	*i*-Pr	
151	*t*-Bu	H	F	Cl	H	Me	
152	*t*-Bu	H	F	Cl	H	Me	
153	*t*-Bu	H	H	Cl	H		H
154	*t*-Bu	H	F	Cl	H	*i*-Pr	
155	*t*-Bu	H	H	Cl	H		Me
156	t-Bu	H	Cl	H	H	CH=CH-CH=N-	

157	Cl	CF_3	Cl	H	H		H
158	Cl	CF_3	Cl	H	H		H
159	Cl	CF_3	Cl	H	H	Ph	H
160	Cl	CF_3	Cl	F	H		H
161	Cl	CF_3	Cl	F	H		$-CONH_2$

[00532] The above compounds and others within the scope of this invention can be made and tested for activity using the following procedures.

[00533] Reagents and solvents used below can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). ^{1}H-NMR were recorded on a Varian Mercury 400 MHz NMR spectrometer. Significant peaks are tabulated in the order: multiplicity (br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet) and number of protons. Mass spectrometry results are reported as the ratio of mass over charge, followed by the relative abundance of each ion (in parenthesis). In tables, a single m/e value is reported for the M+H (or, as noted, M-H) ion containing the most common atomic isotopes. Isotope patterns correspond to the expected formula in all cases. Electrospray ionization (ESI) mass spectrometry analysis was conducted on a Hewlett-Packard MSD electrospray mass spectrometer using the HP1100 HPLC for sample delivery. Normally the analyte was dissolved in methanol at 0.1 mg/mL and 1 microliter was infused with the delivery solvent into the mass spectrometer, which scanned from 100 to 1500 daltons. All compounds could be analyzed in the positive ESI mode, using acetonitrile / water with 1% formic acid as the delivery solvent. The compounds provided below could also be analyzed in the negative ESI mode, using 2 mM NH_4OAc in acetonitrile / water as delivery system.

[00534] General Procedure A – exemplified for 4-tert-Butyl-N-(4-chloro-2-hydrazinocarbonyl-phenyl)benzenesulfonamide



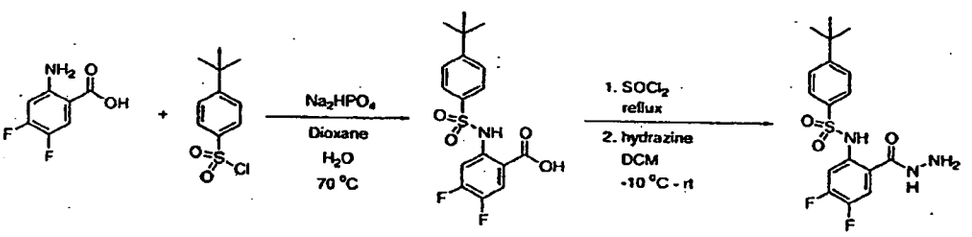
[00535] Step 1: 2-Amino-5-chlorobenzoic acid (200 g, 1.17 mol) was added to a solution of sodium hydrogen phosphate (497 g, 3.50 mol) in water (2.4 L) at 70 °C and was stirred until homogeneous (~10 min). 4-tert-Butylbenzenesulfonyl chloride (353 g, 1.52 mol), dissolved in 800 mL *p*-dioxane, was added to the stirring aniline solution in a steady stream over a ½ hour period via a 1 liter addition funnel. The resultant mixture was stirred at 70 °C overnight. The following day, upon LCMS verification of consumption of the aniline, the reaction mixture was divided into two equal portions for ease of handling. Each portion was poured in a slow stream into two liters of rapidly stirring 2 M HCl/H_2O in a four liter Erlenmeyer flask. The resultant precipitate was collected by vacuum filtration and washed well with water. The precipitate from each portion were subsequently combined and dried *in vacuo* to afford 320 g 2-(4-tert-butyl-benzenesulfonylamino)-5-chloro-benzoic acid as an off-white solid (87% yield): HPLC retention time = 2.76 minutes (Agilent Zorbax SB-C18, 2.1X50 mm, 5µ, 35 °C, using a 1 mL/min flow rate, a 2.5 minute gradient of 20 - 100% B with a 1.1 minute wash at 100% B (A = 0.1% formic acid / 5% acetonitrile / 94.9% water, B = 0.08% formic acid / 5% water/ 94.9% acetonitrile)); MS (ES) M+H expected 368.0, found 368.0.

[00536] Step 2: Thionyl chloride (300 mL, 4.11 mol) was introduced to a 1 liter round bottom flask fitted with a magnetic stir bar. 2-(4-tert-Butyl-benzenesulfonylamino)-5-chloro-benzoic acid (80 g, 218 mmol) was added under rapid agitation and the mixture was heated at reflux under a nitrogen atmosphere. The reaction progress was monitored by the addition of a few drops of the reaction mixture into ~1 mL of 2.0 M dimethylamine in THF,

followed by LCMS analysis. Complete conversion to the dimethyl amide was observed at 1.25 h. The crude mixture was subsequently concentrated *in vacuo* to produce a thick yellow oil which was then dissolved in 100 mL toluene and concentrated again to generate 2-(4-tert-butyl-benzenesulfonylamino)-5-chloro-benzoyl chloride as a pale yellow solid which was utilized directly in the next step.

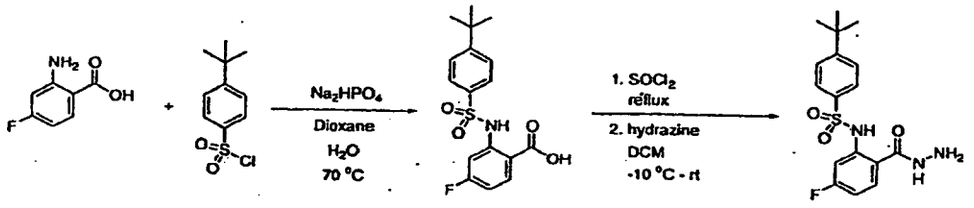
[00537] Step 3: The crude 2-(4-tert-butyl-benzenesulfonylamino)-5-chlorobenzoyl chloride was dissolved in dichloromethane (300 mL) and transferred to an addition funnel. Hydrazine hydrate (212 mL, 4.35 mol), dissolved in 1.2 L dichloromethane in a 4 L Erlenmeyer flask, was cooled to -10 °C in a dry ice- acetone bath and the acyl chloride solution was added in a slow stream to the stirring hydrazine solution over a 15 minute period. The cold bath was subsequently removed following the addition and LCMS analysis at 15 minutes indicated the reaction was complete. The resultant reaction mixture was quenched with water (500 mL), resulting in a voluminous white precipitate that was collected by vacuum filtration. The precipitate was slurried in 800 mL ethyl acetate and acetic acid was added while stirring until a homogeneous solution was formed. The solution was transferred to a separatory funnel and extracted with 3 X 100 mL of water. The aqueous phases were discarded and the organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo* to produce 4-tert-butyl-N-(4-chloro-2-hydrazinocarbonyl-phenyl)benzenesulfonamide (71 g) in an 85% yield: HPLC retention time = 2.49 minutes; MS (ES) M+H expected 382.0, found 382.0.

[00538] <u>4-tert-Butyl-N-(4,5-difluoro-2-hydrazinocarbonyl-phenyl)benzenesulfonamide</u>



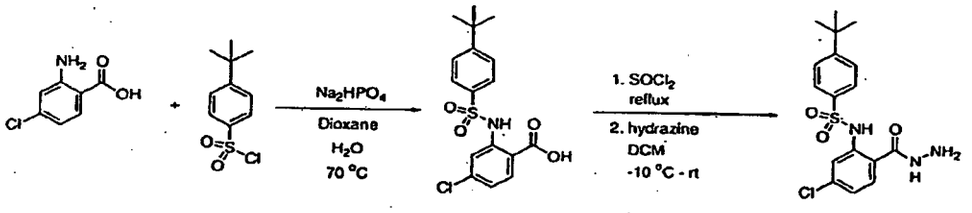
[00539] 4-tert-Butyl-N-(4,5-difluoro-2-hydrazinocarbonyl-phenyl)benzenesulfonamide was synthesized from 2-amino-4,5-difluorobenzoic acid according to general procedure A.

[00540] 4-tert-Butyl-N-(5-fluoro-2-hydrazinocarbonyl-phenyl)benzenesulfonamide



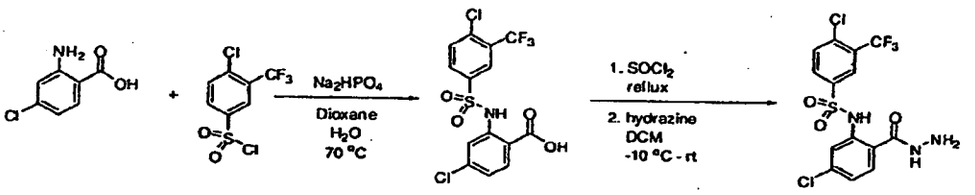
[00541] 4-tert-Butyl-N-(5-fluoro-2-hydrazinocarbonyl-phenyl)benzenesulfonamide was synthesized from 2-amino-4-fluorobenzoic acid according to general procedure A.

[00542] 4-tert-Butyl-N-(5-chloro-2-hydrazinocarbonyl-phenyl)benzenesulfonamide



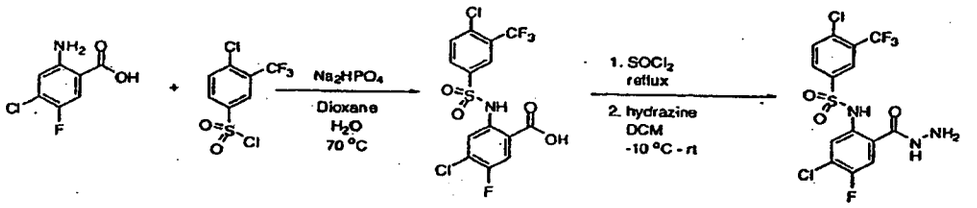
[00543] 4-tert-Butyl-N-(5-fluoro-2-hydrazinocarbonyl-phenyl)benzenesulfonamide was synthesized from 2-amino-4-chlorobenzoic acid according to general procedure A.

[00544] 4-Chloro-N-(5-chloro-2-hydrazinocarbonyl-phenyl)-3-trifluoromethyl-benzenesulfonamide



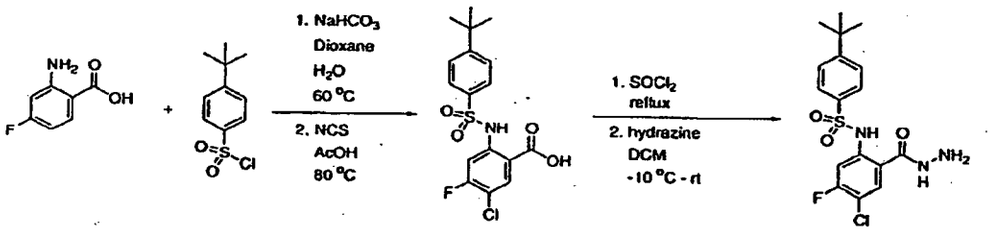
[00545] 4-Chloro-N-(5-chloro-2-hydrazinocarbonyl-phenyl)-3-trifluoromethyl-benzenesulfonamide was synthesized from 2-amino-4-chlorobenzoic acid according to general procedure A.

[00546] 4-Chloro-N-(5-chloro-4-fluoro-2-hydrazinocarbonyl-phenyl)-3-trifluoromethyl-benzenesulfonamide



[00547] 4-Chloro-N-(5-chloro-4-fluoro-2-hydrazinocarbonyl-phenyl)-3-trifluoromethyl-benzenesulfonamide was synthesized from 2-amino-4-chloro-5-fluorobenzoic acid according to general procedure A.

[00548] General Procedure B as exemplified for 4-tert-Butyl-N-(4-chloro-5-fluoro-2-hydrazinocarbonyl-phenyl) benzenesulfonamide



[00549] Step 1: 2-Amino-4-fluorobenzoic acid (25 g, 161 mmol) was added to a solution of sodium bicarbonate (54.1 g, 645 mmol) in water (2.4 L) at room temperature and was stirred until homogeneous. The resultant solution was heated to 60 °C in an oil bath. 4-tert-Butylbenzenesulfonyl

chloride (45.0 g, 193 mmol), dissolved in 200 mL *p*-dioxane, was subsequently added dropwise to the stirring aniline solution in a steady stream over a 30 min period. The reaction mixture was stirred at 60 °C overnight. The following day, upon LCMS verification of consumption of the aniline, the solution was poured in a slow stream into one liter of rapidly stirring 2 M HCl/H_2O. The resultant precipitate was collected by vacuum filtration, washed thoroughly with water, and dried *in vacuo* to afford 46 g of 2-(4-tert-butyl-benzenesulfonylamino)-4-fluoro-benzoic acid as an off-white solid (82% yield): HPLC retention time = 2.68; MS (ES) M+H expected 352.0, found 352.0.

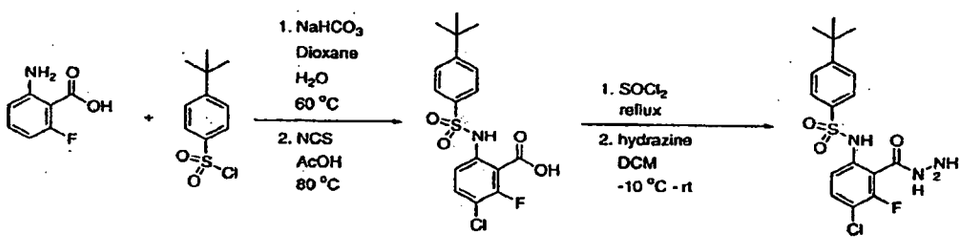
[00550] Step 2: 2-(4-tert-Butyl-benzenesulfonylamino)-4-fluoro-benzoic acid (23 g, 65.5 mmol) was added to 230 mL of stirring acetic acid in a 500 mL round bottom flask. N-chlorosuccinimide (17.5 g, 131 mmol) was then added and the mixture heated to 80 °C under a N_2 atmosphere. The reaction was determined to be complete in seven hours according to LCMS analysis. The heat bath was subsequently removed and the reaction was quenched via the addition of 250 mL of a 50% solution of sodium metabisulfite. The mixture immediately formed a thick white slurry which was allowed to stir for approximately 15 minutes. Vacuum filtration of the slurry resulted in a white solid that was washed with a small amount of water and dried in vacuo to generate 22 g of 2-(4-tert-butyl-benzenesulfonylamino)-5-chloro-4-fluoro-benzoic acid (white solid, 87% yield): HPLC retention time = 2.87 minutes; MS (ES) M+H expected 386.0, found 386.0.

[00551] Step 3: Thionyl chloride (220 mL, 3.02 mol) was introduced to a 1 L round bottom flask fitted with a magnetic stir bar. 2-(4-tert-Butyl-benzenesulfonylamino)-5-chloro-4-fluoro-benzoic acid (22 g, 57.0 mmol) was added under rapid agitation and the mixture was heated at reflux under a nitrogen atmosphere. The reaction progress was monitored by the addition of a few drops of the reaction mixture into ~1 mL of 2.0 M dimethylamine in THF, followed by LCMS analysis. Complete conversion to the dimethyl amide was observed at 1.25 h. The crude mixture was subsequently concentrated *in vacuo* to produce an orange oil. Hexane (50 mL) was added to the flask and the mixture concentrated again to afford 2-(4-tert-butyl-

benzenesulfonylamino)-5-chloro-benzoyl chloride as an orange crystalline solid which was utilized direction in the next step.

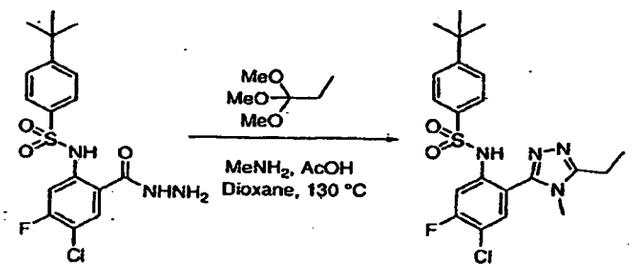
[00552] Step 4: The crude 2-(4-tert-butyl-benzenesulfonylamino)-5-chloro-4-fluoro-benzoyl chloride (57.0 mmol) was dissolved in dichloromethane (100 mL) and transferred to an addition funnel. Anhydrous hydrazine (44 mL, 1.38 mol), dissolved in 300 mL dichloromethane in a one liter Erlenmeyer flask, was cooled to -10 °C in a dry ice- acetone bath and the acyl chloride solution was added in a slow stream to the stirring hydrazine solution over a 15 minute period. The cold bath was subsequently removed following the addition and LCMS analysis at 15 minutes indicated the reaction was complete. The resultant reaction mixture was quenched with water (200 mL), resulting in a voluminous white precipitate that was collected by vacuum filtration. The precipitate was slurried in 500 mL ethyl acetate and acetic acid was added while stirring until a homogeneous solution was formed. The solution was transferred to a separatory funnel and extracted with 2 X 50 mL of water. The aqueous phases were discarded and the organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo* to produce 4-tert-butyl-N-(4-chloro-5-fluoro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (16 g) in a 71% yield: HPLC retention time = 2.63 minutes; MS (ES) M+H expected 400.0, found 400.0.

[00553] <u>4-tert-Butyl-N-(4-chloro-3-fluoro-2-hydrazinocarbonyl-phenyl) benzenesulfonamide</u>



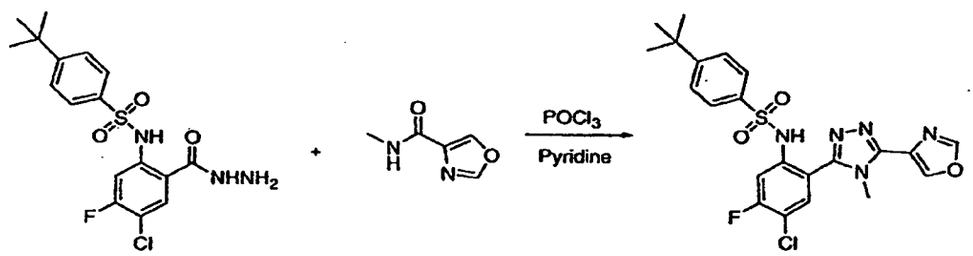
[00554] 4-tert-Butyl-N-(4-chloro-3-fluoro-2-hydrazinocarbonyl-phenyl)benzenesulfonamide was synthesized from 2-amino-6-fluorobenzoic acid according to general procedure B.

[00555] General Procedure C as exemplified for 4-tert-Butyl-N-[4-chloro-2-(5-ethyl-4-methyl-4H-[1,2,4]triazol-3-yl)-5-fluoro-phenyl]-benzenesulfonamide



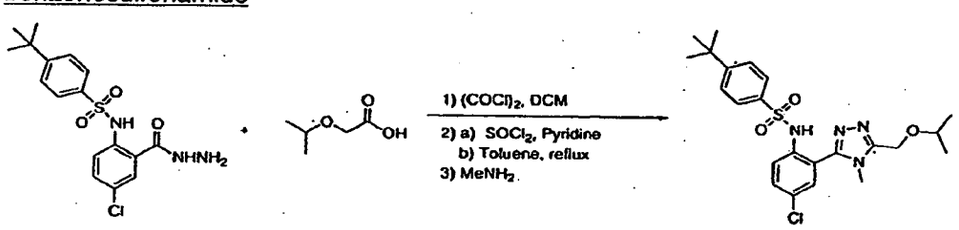
[00556] A 25 mL scintillation vial was charged with 4-tert-butyl-N-(4-chloro-3-fluoro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (1.0 g, 2.51 mmol) and trimethyl orthopropionate (0.534 mL, 3.76 mmol), and then stirred for 1 h at 45 °C. To the above reaction mixture was added methylamine (3.75 mL, 2.0 M in THF), AcOH (0.125 mL), and dioxane (10 mL). The vial was sealed, heated to 130 °C, and stirred overnight. The following day, the reaction mixture was cooled to 0 °C to induce precipitation of the product. The resultant white solid was filtered and dissolved in EtOAc (50 mL). The organics were subsequently washed with saturated $NaHCO_3$ solution (25 mL), saturated NH_4Cl solution (25 mL), water (25 mL), and brine (25 mL); dried with Na_2SO_4, and concentrated *in vacuo* to afford the title compound as a white solid (0.3 g) in 27% yield: ^1H NMR (400 MHz, $CDCl_3$) δ 7.62-7.57 (m, 3H), 7.36 (d, 2H), 7.25 (d, 1H), 3.32 (s, 3H), 2.75 (q, 2H), 1.45 (t, 3H), 1.30 (s, 9H), MS (ES) M+H expected 451.0, found 451.0.

[00557] General Procedure D exemplified for 4-tert-Butyl-N-[4-chloro-5-fluoro-2-(4-methyl-5-oxazol-4-yl-4H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide



[00558] A 25 mL scintillation vial was charged with oxazole-4-carboxylic acid methylamide (132 mg, 1.0 mmol), $POCl_3$ (0.27 mL, 3 mmol), pyridine (0.48 mL, 6 mmol) and CH_3CN (10 mL). The vial was sealed, heated to 40 °C, and stirred for four hours. The volatiles were then evacuated *in vacuo* and to the residue was added 4-tert-butyl-N-(4-chloro-5-fluoro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (400 mg, 1.0 mmol), diisopropylamine (2.0 mL), and dioxane (2.0 mL). The vial was sealed, heated to 130 °C, and stirred for two hours. The volatiles were then removed in *vacuo*, and the residue was purified via automated silica gel chromatography and then HPLC to afford 4-tert-butyl-N-[4-chloro-5-fluoro-2-(4-methyl-5-oxazol-4-yl-4H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide as a white powder: ^1H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 8.48 (d, 1H), 8.04 (d, 1H), 7.67 (d, 1H), 7.50 (d, 2H), 7.33 (d, 1H), 7.3 (d, 2H), 3.59 (s, 3H), 1.23 (s, 9H), MS (ES) M+H expected 490.1, found 490.0.

[00559] <u>General Procedure E exemplified for 4-tert-Butyl-N-[4-chloro-2-(5-isopropoxymethyl-4-methyl-4H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide</u>



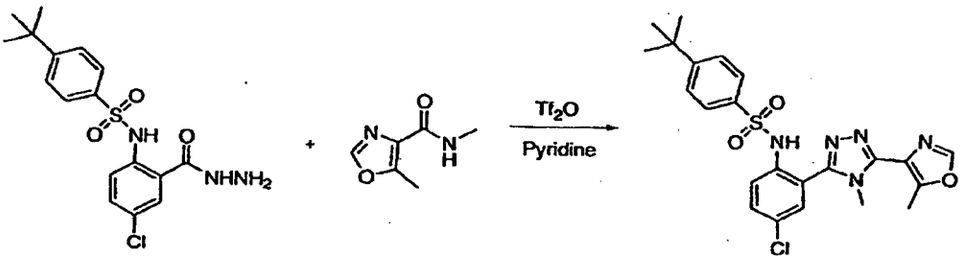
[00560] Step 1: Oxalyl chloride (0.19 mL, 2.20 mmol) was added to a solution of isopropoxyacetic acid (200 mg, 1.69 mmol) in dichloromethane (17 mL) and stirred at room temperature for 2 hours. The reaction was

concentrated and 3 mL of THF was added. The acid chloride solution was subsequently slowly added to a solution of 4-tert-butyl-N-(4-chloro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (645 mg, 1.69 mmol) in 10 mL of THF at 0 °C. After the reaction was stirred for 1 h, it was quenched with water and diluted with ethyl acetate. The aqueous phase was extracted with ethyl acetate (3x) and dichloromethane (2x), and the combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The crude reside was purified by flash column chromatography (0-100% ethyl acetate in hexane) to yield 4-tert-butyl-N-{4-chloro-2-[N'-(2-isopropoxy-acetyl)-hydrazinocarbonyl]-phenyl}-benzenesulfonamide as a yellow solid.

[00561] Step 2: Thionyl chloride was added to a solution of 4-tert-butyl-N-{4-chloro-2-[N'-(2-isopropoxy-acetyl)-hydrazinocarbonyl]-phenyl}-benzenesulfonamide (150 mg, 0.312 mmol) and pyridine (66 µL, 0.811 mmol) in diethyl ether (3 mL). The resultant solution was stirred for 18 h at room temperature followed by removal of the volatiles *in vacuo*. 2 mL toluene was subsequently added and the reaction was heated at reflux for 5 h. The resultant solution was concentrated at reduced pressure and the residue purified via flash column chromatography (0-50% ethyl acetate in hexane) to afford 4-tert-butyl-N-[4-chloro-2-(5-isopropoxymethyl-[1,3,4]oxadiazol-2-yl)-phenyl]-benzenesulfonamide as a white solid.

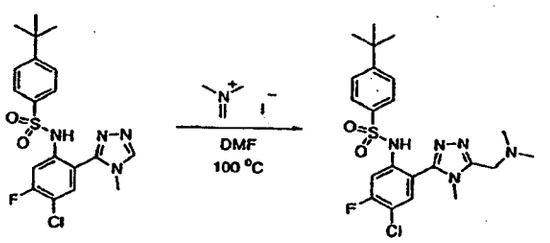
[00562] Step 3: In a pressure vessel, 4-tert-butyl-N-[4-chloro-2-(5-isopropoxymethyl-[1,3,4]oxadiazol-2-yl)-phenyl]-benzenesulfonamide (71 mg, 0.15 mmol) and methyl amine (40% in H_20, 1.5 mL, 0.6 mmol) were heated at 135 °C for 18 h. The reaction was cooled to room temperature, concentrated *in vacuo*, and the residue purified by flash column chromatography (0-50% ethyl acetate in hexane) to yield the title compound as a white solid: MS (ES) M+H expected 477.2, found 477.1.

[00563] General Procedure F exemplified for 4-tert-Butyl-N-[4-chloro-2-[4-methyl-5-(5-methyl-oxazol-4-yl)-4H-[1,2,4]triazol-3-yl]-phenyl]-benzenesulfonamide



[00564] A vial was charged with 5-methyl-oxazole-4-carboxylic acid methylamide (71 mg, 0.5 mmol), pyridine (0.12 mL, 1.5 mmol), and anhydrous dichloromethane (2.5 mL). The reaction vessel was cooled to -40 °C and trifluoromethanesulfonyl anhydride (0.11 mL, 0.65 mmol) was added. The reaction was subsequently warmed to -10 °C over 2.5 h and then 4-tert-butyl-N-(4-chloro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (191 mg, 0.5 mmol) was added. The reaction was warmed to room temperature stirred an additional 2 h. The solvent was concentrated *in vacuo* and ethanol (5 mL) and diisopropylamine (0.5 mL) were added and the solution stirred at 90 °C overnight. The following day, the reaction was concentrated *in vacuo* and the crude material was purified by flash column chromatography (10 - 100% ethyl acetate and hexane), followed by preparative HPLC (10 - 90% gradient of MeCN-water) to yield the title compound: MS (ES) M+H expected 486.1, found 486.0.

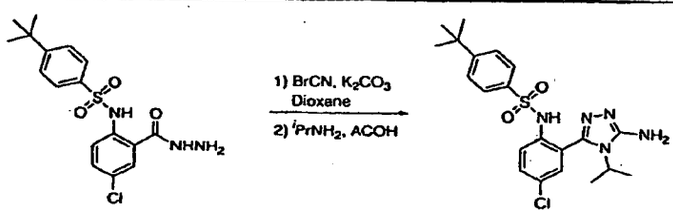
[00565] General Procedure G exemplified for 4-tert-Butyl-N-[4-chloro-2-(5-dimethylaminomethyl-4-methyl-4H-[1,2,4]triazol-3-yl)-5-fluoro-phenyl]-benzenesulfonamide



[00566] A 25 mL pear-shaped flask was charged with 4-tert-butyl-N-[4-chloro-5-fluoro-2-(4-methyl-4H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide (prepared according to general procedure C) (75 mg,

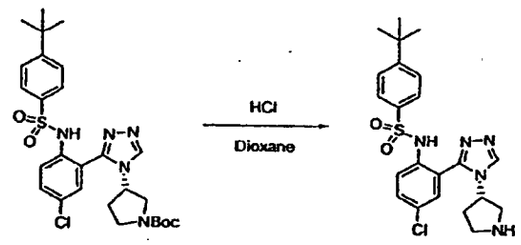
0.18 mmol), N,N-dimethylmethyleneiminium iodide (43 mg, 0.23 mmol), and DMF (0.44 mL). The flask was heated to 100 °C and stirred overnight. The following day, the solvent was evacuated *in vacuo* and the residue was purified via HPLC to afford 4-tert-butyl-N-[4-chloro-2-(5-dimethylaminomethyl-4-methyl-4H-[1,2,4]triazol-3-yl)-5-fluoro-phenyl]-benzenesulfonamide as a white powder: ^{1}H NMR (400 MHz, CD_3OD) δ 7.60 (d, 1H), 7.48-7.54 (m, 4H), 7.28 (d, 1H), 3.70 (s, 2H), 3.46 (s, 3H), 2.36 (s, 6H), 1.33 (s, 9H), MS (ES) M+H expected 480.2, found 480.1.

[00567] General Procedure H exemplified for N-[2-(5-Amino-4-isopropyl-4H-[1,2,4]triazol-3-yl)-4-chloro-phenyl]-4-tert-butyl-benzenesulfonamide



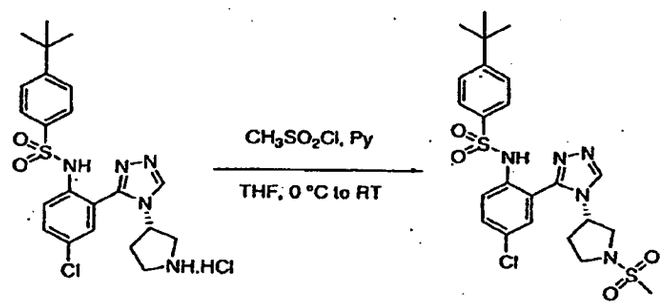
[00568] Cyanogen bromide (111 mg, 1.05 mmol) was added to a solution of 4-tert-butyl-N-(4-chloro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (200 mg, 0.524 mmol) and potassium carbonate (145 mg, 1.05 mmol) in dioxane (2 mL) and the reaction was stirred for 18 h at room temperature. Isopropyl amine (0.18 mL, 2.09 mmol) and acetic acid (0.15 mL) were added and the reaction was heated at 135 °C for an additional 18 h. The resultant solution was partitioned between ethyl acetate/water and the organic phase was washed with 1N HCl, saturated sodium bicarbonate, and brine; dried over magnesium sulfate, and concentrated *in vacuo*. The crude product was finally purified by flash column chromatography (10 - 100% ethyl acetate and hexane) then preparative HPLC (10 - 90% gradient of MeCN-water) to afford the title compound as a white solid: MS (ES) M+H expected 448.2, found 448.1.

[00569] General Procedure I exemplified for 4-tert-Butyl-N-[4-chloro-2-(4-pyrrolidin-3-yl-4H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide



[00570] A 50 mL round-bottom flask was charged with 3-{3-[2-(4-tert-butyl-benzenesulfonylamino)-5-chloro-phenyl]-[1,2,4]triazol-4-yl}-pyrrolidine-1-carboxylic acid tert-butyl ester (prepared according to general procedure C, 750 mg, 1.34 mmol), followed by the addition of HCl in dioxane (13 mL, 4.0 M). The homogeneous solution was stirred overnight, the solvent evacuated *in vacuo*, and the residue was purified via HPLC to afford 4-tert-butyl-N-[4-chloro-5-fluoro-2-(4-pyrrolidin-3-yl-4H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide as a white powder: ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 10.02 (s, 1H), 9.67 (bs, 1H), 9.17 (s, 1H), 9.12 (bs, 1H), 7.71 (d, 2H), 7.51-7.61 (m, 4H), 7.20 (d, 1H), 4.72 (quint, 1H), 3.35-3.62 (m, 3H), 3.18-3.28 (m, 1H), 2.38-2.49 (m, 1H), 2.16-2.28 (m, 1H), 1.29 (s, 9H), MS (ES) M+H expect 460.2, found 460.1.

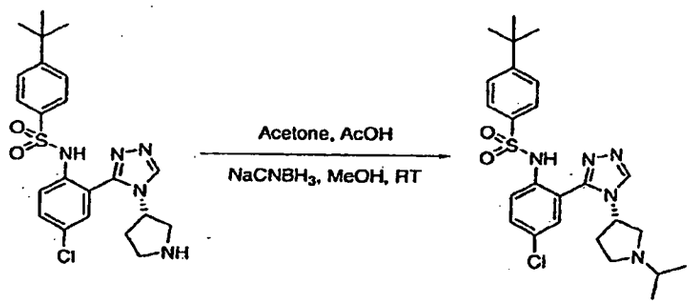
[00571] General Procedure J exemplified for 4-tert-Butyl-N-{4-chloro-2-[(S)-4-(1-methanesulfonyl-pyrrolidin-3-yl)-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide



[00572] To 4-tert-butyl-N-[4-chloro-2-((S)-4-pyrrolidin-3-yl-4H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide hydrochloride (0.25 g, 0.505 mmol) in THF (8 mL) was added pyridine (0.60 mL, 7.4 mmol). The resultant

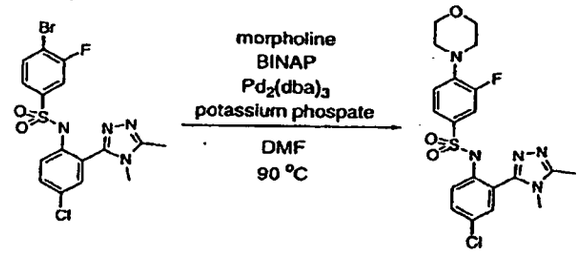
solution was stirred for 20 minutes at room temperature. The reaction mixture was subsequently cooled to 0 °C, methanesulfonyl chloride (0.595 mL, 7.6 mmol) was added, and the mixture was stirred overnight at room temperature. The following day, the volatiles were evaporated and the resultant residue was adsorbed onto silica gel and purified by automated normal-phase chromatography (using 50 → 100% EtOAc in hexanes) to obtain the title compound (0.183 g) in 67.5% yield: MS (ES) M+H expected 538.0, found 538.1.

[00573] General Procedure K exemplified for 4-tert-Butyl-N-[4-chloro-2-[(S)-4-(1-isopropyl-pyrrolidin-3-yl)-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide



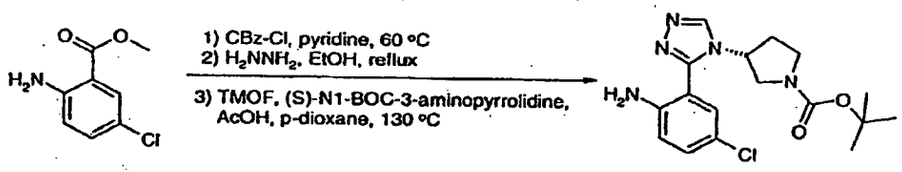
[00574] To a cooled solution of 4-tert-butyl-N-[4-chloro-2-((S)-4-pyrrolidin-3-yl-4H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide (200 mg, 0.43 mmol) in MeOH (5 Ml) was added acetone (0.048 mL, 0.65 mmol) and then $NaCNBH_3$ (0.054 g, 0.86 mmol). The reaction mixture was stirred at room temperature for 2 h, evaporated to dryness, adsorbed onto silica gel, and purified by automated normal-phase chromatography (50% MeOH in EtOAc) and then preparative HPLC (20 → 95% CH_3CN in H_2O with 0.1% TFA). The pure fractions were combined and lyophilized to obtain title compound as a powder: MS (ES) M+H expected 502.0, found 502.1.

[00575] General Procedure L exemplified for N-[4-Chloro-2-(4,5-dimethyl-4H-[1,2,4]triazol-3-yl)-phenyl]-3-fluoro-4-morpholin-4-yl-benzenesulfonamide



A 25 mL scintillation vial was charged with 4-bromo-N-[4-chloro-2-(4,5-dimethyl-4H-[1,2,4]triazol-3-yl)-phenyl]-3-fluoro-benzenesulfonamide (synthesized according to general procedure C, 92 mg, 0.2 mmol), potassium phosphate monohydrate (276 mg, 1.2 mmol), BINAP (30 mg, 0.048 mmol), morpholine (87 mg, 1.0 mmol), $Pd_2(dba)_3$ (10 mg, 0.011 mmol), and DMF (2 mL). The vial was sealed and stirred at 90 °C for 20 h. The crude product was purified by flash column chromatography (10 - 100% ethyl acetate and hexane) followed by preparative HPLC (10 - 90% gradient of MeCN-water) to afford the title compound as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$/HCl) δ 2.4 (s, 3 H), 2.7-3.7 (m, 8 H), 3.8 (s, 3 H), 6.7 (d, 1 H), 7.1-7.3 (m, 3 H), 7.4 (d, 1 H), 7.5 (d, 1 H), MS (ES) M+H expected 466.0, found 466.0.

[00576] General Procedure M exemplified for 3-[(S)-3-(2-Amino-5-chloro-phenyl)-[1,2,4]triazol-4-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester



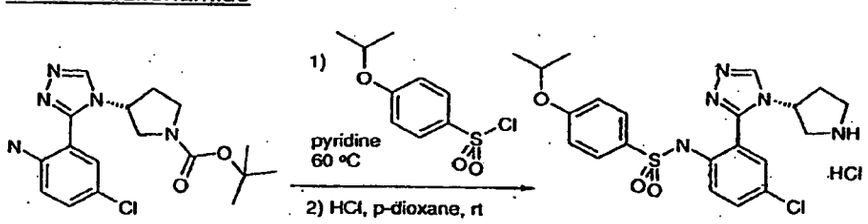
[00577] Step 1: 2-Amino-5-chlorobenzoic acid methyl ester (5 g, 27 mmol) was dissolved in 36 mL pyridine. CBz-Cl (4.2 mL, 29.6 mmol) was then added and the resultant solution was stirred at 60 °C overnight. The following day, LCMS analysis indicated the reaction was complete. The reaction mixture was subsequently poured in a slow stream into 200 mL of rapidly stirring 2 M HCl/H_2O. The mixture was transferred to a separatory funnel and extracted with 2 X 50 mL of EtOAc. The aqueous phase was discarded and the combined organics were dried over sodium sulfate and concentrated *in vacuo* to provide 6 g of 2-benzyloxycarbonylamino-5-chloro-benzoic acid

methyl ester (pale yellow oil, 70% yield): HPLC retention time = 3.15 minutes; MS (ES) M+H expected 320.0, found 320.0.

[00578] Step 2: 2-benzyloxycarbonylamino-5-chloro-benzoic acid methyl ester (3 g, 9.4 mmol) was dissolved in 30 mL ethanol. Hydrazine hydrate (1.5 mL, 30.0 mmol) was added and the resultant solution was heated at reflux under a nitrogen atmosphere for two hours, at which LCMS analysis showed complete conversion of the ester as well as the removal of the CBz protecting group. The reaction mixture was subsequently concentrated *in vacuo* to provide 1.6 g of 2-amino-5-chloro-benzoic acid hydrazide (light brown solid, 92% yield): HPLC retention time = 2.21; MS (ES) M+H expected 186.0, found 186.0.

[00579] Step 3: 2-Amino-5-chloro-benzoic acid hydrazide (0.8 g, 4.3 mmol) was dissolved in 8 mL *p*-dioxane in a 15 mL pressure vessel. Trimethyl orthoformate (0.71 mL, 6.5 mmol), (S)-N_1-Boc-3-aminopyrrolidine (4.0 g, 21.6 mmol), and acetic acid (5 drops) were added and the resultant solution was heated overnight in a 130 °C oil bath. The reaction mixture was subsequently concentrated *in vacuo* to produce a thick oil which was diluted with a small quantity of dichloromethane and purified via column chromatography (MeOH/DCM, 0% to 15 % gradient) to provide 1.4 g of 3-[(S)-3-(2-amino-5-chloro-phenyl)-[1,2,4]triazol-4-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester (white semisolid, 77% yield): HPLC retention time = 1.98; MS (ES) M+H expected 364.0, found 364.1.

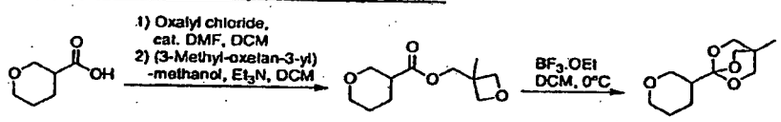
[00580] <u>General Procedure N exemplified for N-[4-Chloro-2-((S)-4-pyrrolidin-3-yl-4H-[1,2,4]triazol-3-yl)-phenyl]-4-isopropoxy-benzenesulfonamide</u>



[00581] Step 1: 3-[(S)-3-(2-Amino-5-chloro-phenyl)-[1,2,4]triazol-4-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester (50 mg, 0.137 mmol) was dissolved in 0.5 mL pyridine in a 4 mL vial. 4-Isopropoxybenzenesulfonyl chloride (42 mg, 0.179 mmol) was added and the mixture heated at 60 °C overnight. Water (~3 mL) was added to the reaction mixture which induced the precipitation of a viscous oil. The mother liquor was discarded and the oil was dissolved in ~3 mL of acetonitrile. The resultant solution was purified by reversed phase HPLC and the pure fractions lyophilized to afford the desired sulfonamide: HPLC retention time = 2.71 minutes; MS (ES) M+H expected 562.0, found 562.1.

[00582] Step 2: The above sulfonamide was dissolved in 1 mL *p*-dioxane and 4 M HCl/*p*-dioxane (4 mL, 16 mmol) was added. The resultant mixture was stirred at room temperature for one hour, during which LCMS indicated complete removal of the BOC protecting group. The reaction mixture was subsequently concentrated *in vacuo* to generate a thick oil, which diluted with 10 mL of acetonitrile/H_2O and lyophilized to afford N-[4-chloro-2-((S)-4-pyrrolidin-3-yl-4H-[1,2,4]triazol-3-yl)-phenyl]-4-isopropoxy-benzenesulfonamide hydrochloride: HPLC retention time = 1.67 minutes; MS (ES) M+H expected 462.0, found 462.4.

[00583] General Procedure O exemplified for 4-Methyl-1-(tetrahydro-pyran-3-yl)-2,6,7-trioxa-bicyclo[2.2.2]octane

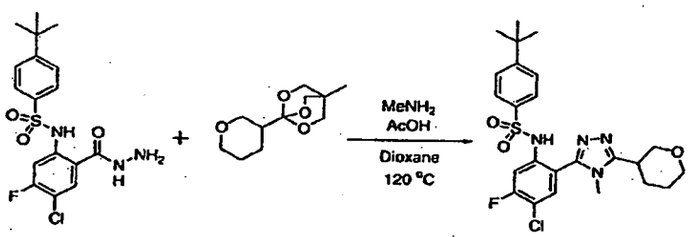


[00584] Step 1: To a stirred solution of tetrahydro-2H-pyran-3-carboxylic acid (231 mg, 1.77 mmol), under an inert atmosphere, in 8 mL of anhydrous DCM and 358 µL DMF was added oxalyl chloride (155 µL, 1.77 mmol). The mixture was stirred at room temperature for 4 h. This solution was then added via syringe to a 4 mL solution of DCM containing (3-methyl-oxetane-3-yl)-methanol (182 µL, 1.77 mmol) and Et_3N (0.62 mL, 4.44 mmol). The resulting mixture was stirred at room temperature for 4 hours. The solvent was subsequently evaporated *in vacuo* and the resultant residue was redissolved

in ethyl acetate and washed with saturated $NaHCO_3$, NH_4Cl solution, and brine. The combined organics were then dried over anhydrous Na_2SO_4 and concentrated to give a crude product, which was used directly in next step without further purification.

[00585] Step 2: The above crude tetrahydro-pyran-3-carboxylic acid 3-methyl-oxetan-3-ylmethyl ester (346 mg, 1.62 mmol) was dissolved in 6 mL of anhydrous DCM. To this solution at 0 °C, under a nitrogen atmosphere, was added $BF_3 \cdot OEt_2$ (41 µL, 0.324 mmol). The mixture was stirred at 0 °C for two hours then warmed to ambient temperature and stirred overnight. The next day, Et_3N (0.23 mL, 91.6 mmol) was added at 0 °C to quench the reaction. After stirring for 5 min, the solvent was removed *in vacuo*. The resultant residue was dissolved in ethyl acetate and washed with 3% of NH_4Cl, saturated $NaHCO_3$, and brine. The combined organics were subsequently dried over anhydrous Na_2SO_4 and concentrated to provide the desired orthoester.

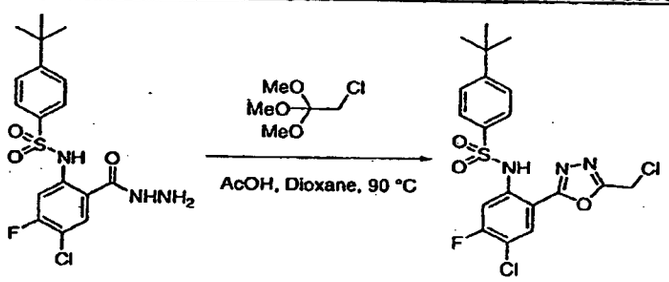
[00586] General Procedure P exemplified for 4-tert-Butyl-N-{4-chloro-5-fluoro-2-[4-methyl-5-(tetrahydro-pyran-3-yl)-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide



[00587] A 25 mL scintillation vial was charged with 4-tert-butyl-N-(4-chloro-3-fluoro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (253 mg, 0.633 mmol), 4-methyl-1-(tetrahydro-pyran-3-yl)-2,6,7-trioxa-bicyclo[2.2.2]octane (136 mg, 0.633 mmol), methylamine (31 µL, 0.886 mmol), AcOH (51 µL, 0.886 mmol), and dioxane (1.0 mL). The vial was sealed, heated to 120 °C, and stirred overnight. The following day, the volatiles were evacuated *in vacuo* and the residue was purified via automated silica gel chromatography to afford 4-tert-butyl-N-{4-chloro-5-fluoro-2-[4-

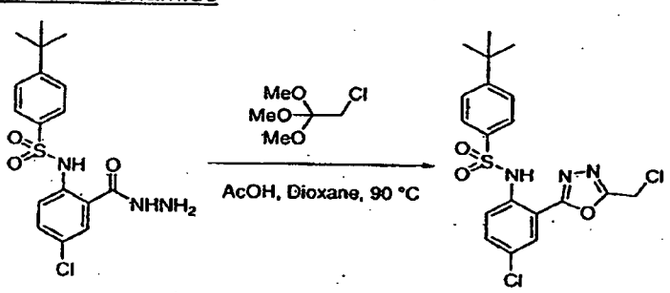
methyl-5-(tetrahydro-pyran-3-yl)-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide as a white powder: MS (ES) M+H expected 507.1, found 507.1.

[00588] General Procedure Q exemplified for 4-tert-Butyl-N-[4-chloro-2-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)-5-fluoro-phenyl]-benzenesulfonamide



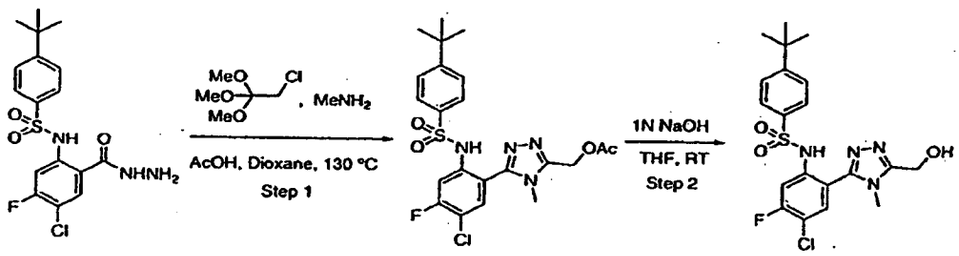
[00589] 2-Chloro-1,1,1-trimethoxy-ethane (0.507 mL, 3.76 mmol) and AcOH (1.5 mL) were added to 4-tert-butyl-N-(4-chloro-3-fluoro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (1.0 g, 2.51 mmol) in dioxane (6 mL) and stirred overnight at 90 °C. The reaction mixture was subsequently cooled to ambient temperature and stored for 1 day to promote precipitation of the product. The resultant white solid was filtered, washed with Et_2O (2 x 10 mL), and dried under vacuum to generate the title compound (0.74 g) in 65% yield as a white solid: MS (ES) M+H expected 458.0, found 458.3.

[00590] 4-tert-Butyl-N-[4-chloro-2-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)-phenyl]-benzenesulfonamide



[00591] 4-tert-Butyl-N-[4-chloro-2-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)-phenyl]-benzenesulfonamide was prepared according to general procedure Q: MS (ES) M+H expected 440.0, found 440.3.

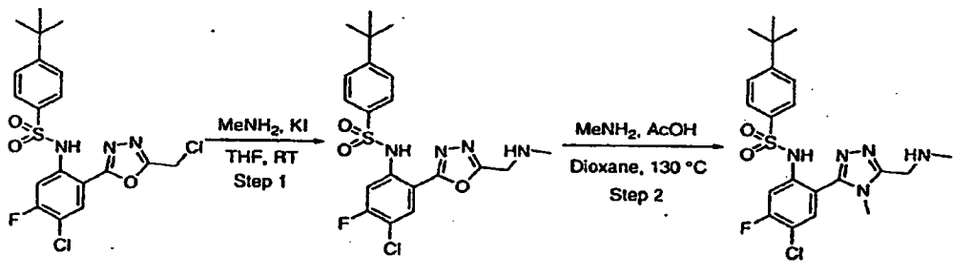
[00592] General Procedure R exemplified for 4-tert-Butyl-N-[4-chloro-5-fluoro-2-(5-hydroxymethyl-4-methyl-4H-1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide



[00593] Step1: 2-Chloro-1,1,1-trimethoxy-ethane (0.220 mL, 3.76 mmol), $MeNH_2$ (0.625 mL, 2.0 M in THF) and AcOH (0.4 mL) were added to 4-tert-butyl-N-(4-chloro-3-fluoro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (0.50 g, 1.25 mmol) in dioxane (5 mL) and stirred 4 h at 130 °C. The resultant reaction mixture was evaporated to dryness, adsorbed onto silica gel, and purified by automated normal-phase chromatography (30% EtOAc in hexanes) to afford the 'triazole-acetate' as a minor product.

[00594] Step 2: To a solution of 'triazole-acetate' (20 mg) in THF (2 mL) was added 1 N aqueous NaOH (2 mL), and the solution was stirred at room temperature for 30 min. 2 N HCl (aqueous) (2 mL) was subsequently added and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organics were dried (Na_2SO_4), concentrated *in vacuo*, and purified by automated normal-phase chromatography (50% EtOAc in hexanes) to generate the title compound as white powder following lyophilization: MS (ES) M+H expected 453.0, found 453.1.

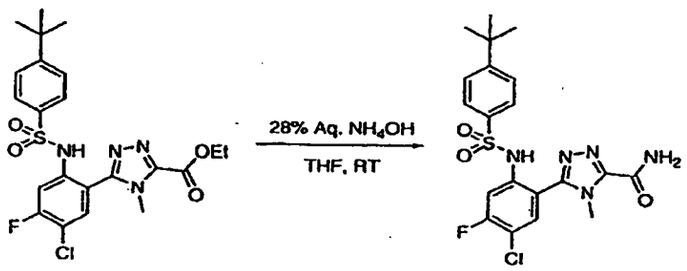
[00595] General Procedure S exemplified for 4-tert-Butyl-N-[4-chloro-5-fluoro-2-(4-methyl-5-methylaminomethyl-H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide



[00596] Step 1: To a solution of 4-tert-butyl-N-[4-chloro-2-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)-5-fluoro-phenyl]-benzenesulfonamide (400 mg, 0.875 mmol) in THF (5 mL) was added KI (0.145 g, 0.875 mmol) and $MeNH_2$ (1.31 mL, 2.62 mmol, 2.0 M in THF). The resultant solution was stirred at room temperature overnight. The following day, the reaction mixture was diluted with EtOAc (30 mL) and the organic layer was washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford the desired 'methylaminomethyl-oxadiazole' (400 mg) as a white solid in quantitative yield: MS (ES) M+H expected 453.0, found 453.0.

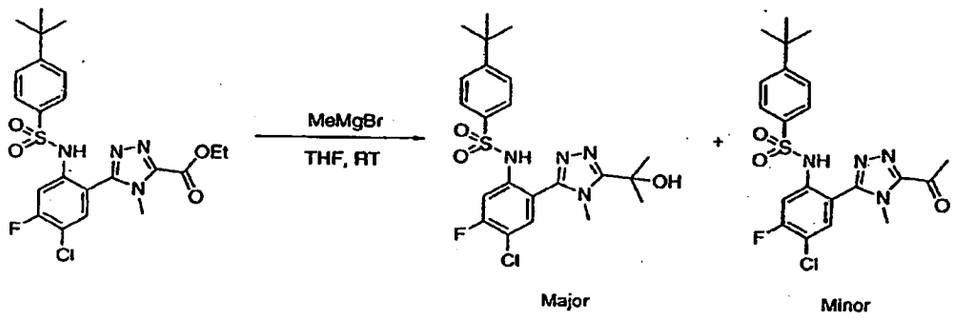
[00597] Step 2: To the above oxadiazole intermediate (100 mg, 0.22 mmol) in 1,4-dioxane (3 mL) was added $MeNH_2$ (1.1 mL, 2.0 M in THF), followed by AcOH (0.125 mL). The homogeneous solution was heated to 130 °C and stirred at for 4 h. Upon cooling to room temperature, the reaction mixture was diluted with EtOAc (25 mL) and the organic layer was washed with saturated $NaHCO_3$ solution (25 mL), dried (Na_2SO_4), concentrated *in vacuo*, and purified via automated normal-phase chromatography (5% MeOH in EtOAc). The pure fractions were combined and lyophilized to produce the title compound as a powder: ^1H NMR (400 MHz, CD_3OD) δ 7.65 (d, 1H), 7.60-7.52 (m, 4H), 7.0 (d, 1H), 4.58 (s, 2H), 3.58 (s, 3H), 2.95 (s, 3H), 1.35 (s, 9H), MS (ES) M+H expected 466.0, found 466.1.

[00598] General Procedure T exemplified for 5-[2-(4-tert-Butyl-benzenesulfonylamino)-5-chloro-4-fluoro-phenyl]-4-methyl-4H-[1,2,4]triazole-3-carboxylic acid amide



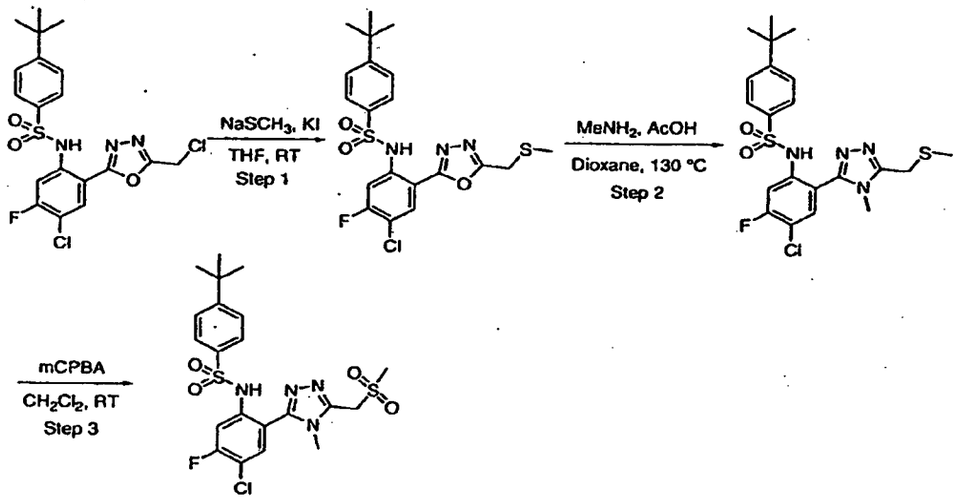
[00599] To a vial containing ethyl 5-[2-(4-tert-butyl-benzenesulfonylamino)-5-chloro-4-fluoro-phenyl]-4-methyl-4H-[1,2,4]triazole-3-carboxylic acid ethyl ester (synthesized according to general procedure C, 100 mg, 0.202 mmol) was added THF (2 mL) and 28% NH_4OH in water (2 mL), and the resultant solution was stirred at room temperature for 1 h. The reaction mixture was subsequently diluted with EtOAc (30 mL) and the organics were washed with water (2 x 10 mL), dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography (50 → 100% gradient of EtOAc in hexanes). The pure fractions were collected and the solvent was removed. The isolated product was dissolved in $MeCN/H_2O$ and the solvent removed via lyophilization to afford the title compound as a white powder: MS (ES) M+H expected 466.0, found 466.0.

[00600] General Procedure U exemplified for 4-tert-Butyl-N-[4-chloro-5-fluoro-2-[5-(1-hydroxy-1-methyl-ethyl)-4-methyl-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide and N-[2-(5-Acetyl-4-methyl-4H-[1,2,4]triazol-3-yl)-4-chloro-5-fluoro-phenyl]-4-tert-butyl-benzenesulfonamide



[00601] To a solution of ethyl 5-[2-(4-tert-butyl-benzenesulfonylamino)-5-chloro-4-fluoro-phenyl]-4-methyl-4H-[1,2,4]triazole-3-carboxylic acid ethyl ester (synthesized according to general procedure C, 100 mg, 0.254 mmol) in THF (3 mL) at room temperature was added MeMgBr (3 mL, 3.0 M in Et_2O). The resultant solution was stirred 30 min, followed by the slow addition of saturated aqueous NH_4Cl solution to quench the excess MeMgBr. The aqueous layer was subsequently extracted with EtOAc (2 x 25 mL) and the combined organics were dried (Na_2SO_4), concentrated *in vacuo*, and purified by automated normal-phase chromatography (EtOAc/hexanes) to afford the tertiary alcohol (0.026g, 21% yield) as the major product and the methyl ketone as the minor product (0.020 g, 17% yield): MS (ES) M+H (major product) expected 481.0, found 481.0, MS (ES) M+H (minor product) expected 465.0, found 465.0.

[00602] General Procedure V exemplified for 4-tert-Butyl-N-[4-chloro-5-fluoro-2-(5-methanesulfonylmethyl-4-methyl-4H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide



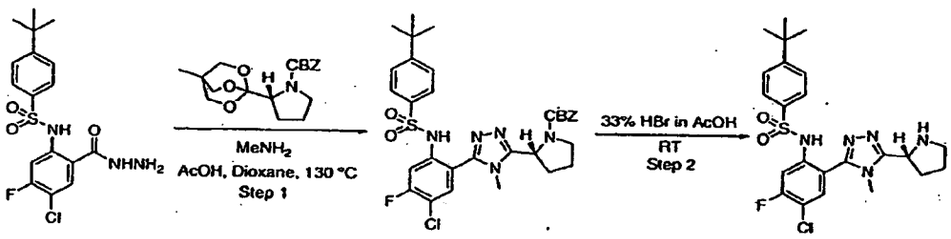
[00603] Step 1: KI (0.036 g, 0.218 mmol), followed by sodium thiomethoxide (0.046 g, 0.654 mmol) were added to 4-tert-butyl-N-[4-chloro-2-(5-chloromethyl-[1,3,4]oxadiazol-2-yl)-5-fluoro-phenyl]-benzenesulfonamide (100 mg, 0.218 mmol) in THF (3 mL) and stirred at room temperature overnight. The resultant reaction mixture was diluted with EtOAc (30 mL), and the organic layer was washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated *in vacuo* to generate the desired 'oxadiazole methylthioether' (100 mg) as a yellow thick syrup in quantitative yield: MS (ES) M+H expected 470.0, found 470.0.

[00604] Step 2: To the above 'oxadiazole methylthioether' (100 mg, 0.21 mmol) in 1,4-dioxane (3 mL) was added $MeNH_2$ (1.1 mL, 2.0 M in THF) and AcOH (0.128 mL) and the resultant mixture was stirred at 130 °C for 4 h. Upon cooling to room temperature, the reaction mixture was diluted with EtOAc (25 mL), and the organic layer was washed with saturated $NaHCO_3$ solution (25 mL), dried (Na_2SO_4), concentrated *in vacuo*, and purified via automated normal-phase chromatography (EtOAc) to produce the

corresponding 'triazole methylthioether': MS (ES) M+H expected 483.0, found 483.4.

[00605] Step 3: To a solution of the above 'triazole methylthioether' (0.025 g, 0.05 mmol) in CH_2Cl_2 (3 mL) was added *m*CPBA (0.027g, 0.155 mmol) and the resultant mixture was stirred at room temperature overnight. The volatiles were subsequently removed and the product was purified utilizing preparative HPLC (20 → 95% CH_3CN in H_2O with 0.1% TFA). The pure fractions were combined and lyophilized to generate the title compound as a yellow powder: MS (ES) M+H expected 515.0, found 515.4.

[00606] General Procedure W exemplified for 4-tert-Butyl-N-[4-chloro-5-fluoro-2-((R)-4-methyl-5-pyrrolidin-2-yl-4H-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide

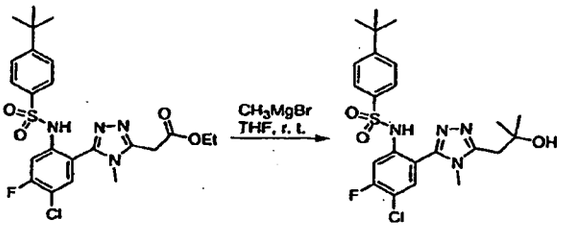


[00607] Step 1: (R)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-pyrrolidine-1-carboxylic acid benzyl ester (synthesized according to general procedure O, 0.296 g, 0.888 mmol), $MeNH_2$ (0.888 mL, 2.0 M in THF), and AcOH (0.125 mL) were added to 4-tert-butyl-N-(4-chloro-3-fluoro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (0.236 g, 0.59 mmol) in dioxane (5 mL) and the solution was stirred overnight at 130 °C. The following day, the reaction mixture was evaporated to dryness and the resultant crude triazole was utilized directly in the next step.

[00608] Step 2: To the above crude triazole was added 33% HBr in AcOH (3 mL) and the resultant reaction mixture was stirred overnight at room temperature. The following day, the volatiles were removed *in vacuo* and the resultant residue was dissolved in a small quantity of MeOH and purified via preparative HPLC (20 → 95% CH_3CN in H_2O with 0.1% TFA). The pure

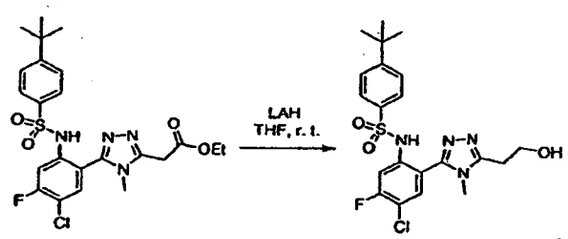
fractions were collected and lyophilized to afford the title compound as a yellow powder: MS (ES) M+H expected 492.0, found 492.4.

[00609] General Procedure X exemplified for 4-tert-Butyl-N-{4-chloro-5-fluoro-2-[5-(2-hydroxy-2-methyl-propyl)-4-methyl-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide



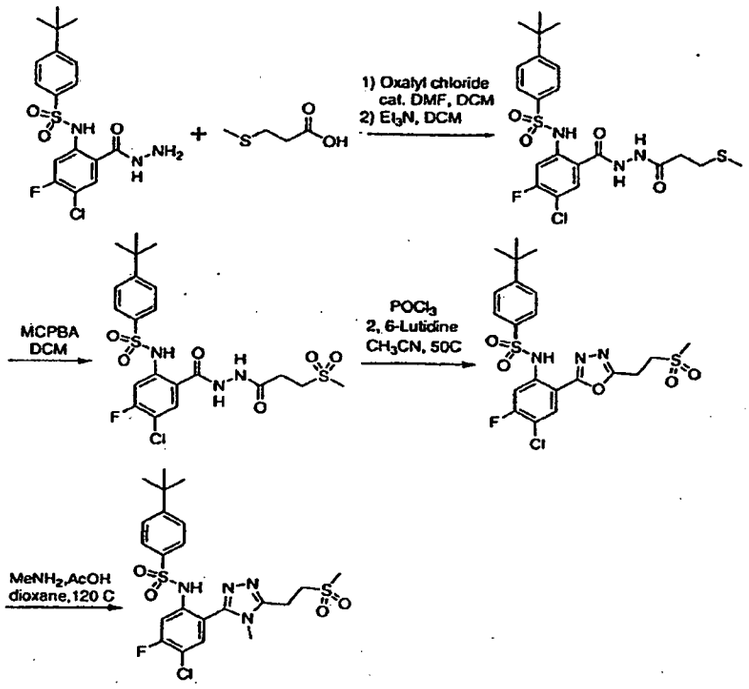
[00610] A 25 mL scintillation vial was charged with {5-[2-(4-tert-butyl-benzenesulfonylamino)-5-chloro-4-fluoro-phenyl]-4-methyl-4H-[1,2,4]triazol-3-yl}-acetic acid ethyl ester (prepared according to general procedure P, 178 mg, 0.349 mmol) in 7 mL of anhydrous THF. To this solution under a nitrogen atmosphere was added of methyl magnesium bromide (0.47 mL, 3.0 M in THF) at room temperature. Upon complete consumption of the starting material (via LCMS), the reaction was quenched by the addition of an NH_4Cl solution. The solvent was subsequently removed *in vacuo* and the residue was purified via automated silica gel chromatography to afford 4-tert-butyl-N-{4-chloro-5-fluoro-2-[5-(2-hydroxy-2-methyl-propyl)-4-methyl-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide as a white powder: ^1H NMR (400 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.64 (d, 1H), 7.60 (d, 2H), 7.41 (d, 2H), 7.30 (d, 1H), 4.0 (s, 1H), 3.81 (s, 2H), 3.41 (s, 3H), 1.57 (s, 9H), 1.31 (s, 6H), MS (ES) M+H expected 495.2, found 495.4.

[00611] General Procedure Y exemplified for 4-tert-Butyl-N-{4-chloro-5-fluoro-2-[5-(2-hydroxy-ethyl)-4-methyl-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide



[00612] A 25 mL scintillation vial was charged with {5-[2-(4-tert-butyl-benzenesulfonylamino)-5-chloro-4-fluoro-phenyl]-4-methyl-4H-[1,2,4]triazol-3-yl}-acetic acid ethyl ester (synthesized according to general procedure P, 95 mg, 0.186 mmol) in 2 mL of anhydrous MeOH. To this solution under a nitrogen atmosphere was added of lithium aluminum hydride (14 mg, 0.372 mmol) at room temperature. LCMS indicated completion of the reaction after 30 minutes and 1 mL of 20% H_2SO_4 was added. The solvent was subsequently removed *in vacuo* and the residue was extracted with DCM. The organic layer was then washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resultant residue was purified via automated silica gel chromatography to afford 4-tert-butyl-N-{4-chloro-5-fluoro-2-[5-(2-hydroxy-ethyl)-4-methyl-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide as a white powder: MS (ES) M+H expected 467.1, found 467.4.

[00613] General Procedure Z exemplified for 4-tert-Butyl-N-{4-chloro-5-fluoro-2-[5-(2-methanesulfonyl-ethyl)-4-methyl-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide



[00614] Step 1: To a stirred solution of 3-methylsulfanyl-propionic acid (120 mg, 1.0 mmol) under an inert atmosphere in 6 mL of anhydrous DCM and DMF (200 µL) was added oxalyl chloride (89 µL, 1.0 mmol). The resultant solution was stirred at room temperature overnight and then added to a solution of 4-tert-butyl-N-(4-chloro-5-fluoro-2-hydrazinocarbonyl-phenyl)-benzenesulfonamide (400 mg, 1.0 mmol) and Et_3N (0.35 mL, 2.5 mmol) at 0 °C. The resultant solution was stirred at room temperature for 4 hours and the solvent was removed *in vacuo*. The residue was purified via automated silica gel chromatography to afford 4-tert-butyl-N-{4-chloro-5-fluoro-2-[N'-(3-methylsulfanyl-propionyl)-hydrazinocarbonyl]-phenyl}-benzenesulfonamide as an oil: MS (ES) M+H expected 502.1, found 502.0.

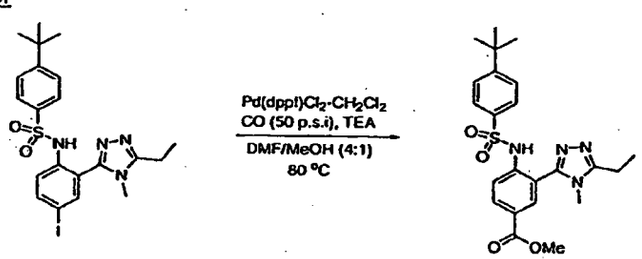
[00615] Step 2: To a solution of the above diamide (422 mg, 0.841 mmol) in 10 mL of DCM was added 3-chloroperoxybenzoic acid (386 mg, 1.72

mmol) at 0 °C. The reaction mixture was subsequently stirred at room temperature overnight. The following day, the product had precipitated from solution and was collected via vacuum filtration and used directly in the next step: MS (ES) M+H expected 534.1, found 534.0.

[00616] Step 3: A 25 mL scintillation vial was charged with the above crude sulfone (307 mg, 0.574 mmol), 2,6-lutidine (148 mg, 1.378 mmol), $POCl_3$ (106 mg, 0.689 mmol), and CH_3CN (1.0 mL). The vial was sealed, heated to 50 °C, and stirred overnight. The following day, the volatiles were evacuated *in vacuo* and the residue was purified via automated silica gel chromatography to afford 4-tert-butyl-N-{4-chloro-5-fluoro-2-[5-(2-methanesulfonyl-ethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-benzenesulfonamide as the desired product: MS (ES) M+H expected 516.1, found 516.0.

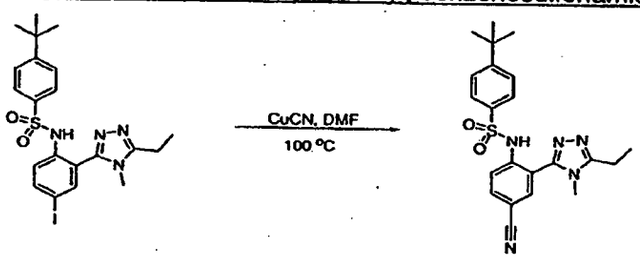
[00617] Step 4: A 25 mL scintillation vial was charged with 4-tert-butyl-N-{4-chloro-5-fluoro-2-[5-(2-methanesulfonyl-ethyl)-[1,3,4]oxadiazol-2-yl]-phenyl}-benzenesulfonamide (48 mg, 0.093 mmol), methylamine (13 µL, 0.372 mmol), AcOH (21 µL, 0.372 mmol), and dioxane (1.0 mL). The vial was sealed, heated to 120 °C, and stirred overnight. The following day, the volatiles were evacuated *in vacuo* and the residue was purified via automated silica gel chromatography to afford 4-tert-butyl-N-{4-chloro-5-fluoro-2-[5-(2-methanesulfonyl-ethyl)-4-methyl-4H-[1,2,4]triazol-3-yl]-phenyl}-benzenesulfonamide as a white powder: MS (ES) M+H expected 529.1, found 529.0.

[00618] General Procedure AA exemplified for 4-(4-tert-Butyl-benzenesulfonylamino)-3-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-benzoic acid methyl ester



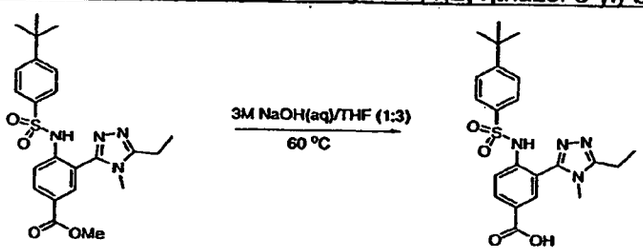
[00619] A 15 mL pressure vessel was charged with 4-tert-butyl-*N*-[4-iodo-2-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide (prepared according to general procedure C, 551 mg, 1.05 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with CH_2Cl_2 (1:1) (86 mg, 0.105 mmol), triethylamine (290 µL, 2.1 mmol), and DMF/MeOH (4:1) (5 mL). The vessel was placed under an atmosphere of CO (50 p.s.i.), heated to 80 °C, and stirred overnight. The following day, the volatiles were removed *in vacuo*, the residue dissolved in EtOAc, and the organics washed twice with 1 M HCl. The aqueous solution was then extracted three times with EtOAc. The EtOAc extractions were then pooled together and washed with brine. The organic solvent was then removed and the resultant residue was purified by silica gel chromatography to afford 4-(4-tert-butyl-benzenesulfonylamino)-3-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-benzoic acid methyl ester as a yellow foam: MS (ES) M+H expected 457.2, found 457.1.

[00620] General Procedure BB exemplified for 4-tert-Butyl-*N*-[4-cyano-2-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide



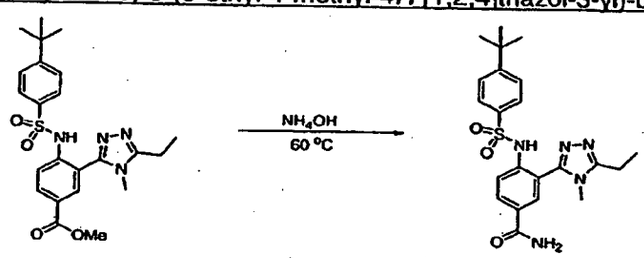
[00621] A 4 mL scintillation vial was charged with 4-tert-butyl-*N*-[4-iodo-2-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide (prepared according to general procedure C, 18 mg, 0.034 mmol), CuCN (15 mg, 0.17 mmol), and DMF (500 µL). The reaction was then heated to 100 °C and stirred for 48 hours. The solution was then diluted with EtOAc and washed with an aqueous solution of EDTA (5% wt/wt). The organic layer was then concentrated and the residue purified by preparative TLC to afford 4-tert-butyl-*N*-[4-cyano-2-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-phenyl]-benzenesulfonamide as a white solid: MS (ES) M+H expected 424.2, found 424.4.

[00622] General Procedure CC exemplified for 4-(4-tert-Butyl-benzenesulfonylamino)-3-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-benzoic acid



[00623] A 10 mL scintillation vial was charged with 4-(4-tert-butyl-benzenesulfonylamino)-3-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-benzoic acid methyl ester (20 mg, 0.044 mmol) and 3 M NaOH (aq)/THF (1:3) (1.5 mL). The reaction was heated to 60 °C and stirred overnight. The following day, the volatiles were removed *in vacuo* to about 200 µL at which point the solution was purified by preparative TLC to afford 4-(4-*tert*-butyl-benzenesulfonylamino)-3-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-benzoic acid as a light yellow solid: MS (ES) M+H expect 443.2, found 443.4.

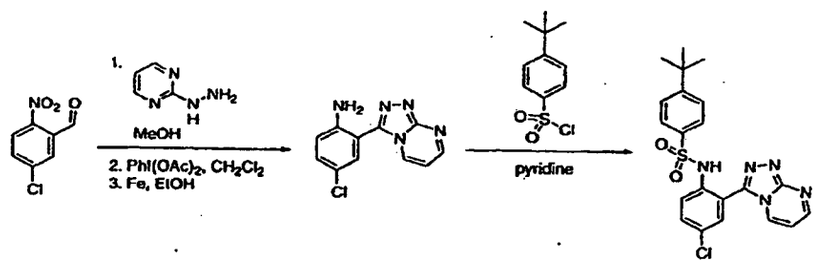
[00624] General Procedure DD exemplified for 4-(4-tert-Butyl-benzenesulfonylamino)-3-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-benzamide



[00625] A 10 mL scintillation vial was charged with 4-(4-tert-butyl-benzenesulfonylamino)-3-(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-benzoic acid methyl ester (20 mg, 0.044 mmol) and 30% NH_3 in H_2O (1.5 mL). The reaction was heated to 60 °C and stirred overnight. The following day, the volatiles were removed *in vacuo* to about 200 µL at which point the solution was purified by preparative TLC to afford 4-(4-*tert*-butyl-benzenesulfonylamino)-3-

(5-ethyl-4-methyl-4*H*-[1,2,4]triazol-3-yl)-benzamide as a colorless oil: MS (ES) M+H expected 442.2, found 442.4.

[00626] General Procedure EE exemplified for 4-tert-Butyl-*N*-(4-chloro-2-[1,2,4]triazolo[4,3-a]pyrimidin-3-yl-phenyl)-benzenesulfonamide



[00627] Step 1: A 5 mL scintillation vial was charged with 2-hydrazinopyrimidine (61 mg, 0.55 mmol), 2-nitro-5-chlorobenzaldehyde (112 mg, 0.60 mmol) and MeOH (500 µL) and heated to 60 °C for 30 minutes. The MeOH was then removed *in vacuo* and the resultant solid was washed with Et_2O. The crude solid (30 mg) was then suspended in CH_2Cl_2 (1 mL) and iodobenzene diacetate (39 mg, 0.12 mmol) was added. The reaction was stirred at room temperature for 30 minutes after which the solvent was removed *in vacuo*. The resultant residue was then dissolved in a 10% solution of saturated NH_4Cl(aq) in EtOH and iron (19 mg, 0.33 mmol) was then added and the reaction was stirred at 80 °C for 4 h. The solvent was then removed *in vacuo* and the product was purified by silica gel chromatography to afford 4-chloro-2-[1,2,4]triazolo[4,3-a]pyrimidin-3-yl-phenylamine as a light yellow oil.

[00628] Step 2: A 4 mL scintillation vial was charged with the above aniline (10 mg, 0.04 mmol), tert-butylphenylsulfonyl chloride (11 mg, 0.05 mmol), and pyridine (300 µL). The mixture was subsequently warmed to 60 °C and stirred overnight. The following day, the reaction mixture was diluted in EtOAc and washed with 1 N HCl (aqueous). The organic layer was then concentrated and the obtained residue was purified by preparative TLC to afford the desired sulfonamide: MS (ES) M+H expected 442.1, found 442.3.

[00629] The compounds in Table 2 were prepared by the indicated general procedure described above. MS (ES) $[M+H]^+$ data was collected and compared to the expected value to confirm the identity of the compound.

[00630] **Table 2 – Compounds prepared by General Procedures and MS Data.**

Compound	General Procedure	$[M+H]^+$ expected	$[M+H]^+$ found
1	C	432.14	433.0
2	C	466.12	467.0
3	C	446.15	447.1
4	C	480.14	481.0
5	C	432.14	433.1
6	C	418.12	419.1
7	C	444.14	445.1
8	C	446.15	447.0
9	D	488.16	489.1
10	D	448.13	449.1
11	C	474.19	475.1
12	C	488.16	489.1
13	C	460.17	461.1
14	C	472.17	473.1
15	C	448.13	449.1
16	C	470.13	471.1
17	C	434.12	435.0
18	C	432.14	433.1
19	C	460.17	461.1
20	I	487.18	488.1
21	D	518.18	519.1
22	C	420.14	421.1
23	C	402.15	403.1
24	C	430.18	431.1
25	C	436.11	437.0
26	C	462.15	463.0
27	C	489.16	490.1
28	C	436.11	437.0
29	C	450.13	451.1
30	C	404.11	405.0
31	C	418.12	419.0
32	I	459.15	460.1
33	D	474.15	475.0
34	D	474.15	475.0
35	C	460.13	461.0
36	C	436.11	437.1
37	I	461.17	462.0
38	C	446.15	447.1

39	G	479.16	480.1
40	D	471.11	472.0
41	P	462.15	463.1
42	C	462.15	463.1
43	C	460.17	461.1
44	I	491.16	492.1
45	S	465.14	466.1
46	D	516.20	517.1
47	C	506.16	507.0
48	S	479.16	480.0
49	S	493.17	494.1
50	S	491.16	492.0
51	P	494.16	495.1
52	P	522.15	523.1
53	C	478.12	479.0
54	C	478.12	479.0
55	T	465.10	466.0
56	T	479.12	480.0
57	U	480.14	481.0
58	U	464.11	465.0
59	P	466.12	467.0
60	P	466.12	467.4
61	P	466.12	467.0
62	P	480.14	481.0
63	P	506.16	507.1
64	P	508.13	509.0
65	X	494.16	495.4
66	S	521.17	522.4
67	V	514.09	515.4
68	C	420.10	421.0
69	C	434.12	435.1
70	W	487.18	488.1
71	C	434.16	435.1
72	C	402.15	403.1
73	I	473.17	474.1
74	C	416.17	417.1
75	I	459.15	460.1
76	C	422.10	423.0
77	I	475.19	476.0
78	C	450.13	451.1
79	F	503.12	504.0
80	C	492.14	493.0
81	C	520.17	521.1
82	P	520.17	521.2
83	C	447.15	448.1
84	C	458.15	459.1
85	I	463.12	464.1
86	C	500.13	501.0

87	C	478.16	479.1
88	I	505.17	506.1
89	Z	528.11	529.0
90	C	491.12	492.0
91	C	529.19	530.1
92	H	447.15	448.1
93	J	565.16	566.1
94	J	530.19	531.1
95	C	446.15	447.1
96	D	476.16	477.1
97	D	481.13	482.1
98	G	489.20	490.1
99	I	473.17	474.1
100	C	420.14	421.1
101	C	474.15	475.1
102	D	474.15	475.1
103	E	476.16	477.1
104	C	474.15	475.1
105	C	432.14	433.1
106	I	491.16	492.1
107	P	466.12	467.1
108	C	492.14	493.1
109	I	477.14	478.1
110	C	450.13	451.1
111	D	489.10	490.0
112	I	491.16	492.1
113	I	473.17	474.1
114	I	487.18	488.2
115	P	492.14	493.1
116	P	506.16	507.1
117	F	485.13	486.0
118	I	501.20	502.1
119	I	487.18	488.1
120	C	478.12	479.1
121	S	505.17	506.1
122	S	491.16	492.1
123	R	452.11	453.0
124	C	515.18	516.1
125	C	475.18	476.1
126	C	461.17	462.1
127	I	473.17	474.1
128	BB	423.17	424.4
129	DD	441.18	442.4
130	CC	442.17	443.4
131	I	445.13	446.0
132	S	447.15	448.4
133	AA	456.18	457.1
134	N	461.13	462.1

135	L	465.10	466.0
136	C	466.12	467.4
137	Y	466.12	467.4
138	S	475.18	476.4
139	P	480.14	481.4
140	W	491.16	492.4
141	K	501.20	502.1
142	N	501.16	502.1
143	J	502.16	503.1
144	S	503.18	504.5
145	W	505.17	506.5
146	I	519.19	520.1
147	S	520.18	521.5
148	S	521.17	522.5
149	S	523.18	524.5
150	D	530.21	531.1
151	S	534.20	535.6
152	S	535.18	536.5
153	J	537.13	538.0
154	S	549.20	550.5
155	C	501.20	502.4
156	EE	441.1	442.1
157	C	502.00	502.9
158	C	516.01	516.9
159	C	512.01	512.9
160	C	519.99	520.9
161	T	563.00	563.9

[00631] **Measuring Efficacy of Chemokine Modulators**

[00632] *In Vitro Assays*

[00633] A variety of assays can be used to evaluate the compounds provided herein, including signaling assays, migration assays, ligand binding assays, and other assays of cellular response. Chemokine receptor signaling assays can be used to measure the ability of a compound, such as a potential CCR2 antagonist, to block CCR2 ligand- (e.g. MCP-1)-induced signaling or a potential CCR9 antagonist, to block CCR9 ligand- (e.g. TECK)-induced signaling. A migration assay can be used to measure the ability of a compound of interest, such as a possible chemokine antagonist, to block chemokine-mediated cell migration in vitro. The latter is believed to resemble chemokine-induced cell migration in vivo. A ligand binding assay can be used to measure the ability of a compound, such as a potential CCR2 antagonist, to

block the interaction of MCP-1 with its receptor or a potential CCR9 antagonist, to block the interaction of TECK with its receptor.

[00634] In a suitable assay, a chemokine protein (whether isolated or recombinant) is used which has at least one property, activity, or functional characteristic of a mammalian chemokine protein. The property can be a binding property (to, for example, a ligand or inhibitor), a signaling activity (e.g., activation of a mammalian G protein, induction of rapid and transient increase in the concentration of cytosolic free calcium ion), cellular response function (e.g., stimulation of chemotaxis or inflammatory mediator release by leukocytes), and the like.

[00635] The assay can be a cell-based assay that utilizes cells stably or transiently transfected with a vector or expression cassette having a nucleic acid sequence that encodes the chemokine receptor. Cell lines naturally expressing the chemokine can also be used. The cells are maintained under conditions appropriate for expression of the receptor and are contacted with a putative agent under conditions appropriate for binding to occur. Binding can be detected using standard techniques. For example, the extent of binding can be determined relative to a suitable control (for example, relative to background in the absence of a putative agent, or relative to a known ligand). Optionally, a cellular fraction, such as a membrane fraction, containing the receptor can be used in lieu of whole cells.

[00636] Detection of binding or complex formation can be detected directly or indirectly. For example, the putative agent can be labeled with a suitable label (e.g., fluorescent label, chemiluminescent label, isotope label, enzyme label, and the like) and binding can be determined by detection of the label. Specific and/or competitive binding can be assessed by competition or displacement studies, using unlabeled agent or a ligand (e.g., MCP-1 or TECK) as a competitor.

[00637] Binding inhibition assays can be used to evaluate the present compounds. In these assays, the compounds are evaluated as inhibitors of ligand binding using, for example, MCP-1 or TECK. In one embodiment, the CCR2 receptor is contacted with a ligand such as MCP-1 and a measure of ligand binding is made. The receptor is then contacted with a test agent in the

presence of a ligand (e.g., MCP-1) and a second measurement of binding is made. In another embodiment, the CCR9 receptor is contacted with a ligand such as TECK and a measure of ligand binding is made. The receptor is then contacted with a test agent in the presence of a ligand (e.g., TECK) and a second measurement of binding is made. A reduction in the extent of ligand binding is indicative of inhibition of binding by the test agent. The binding inhibition assays can be carried out using whole cells which express the chemokine, or a membrane fraction from cells which express the chemokine.

[00638] The binding of a G protein coupled receptor by, for example, an agonist, can result in a signaling event by the receptor. Accordingly, signaling assays can also be used to evaluate the compounds of the present invention and induction of signaling function by an agent can be monitored using any suitable method. For example, G protein activity, such as hydrolysis of GTP to GDP, or later signaling events triggered by receptor binding can be assayed by known methods (see, for example, PCT/US97/15915; Neote et al., *Cell*, 72:415425 (1993); Van Riper et al., *J. Exp. Med.*, 177:851-856 (1993) and Dahinden et al., *J. Exp. Med.*, 179:751-756 (1994)).

[00639] Chemotaxis assays can also be used to assess receptor function and evaluate the compounds provided herein. These assays are based on the functional migration of cells in vitro or in vivo induced by an agent, and can be used to assess the binding and/or effect on chemotaxis of ligands, inhibitors, or agonists. A variety of chemotaxis assays are known in the art, and any suitable assay can be used to evaluate the compounds of the present invention. Examples of suitable assays include those described in PCT/US97/15915; Springer et al., WO 94/20142; Berman *et al.*, *Immunol. Invest.*, 17:625-677 (1988); and Kavanaugh *et al.*, *J. Immunol.*, 146:4149-4156 (1991)).

[00640] Calcium signaling assays measure calcium concentration over time, preferably before and after receptor binding. These assays can be used to quantify the generation of a receptor-signaling mediator, Ca^{++}, following receptor binding (or absence thereof). These assays are useful in determining the ability of a compound, such as those of the present invention, to generate the receptor signaling mediator by binding to a receptor of

interest. Also, these assays are useful in determining the ability of a compound, such as those of the present invention, to inhibit generation of the receptor signaling mediator by interfering with binding between a receptor of interest and a ligand.

[00641] In calcium signaling assays used to determine the ability of a compound to interfere with binding between a chemokine receptor and a known chemokine ligand, chemokine receptor-expressing cells (CCR2-expressing cells such as THP-1 cells or CCR9-expressing cells such as T cell line MOLT-4 cells) are first incubated with a compound of interest, such as a potential chemokine antagonist, at increasing concentrations. The cell number can be from 10^5 to 5 x 10^5 cells per well in a 96-well microtiter plate. The concentration of the compound being tested may range from 0 to 100 μM. After a period of incubation (which can range from 5 to 60 minutes), the treated cells are placed in a Fluorometric Imaging Plate Reader (FLIPR®) (available from Molecular Devices Corp., Sunnyvale, CA) according to the manufacturer's instruction. The FLIPR® system is well known to those skilled in the art as a standard method of performing assays. The cells are then stimulated with an appropriate amount of the chemokine ligand (MCP-1 for CCR2 or TECK for CCR9) at 5-100 nM final concentration, and the signal of intracellular calcium increase (also called calcium flux) is recorded. The efficacy of a compound as an inhibitor of binding between the chemokine and the ligand can be calculated as an IC_{50} (the concentration needed to cause 50% inhibition in signaling) or IC_{90} (at 90% inhibition).

[00642] In vitro cell migration assays can be performed (but are not limited to this format) using the 96-well microchamber (called ChemoTX™). The ChemoTX™ system is well known to those skilled in the art as a type of chemotactic/cell migration instrument. In this assay, CCR2-expressing cells (such as THP-1) or CCR9-expressing cells (such as MOLT-4) are first incubated with a compound of interest, such as a possible CCR2 or CCR9 antagonist, respectively, at increasing concentrations. Typically, fifty thousand cells per well are used, but the amount can range from 10^3-10^6 cells per well. The chemokine ligand (for example, CCR2 ligand MCP-1, typically at 0.1 nM (but can range from 5-100 nM); or CCR9 ligand TECK, typically at

50 nM (but can range from 5-100 nM)), is placed at the lower chamber and the migration apparatus is assembled. Twenty microliters of test compound-treated cells are then placed onto the membrane. Migration is allowed to take place at 37 °C for a period of time, typically 1.5 hours for CCR2 or 2.5 hours for CCR9. At the end of the incubation, the number of cells that migrated across the membrane into the lower chamber is then quantified. The efficacy of a compound as an inhibitor of chemokine-mediated cell migration is calculated as an IC_{50} (the concentration needed to reduce cell migration by 50%) or IC_{90} (for 90% inhibition).

[00643] In vivo efficacy models for human IBD

[00644] T cell infiltration into the small intestine and colon have been linked to the pathogenesis of human inflammatory bowel diseases which include Coeliac disease, Crohn's disease and ulcerative colitis. Blocking trafficking of relevant T cell populations to the intestine is believed to be an effective approach to treat human IBD. CCR9 is expressed on gut-homing T cells in peripheral blood, elevated in patients with small bowel inflammation such as Crohn's disease and Coeliac disease. CCR9 ligand TECK is expressed in the small intestine. It is thus believed that this ligand-receptor pair plays a role in IBD development by mediating migration of T cells to the intestine. Several animal models exist and can be used for evaluating compounds of interest, such as potential CCR9 antagonists, for an ability to affect such T cell migration and/or condition or disease, which might allow efficacy predictions of antagonists in humans.

[00645] *Animal models with pathology similar to human ulcerative colitis*

[00646] A murine model described by Panwala and coworkers (Panwala, et al., *J Immunol.*, 161(10):5733-44 (1998)) involves genetic deletion of the murine multi-drug resistant gene (MDR). MDR knockout mice (MDR-/-) are susceptible to developing a severe, spontaneous intestinal inflammation when maintained under specific pathogen-free facility conditions. The intestinal inflammation seen in MDR-/- mice has a pathology similar to that of human inflammatory bowel disease (IBD) and is defined by Th1 type T cells infiltration into the lamina propria of the large intestine.

[00647] Another murine model was described by Davidson *et al., J. Exp. Med.*, 184(1):241-51(1986). In this model, the murine IL-10 gene was deleted and mice rendered deficient in the production of interleukin 10 (IL-10-/-). These mice develop a chronic inflammatory bowel disease (IBD) that predominates in the colon and shares histopathological features with human IBD.

[00648] Another murine model for IBD has been described by *Powrie et al., Int Immunol.*, 5(11):1461-71 (1993), in which a subset of CD4+ T cells (called CD45RB(high)) from immunocompetent mice are purified and adoptively transferred into immunodeficient mice (such as C.B-17 scid mice). The animal restored with the CD45RBhighCD4+ T cell population developed a lethal wasting disease with severe mononuclear cell infiltrates in the colon, pathologically similar with human IBD.

[00649] *Murine models with pathology similar to human Crohn's disease*

[00650] The TNF ARE(-/-) model. The role of TNF in Crohn's disease in human has been demonstrated more recently by success of treatment using anti-TNF alpha antibody by Targan *et al., N. Engl. J. Med.*, 337(15):1029-35 (1997). Mice with aberrant production of TNF-alpha due to genetic alteration in the TNF gene (ARE-/-) develop Crohn's-like inflammatory bowel diseases (*see* Kontoyiannis *et al., Immunity*, 10(3):387-98 (1999)).

[00651] The SAMP/yit model. This is model described by Kosiewicz *et al., J. Clin. Invest.*, 107(6):695-702 (2001). The mouse strain, SAMP/Yit, spontaneously develops a chronic inflammation localized to the terminal ileum. The resulting ileitis is characterized by massive infiltration of activated T lymphocytes into the lamina propria, and bears a remarkable resemblance to human Crohn's disease.

[00652] **Examples of in vitro assays**

[00653] *Reagents*

[00654] THP-1 cells and MOLT-4 cells were obtained from the American Type Culture Collection (Manassas, VA) and cultured in RPMI tissue culture medium supplemented with 10% fetal calf serum (FCS) in a humidified 5% CO_2 incubator at 37 °C. Recombinant human chemokine proteins MCP-1 and

TECK were obtained from R&D Systems (Minneapolis, MN). ^{125}I-labeled MCP-1 protein was obtained from Amersham (Piscataway, NJ). ChemoTX® chemotaxis microchambers were purchased from Neuro Probe (Gaithersburg, MD). CyQUANT® cell proliferation kits were purchased from Molecular Probes (Eugene, Oregon). Calcium indicator dye Fluo-4 AM was purchased from Molecular Devices (Mountain View, CA).

[00655] *Conventional migration assay*

[00656] Conventional migration assay was used to determine the efficacy of potential receptor antagonists in blocking migration mediated through chemokines (such as CCR2 or CCR9). This assay was routinely performed using the ChemoTX® microchamber system with a 5-μm pore-sized polycarbonate membrane. To begin such an assay, chemokine expressing cells (such as THP-1 cells for CCR2 assay or MOLT-4 cells for CCR9 assay) were harvested by centrifugation of cell suspension at 1000 RPM on a GS-6R Beckman centrifuge. The cell pellet was resuspended in chemotaxis buffer (HBSS with 0.1% BSA) at $10x10^6$ cells/mL for CCR2 assay ($5 x10^6$ cells/mL for CCR9 assay). Test compounds at desired concentrations were prepared from 10 mM stock solutions by serial dilutions in chemotaxis buffer. An equal volume of cells and compounds were mixed and incubated at room temperature for 15 minutes. Afterwards, 20 μL of the mixture was transferred onto the porous membrane of a migration microchamber, with 29 μL of chemokine ligand (0.1 nM chemokine MCP-1 protein for CCR2 assay or 50 nm chemokine TECK protein for CCR9 assay) placed at the lower chamber. Following an incubation at 37 °C (90-minute for CCR2;150-minute for CCR9), during which cells migrated against the chemokine gradient, the assay was terminated by removing the cell drops from atop the filter. To quantify cells migrated across the membrane, 5 μL of 7X CyQUANT® solution was added to each well in the lower chamber, and the fluorescence signal measured on a Spectrafluor Plus fluorescence plate reader (TECAN, Durham, NC). The degree of inhibition was determined by comparing migration signals between compound-treated and untreated cells. IC_{50} calculation was further

performed by non-linear squares regression analysis using Graphpad Prism (Graphpad Software, San Diego, CA).

[00657] *BiRAM Assay*

[00658] The primary screen to identify chemokine antagonists was carried out using BiRAM assay (WO 02101350, US2004023286), which detects potential hits by their ability to activate cell migration under inhibitory chemokine concentration. To begin such an assay, chemokine expressing cells (such as THP-1 cells for CCR2 assay or MOLT-4 cells for CCR9 assay) were harvested by centrifugation of cell suspension at 1000 RPM on a GS-6R Beckman centrifuge. The cell pellet was resuspended in chemotaxis buffer (HBSS/0.1% BSA) at 10 x 10^6 cells/mL for CCR2 assay (5 x 10^6 cells/mL for CCR9 assay). Twenty-five microliters of cells was mixed with an equal volume of a test compound diluted to 20 μM in the same buffer. Twenty microliters of the mixture was transferred onto the filter in the upper chemotaxis chamber, with 29 μL of chemokine solution containing chemokine ligand (100 nM chemokine MCP-1 and MIP-1α protein for CCR2 assay or 500 nm chemokine TECK protein for CCR9 assay) was placed in the lower chamber. Following an incubation at 37 °C (90-minute for CCR2; 150-minute for CCR9), the assay was terminated by removing the cell drops from atop the filter. To quantify cells migrated across the membrane, 5 μL of 7X CyQUANT® solution was added to each well in the lower chamber, and the fluorescence signal measured on a Spectrafluor Plus fluorescence plate reader (TECAN, Durham, NC).

[00659] For selection of potential hits, the level of migration activation was calculated as a RAM index-the ratio between the signal of a particular well and the median signal of the whole plate. Compounds with a RAM index of greater than 1.5 for CCR2 assay (1.8 for CCR9 assay) were regarded as RAM positive, and were selected for IC_{50} determinations in conventional functional assays.

[00660] *Calcium flux assay*

[00661] Calcium flux assay measures an increase in intracellular calcium following ligand-induced receptor activation. In the screen of chemokine antagonists, it was used as a secondary assay carried out on a FLIPR® machine (Molecular Devices, Mountain View, CA). To begin an assay, chemokine expressing cells (such as THP-1 cells for CCR2 assay or MOLT-4 cells for CCR9 assay) were harvested by centrifugation of cell suspension, and resuspended to 1.5 x 10^6 cells/mL in HBSS (with 1% fetal calf serum). Cells were then labeled with a calcium indicator dye Fluo-4 AM for 45 minutes at 37 °C with gentle shaking. Following incubation, cells were pelletted, washed once with HBSS and resuspended in the same buffer at a density of 1.6 x 10^6 cells/mL. One hundred microliters of labeled cells were mixed with 10 µL of test compound at the appropriate concentrations on an assay plate. Chemokine protein (MCP-1 at a final concentration of 0.1 nM for CCR2 assay or TECK at a final concentration of 25 nM for CCR9 assay) to activate the receptor. The degree of inhibition was determined by comparing calcium signals between compound-treated and untreated cells. IC_{50} calculations were further performed by non-linear squares regression analysis using Graphpad Prism (Graphpad Software, San Diego, CA).

[00662] **Ligand binding assay**

[00663] Ligand binding assay was used to determine the ability of potential CCR2 antagonists to block the interaction between CCR2 and its ligand MCP-1. CCR2 expressing THP-1 cells were centrifuged and resuspended in assay buffer (20 mM HEPES pH 7.1, 140 mM NaCl, 1 mM $CaCl_2$, 5 mM $MgCl_2$, and with 0.2% bovine serum albumin) to a concentration of 2.2 x 10^5 cells/mL. Binding assays were set up as follows. First, 0.09 mL of cells (1 x 10^5 THP-1 cells/well) was added to the assay plates containing the compounds, giving a final concentration of ~2-10 µM each compound for screening (or part of a dose response for compound IC_{50} determinations). Then 0.09 mL of ^{125}I labeled MCP-1 (obtained from Amersham; Piscataway, NJ) diluted in assay buffer to a final concentration of ~50 pM, yielding ~30,000 cpm per well, was added, the plates sealed and incubated for approximately 3 hours at 4 °C on a shaker platform. Reactions were aspirated onto GF/B

glass filters pre-soaked in 0.3% polyethyleneimine (PEI) solution, on a vacuum cell harvester (Packard Instruments; Meriden, CT). Scintillation fluid (50 µL; Microscint 20, Packard Instruments) was added to each well, the plates were sealed and radioactivity measured in a Top Count scintillation counter (Packard Instruments). Control wells containing either diluent only (for total counts) or excess MCP-1 (1 µg/mL, for non-specific binding) were used to calculate the percent of total inhibition for compound. The computer program Prism from GraphPad, Inc. (San Diego, Ca) was used to calculate IC_{50} values. IC_{50} values are those concentrations required to reduce the binding of labeled MCP-1 to the receptor by 50%.

[00664] Discovery of chemokine antagonists

[00665] The discovery of chemokine antagonists was carried out in two steps: First, BiRAM assay was used to screen a compound library in a high-throughput manner. The assay detected compounds by their ability to cause a positive migration signal under BiRAM condition. Secondly, BiRAM positive compounds were tested to determine their IC_{50} values using the conventional migration, calcium flux assays and ligand binding assays.

[00666] For instance, in a screen of approximately 100,000 compounds, 2000 individual wells representing approximately 2% of total compounds showed a desired RAM index (greater than 1.5 for CCR2; greater than 1.8 for CCR9). These compounds were cheery-picked and retested in duplicate wells by RAM assay. A total of 156 compounds were confirmed BiRAM positives.

[00667] Since a BiRAM positive signal indicates only the presence of a receptor antagonist and not how strongly it blocks receptor functions, the BiRAM positive compounds were further tested for potency in conventional migration, calcium flux and ligand binding assays. IC_{50} determinations on this subset discovered several compounds with an IC_{50} less than 1 µM and that did not inhibit other chemokine receptors examined at significant levels.

[00668] In Vivo Efficacy

[00669] A 17-day study of type II collagen-induced arthritis is conducted to evaluate the effects of a modulator on arthritis-induced clinical ankle

swelling. Rat collagen-induced arthritis is an experimental model of polyarthritis that has been widely used for preclinical testing of numerous anti-arthritic agents (see Trentham et al., *J. Exp. Med.*, **146(3):**857-868 (1977), Bendele et al., *Toxicologic Pathol.*, **27:**134-142 (1999), Bendele et al., *Arthritis Rheum.*, **42:**498-506 (1999)). The hallmarks of this model are reliable onset and progression of robust, easily measurable polyarticular inflammation, marked cartilage destruction in association with pannus formation and mild to moderate bone resorption and periosteal bone proliferation.

[00670] Female Lewis rats (approximately 0.2 kilograms) are anesthetized with isoflurane and injected with Freund's Incomplete Adjuvant containing 2 mg/mL bovine type II collagen at the base of the tail and two sites on the back on days 0 and 6 of this 17-day study. The test modulator is dosed daily by sub-cutaneous injection from day 9 to day 17 at a dose of 100 mg/kg and a volume of 1 mL/kg in the following vehicle (24.5 % Cremaphore EL, 24.5% common oil, 1% Benzylalcohol and 50% Distilled water). Caliper measurements of the ankle joint diameter are taken daily, and reducing joint swelling is taken as a measure of efficacy.

[00671] The MDR1a-knockout mice, which lack the P-glycoprotein gene, spontaneously develop colitis under specific pathogen-free condition. The pathology in these animals has been characterized as Th1-type T cell-mediated inflammation similar to ulcerative colitis in humans. Disease normally begins to develop at around 8-10 weeks after birth. However the ages at which disease emerges and the ultimate penetrance level often vary considerably among different animal facilities.

[00672] In a study using the MDR1a-knockout mice, a CCR9 antagonist is evaluated by prophylactic administration for its ability to delay disease onset. Female mice (n=34) are dosed with 50 mg/kg twice a day by subcutaneous injections for 14 consecutive weeks starting at age 10 weeks. The study is evaluated for IBD-associated growth retardation.

[00673] *Evaluation of a test modulator in a rat model of thioglycollate-induced peritoneal inflammation*

[00674] A 2-day study of thioglycollate-induced inflammation is conducted to evaluate the effects of the test modulator. The hallmarks of this model are reliable onset and progression of robust, easily measurable inflammatory cellular infiltrate. For the induction of inflammatory peritonitis in Lewis rats, Brewer-Thioglycollate (1.0 mL, 4 % solution in distilled water) is injected intra peritoneal (i.p.). Before this injection, the treatment group received test modulator or vehicle and the control group received the same volume of PBS as i.p. injection. After 2 days, a peritoneal lavage ias performed with ice-cold PBS containing 1 mM EDTA. The recovered cells are counted with a cell counter (Coulter Counter; Coulter Pharmaceutical, Palo Alto, CA) and monocytes/macrophages were identified by flow cytometry using light-scatter properties.

[00675] *Evaluation of a test modulator in a mouse model of bacterial infection*

[00676] A 1-day study of streptococcus *pneumoniae* infection is conducted to evaluate the effects of the test modulator. The model measures bacterial infection and spread in an animal following pulmonary infection with live bacterial cultures, measured by inflammatory cellular infiltrate, and assessment of bacterial burden. C57/B6 mice are inoculated intra nasally with LD50 400 CFU at day 0. Groups are either test modulator or vehicle control treated 1 day prior to bacterial inoculation and twice daily throughout the study. Bacterial burden is measured at 24 hours by plating serial dilutions of homogenized lung tissue on agar plates and counting colonies.

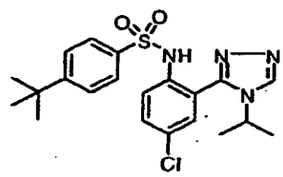
[00677] Pharmacologics to be used in conjunction with CCR2 compounds

[00678] Pharmacological agents that can be used in conjunction with the CCR2 antagonists of the current invention include those used for the treatments of atherosclerosis, restenosis, multiple sclerosis, pulmonary fibrosis, inflammatory bowel disease, rheumatoid arthritis, graft-versus-host disease, renal fibrosis, psoriasis, transplantation rejection, obesity, diabetes, hypercholesterolemia and cancer.

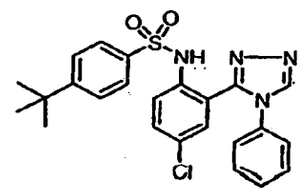
[00679] In the tables below, structures and activity are provided for representative compounds described herein. Activity is provided as follows for either or both of the chemotaxis assay and/or calcium mobilization assays, described above.

[00680] **Table 3: Compounds with CCR9 activity in one of the chemotaxis, binding or calcium mobilization assays, with IC50 < 1000 nM**

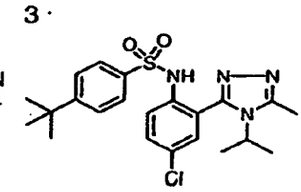
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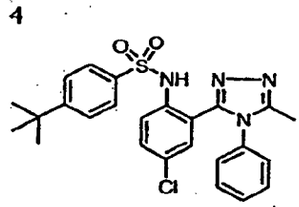
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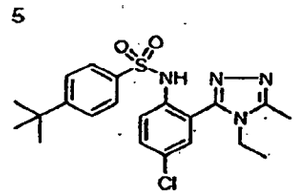
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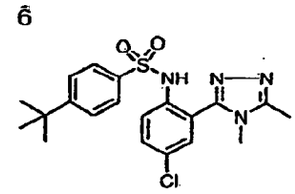
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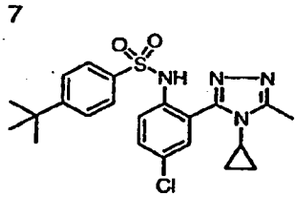
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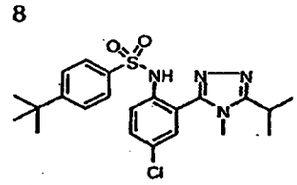
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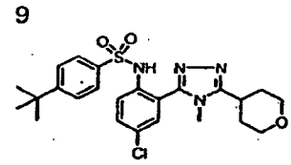
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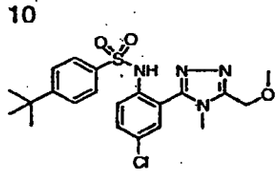
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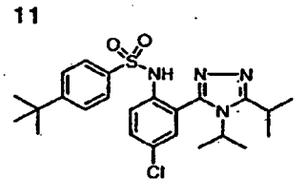
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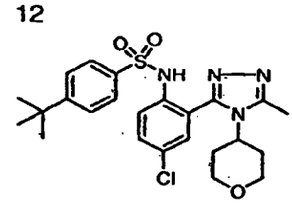
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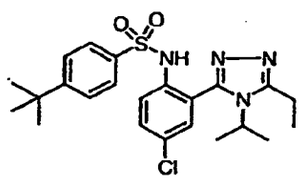
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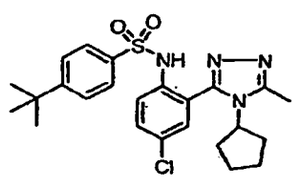


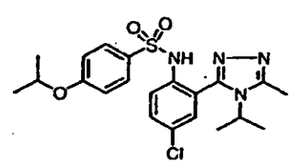
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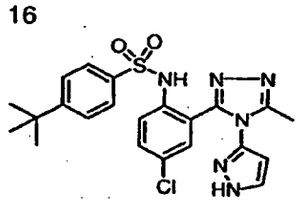
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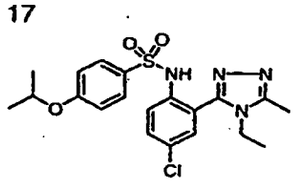




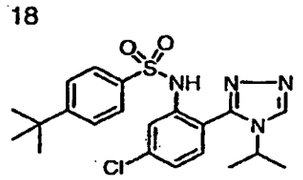
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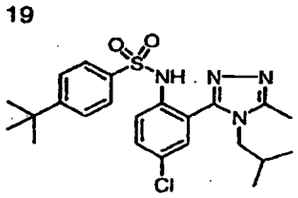
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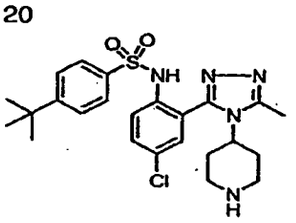
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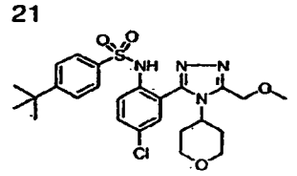
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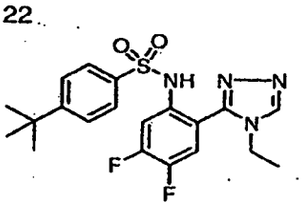
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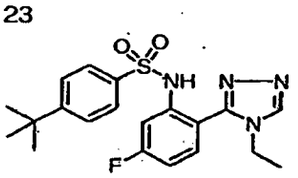
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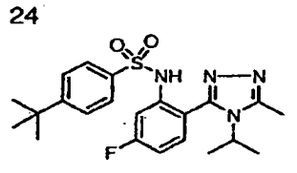
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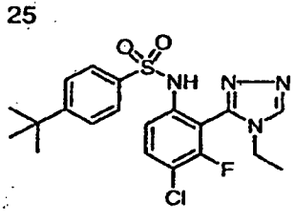
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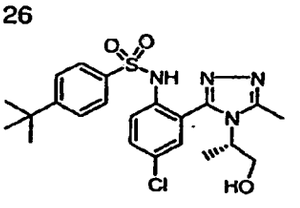
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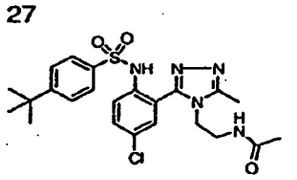
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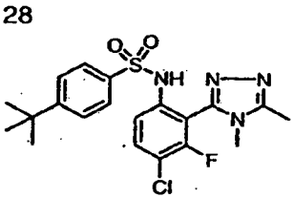
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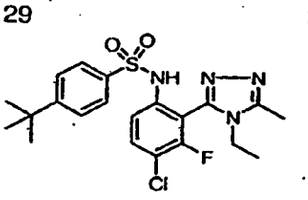
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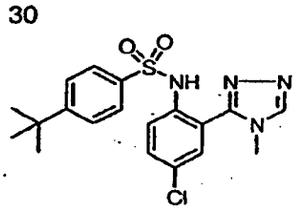
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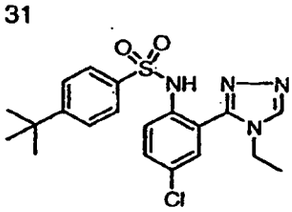
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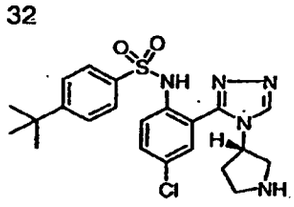
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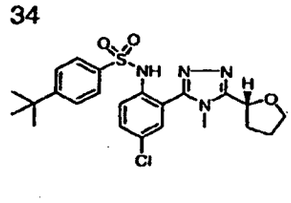
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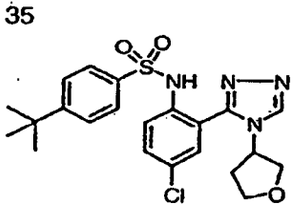
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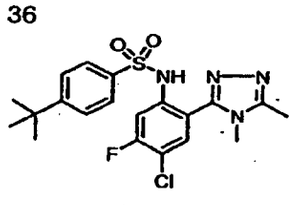
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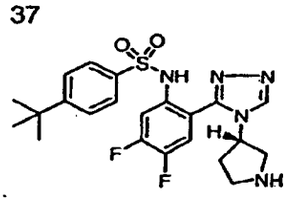
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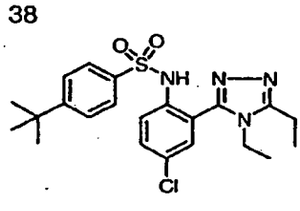
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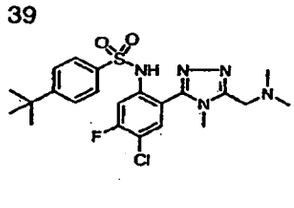
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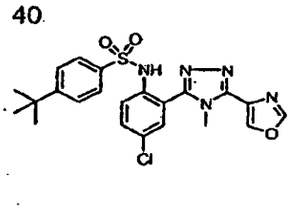
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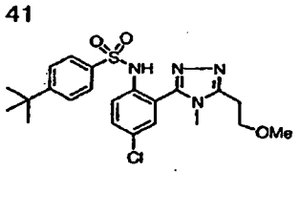
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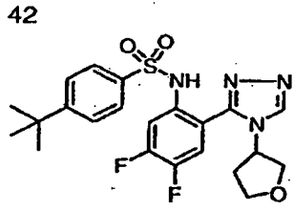
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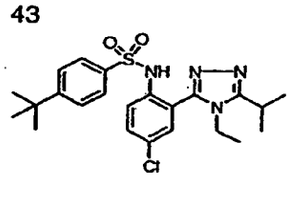
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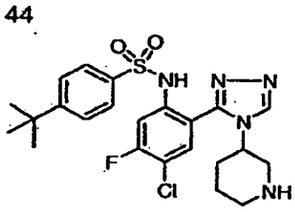
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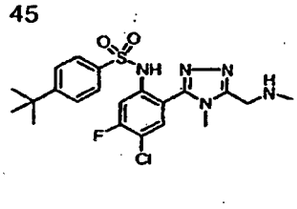
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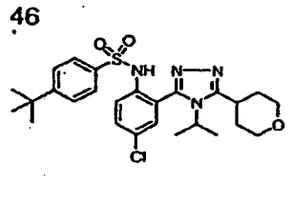
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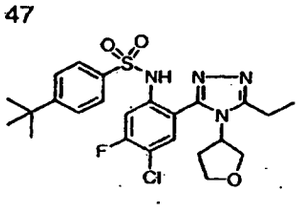
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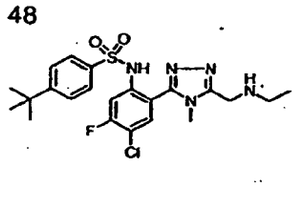
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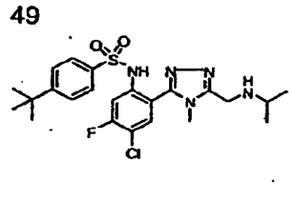
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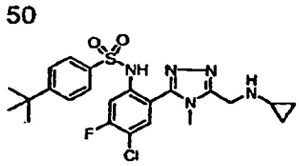


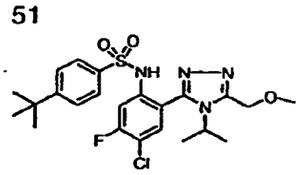
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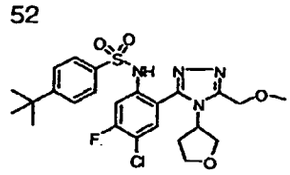


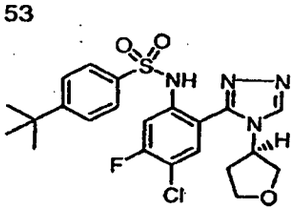
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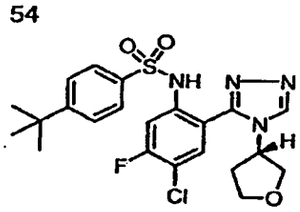


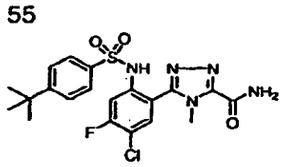
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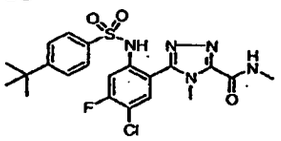
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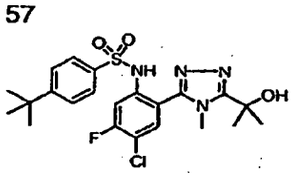
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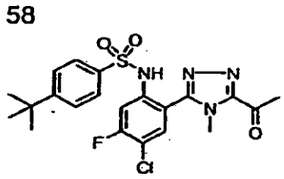
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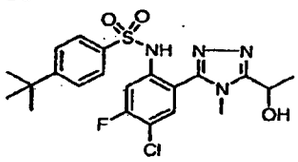
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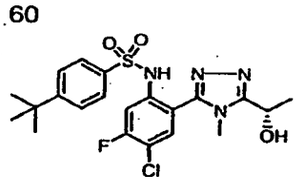
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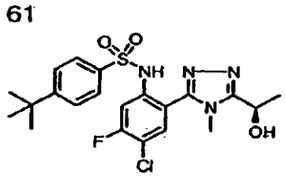
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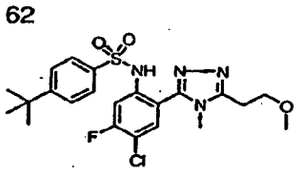
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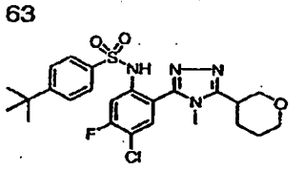
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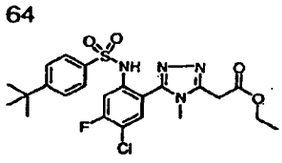
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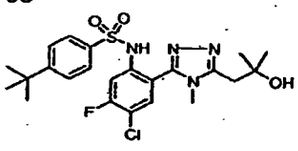
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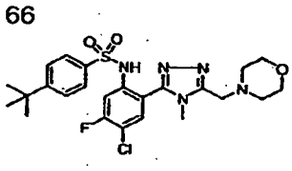
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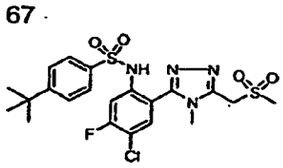
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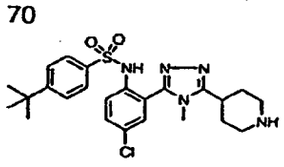
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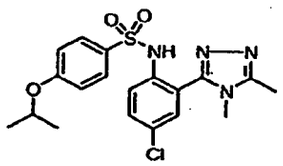
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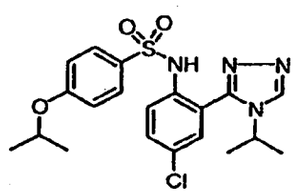
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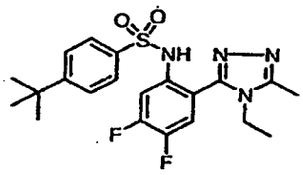
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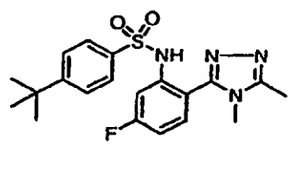




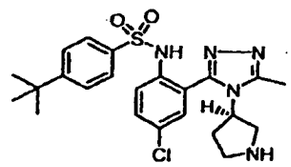
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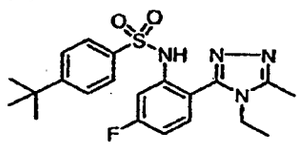
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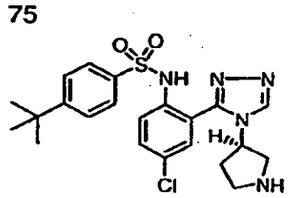
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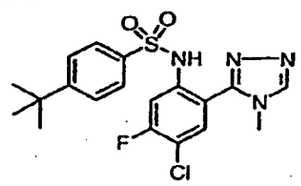
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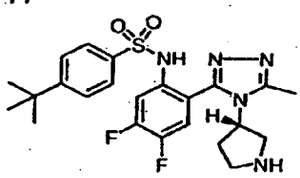
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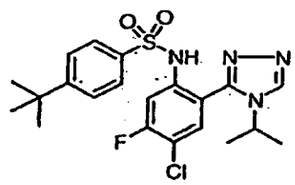
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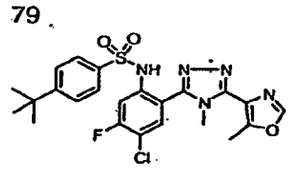
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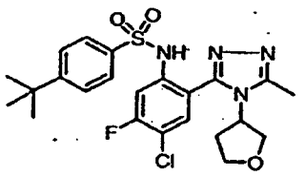
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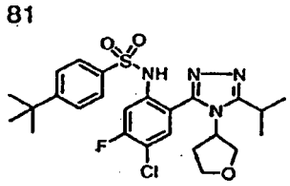
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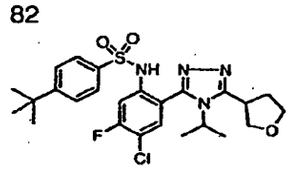
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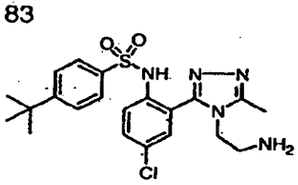
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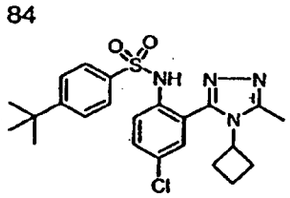
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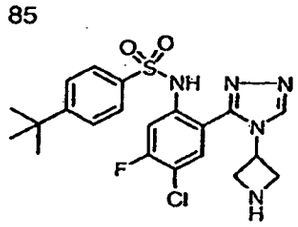
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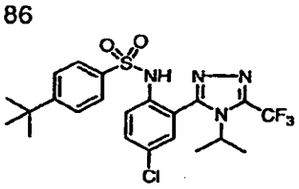
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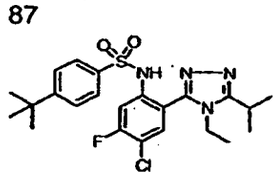
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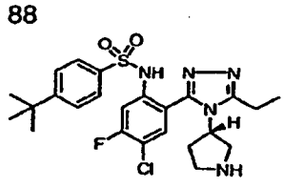
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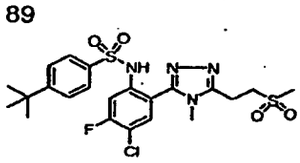
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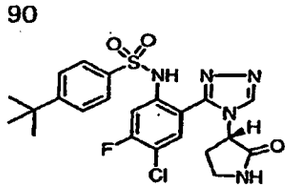
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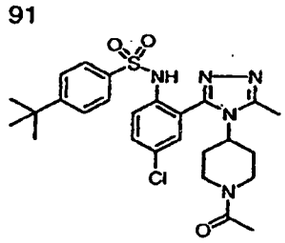
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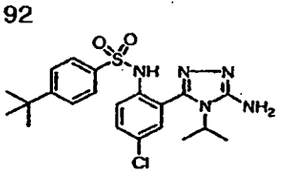
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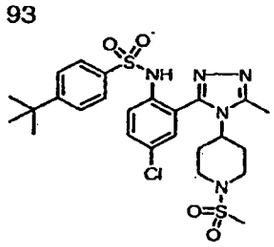
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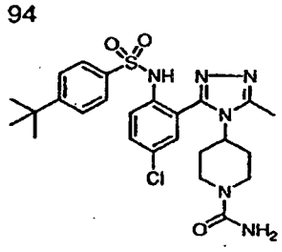
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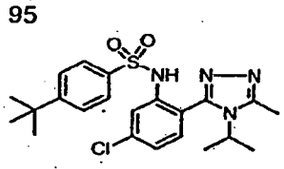
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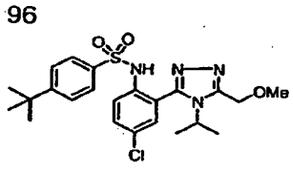
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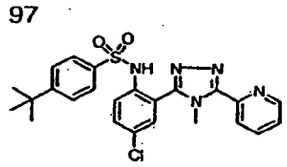
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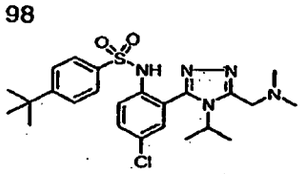
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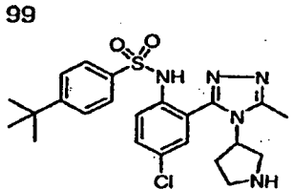
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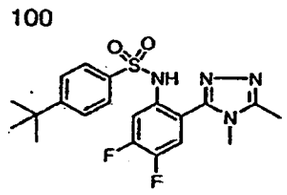
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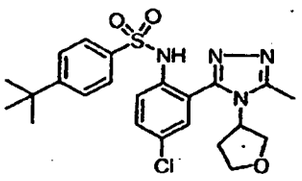
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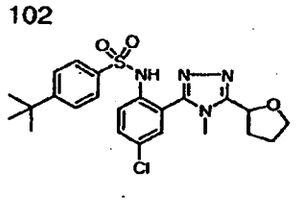
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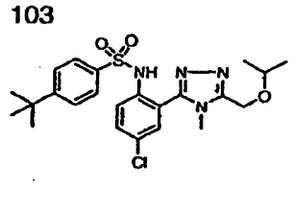
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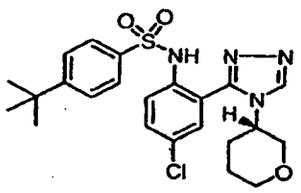
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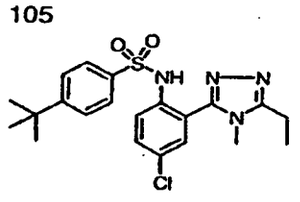
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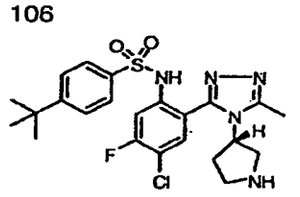
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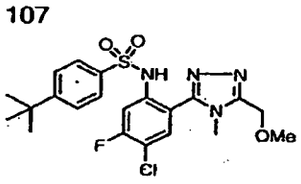
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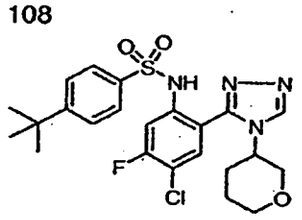
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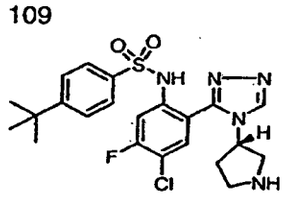
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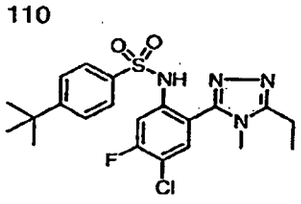
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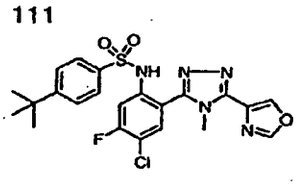
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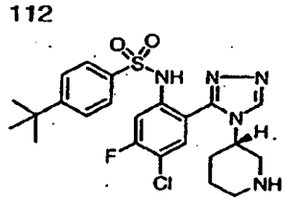
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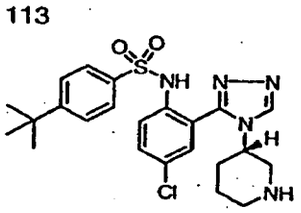
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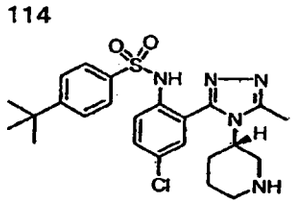
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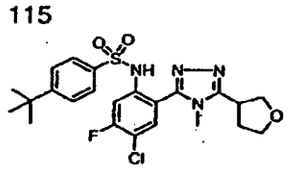
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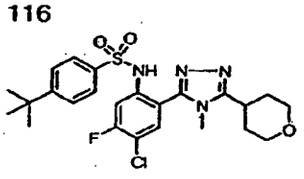
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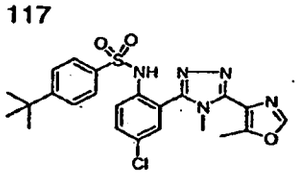
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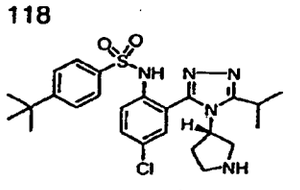
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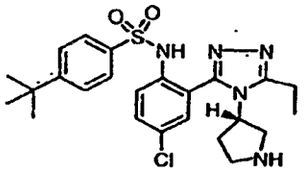
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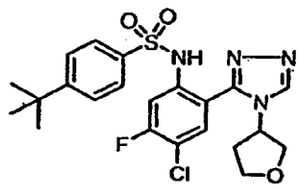


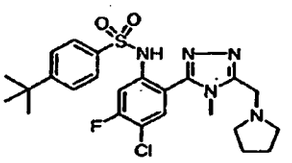
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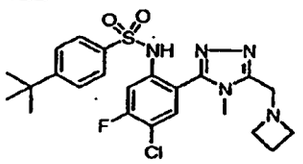
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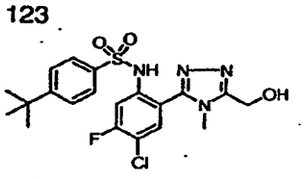




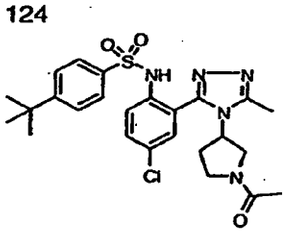
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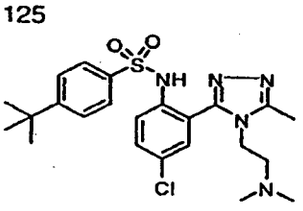
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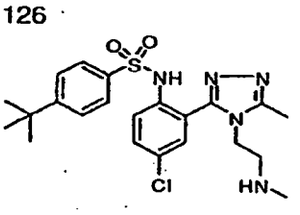
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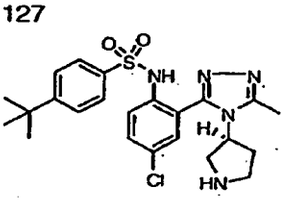
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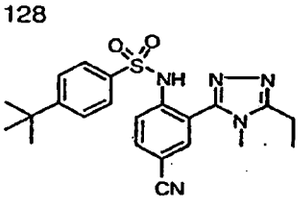
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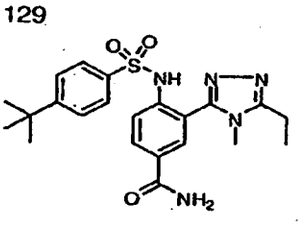
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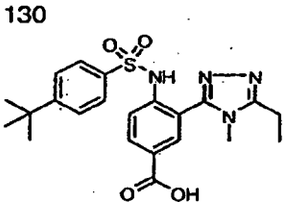
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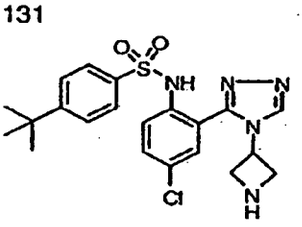
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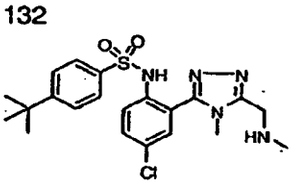
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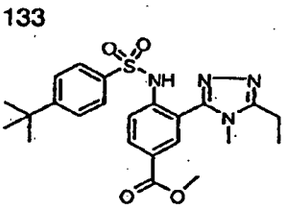
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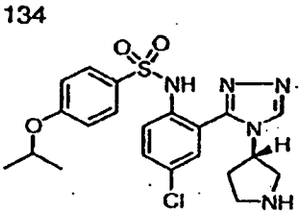
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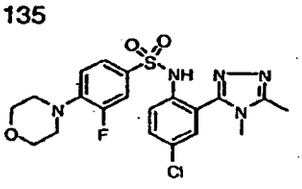
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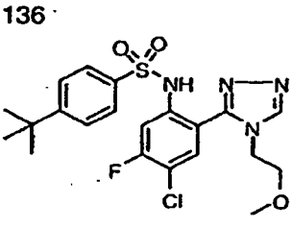
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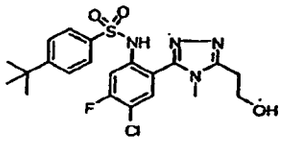
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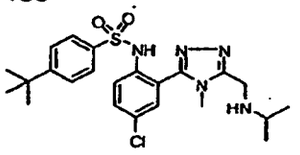
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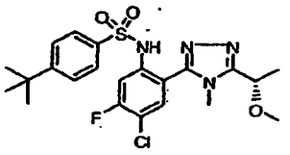
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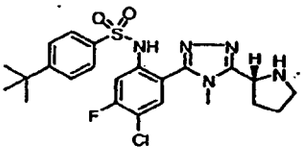
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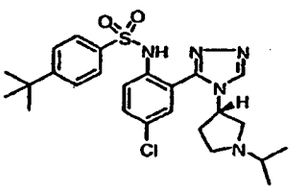
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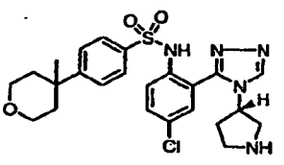
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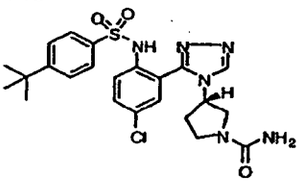
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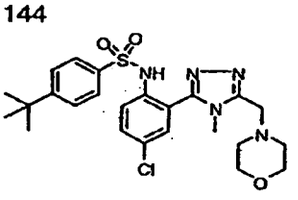
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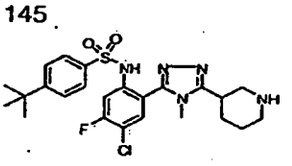
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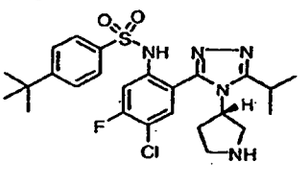
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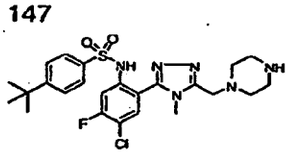
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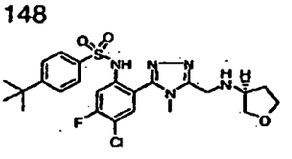
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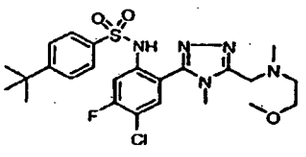
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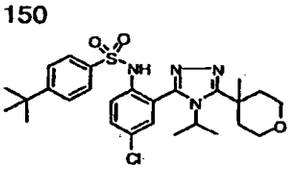
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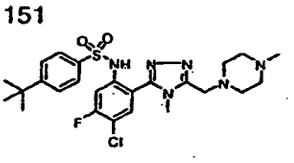
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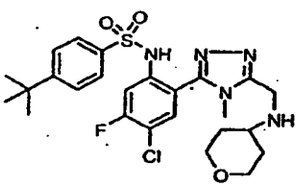
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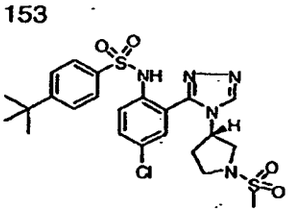
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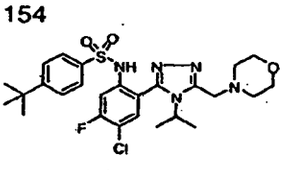
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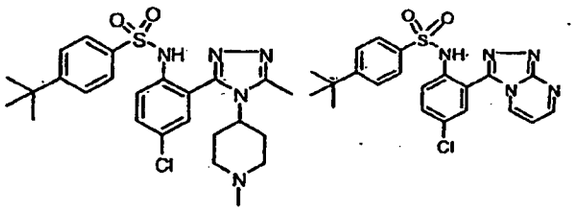


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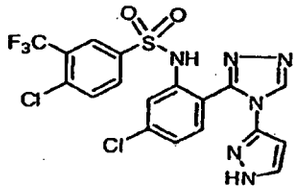
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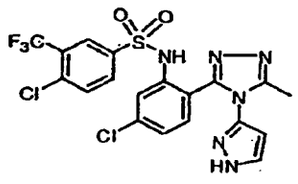


[00681] Table 4: Compounds with CCR2 activity in one of the chemotaxis, binding or calcium mobilization assays, with IC50 < 1000 nM

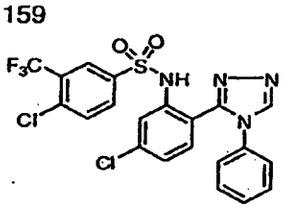
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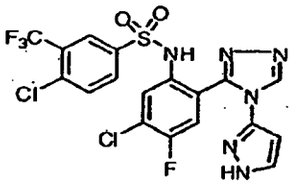
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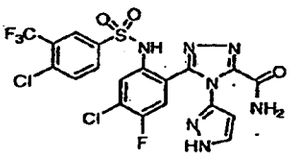
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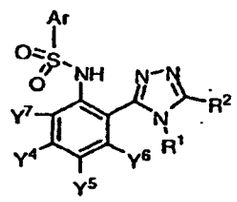
161



[00682] It is therefore intended that the foregoing detailed description be regarded as illustrative rather than limiting, and that it be understood that it is the following claims, including all equivalents, that are intended to define the spirit and scope of this invention.

CLAIMS

1. A compound of the formula (I), or a salt thereof:



(I)

where

Ar is selected from the group consisting of substituted or unsubstituted C_{6-10} aryl and substituted or unsubstituted 5- to 10-membered heteroaryl;

Y^4, Y^5, Y^6, and Y^7 are each independently selected from the group consisting of hydrogen, halogen, -CN, $-C(O)R^{15}$, $-CO_2R^{15}$, $-C(O)NR^{15}R^{16}$, $-OR^{15}$, $-OC(O)R^{15}$, $-OC(O)NR^{15}R^{16}$, $-SR^{15}$, $-S(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2NR^{15}R^{16}$, $-NO_2$, $-NR^{15}R^{16}$, $-NR^{15}C(O)R^{16}$, $-NR^{15}C(O)OR^{16}$, $-NR^{15}S(O)_2R^{16}$, $-NR^{15}C(O)NR^{16}R^{17}$, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl;

R^{15}, R^{16} and R^{17} are each independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl; and

R^{15} and R^{16}, R^{16} and R^{17} or R^{15} and R^{17} may, together with the atoms to which they are attached, form a substituted or unsubstituted 5-, 6-, or 7-membered ring;

R^1 is selected from the group consisting of hydrogen, $-C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2NR^7R^8$, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 3- to 10-membered heterocyclyl,

substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl;

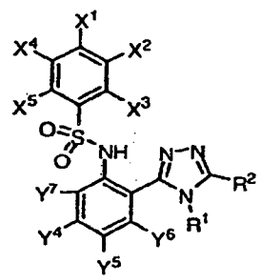
R^2 is selected from the group consisting of hydrogen, halogen, -CN, -$C(O)R^7$, -CO_2R^7, -$C(O)NR^7R^8$, -OR^7, -$OC(O)R^7$, -$OC(O)NR^7R^8$, -SR^7, -$S(O)R^7$, -$S(O)_2R^7$, -$S(O)_2NR^7R^8$, -NO_2, -NR^7R^8, -$NR^7C(O)R^8$, -$NR^7C(O)OR^8$, -$NR^7S(O)_2R^8$, -$NR^7C(O)NR^8R^9$, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl;

R^7, R^8, and R^9 are each independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl;

R^7 and R^8, R^8 and R^9 or R^7 and R^9 may, together with the atoms to which they are attached, form a substituted or unsubstituted 5-, 6-, or 7-membered ring; and

where R^1 and R^2 may, together with the atoms to which they are attached, form a substituted or unsubstituted 5-, 6-, or 7-membered ring.

2. The compound of claim 1, or a salt thereof, of the formula (II):



(II)

where

X^1, X^2, X^3, X^4, and X^5 are each independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted C_{1-8} alkyl,

substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, -CN, -NO_2, -$C(O)R^{18}$, -CO_2R^{18}, -$C(O)NR^{18}R^{19}$, –OR^{18}, -$OC(O)R^{19}$, -$OC(O)NR^{18}R^{19}$, -NO_2, -$NR^{18}C(O)R^{19}$, -$NR^{18}C(O)NR^{19}R^{20}$, -$NR^{18}R^{19}$, -$NR^{18}CO_2R^{19}$, -$NR^{18}S(O)_2R^{19}$, -SR^{18}, -$S(O)R^{18}$, -$S(O)_2R^{18}$, -$S(O)_2NR^{18}R^{19}$, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl;

R^{18}, R^{19} and R^{20} are each independently selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted C_{2-8} alkenyl, substituted or unsubstituted C_{2-8} alkynyl, substituted or unsubstituted C_{6-10} aryl, substituted or unsubstituted 5- to 10-membered heteroaryl, and substituted or unsubstituted 3- to 10-membered heterocyclyl; and

R^{18} and R^{19}, R^{19} and R^{20} or R^{18} and R^{20} may, together with the atoms to which they are attached, form a substituted or unsubstituted 5-, 6-, or 7-membered ring.

3. The compound of claim 2, or a salt thereof, where

X^1 is selected from the group consisting of halogen, substituted or unsubstituted C_{1-8} alkyl, –OR^{18}, -$NR^{18}R^{19}$, and substituted or unsubstituted 3- to 10-membered heterocyclyl;

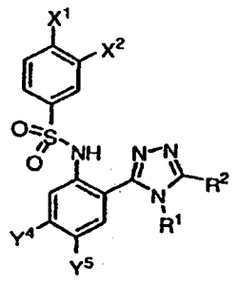
Y^7 is hydrogen;

Y^4, Y^5, and Y^6 are each independently selected from the group consisting of hydrogen, halogen, -CN, -CO_2R^{15}, -$C(O)NR^{15}R^{16}$;

R^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl; and

R^2 is selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl.

4. The compound of claim 2, or a salt thereof, of the formula (III):



(III)

where at least one of X^1 and X^2 is other than hydrogen and at least one of Y^4 and Y^5 is other than hydrogen.

5. The compound of claim 4, or a salt thereof, of the formula (III):

where X^2 is hydrogen or halogen; Y^4 is hydrogen, halogen or -CN; and X^1 and Y^5 are other than hydrogen.

6. The compound of claim 5, or a salt thereof, where

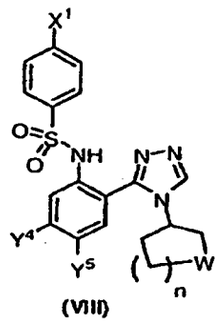
X^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, $-OR^{18}$, $-NR^{18}R^{19}$, and substituted or unsubstituted 3- to 10-membered heterocyclyl;

Y^5 is selected from the group consisting of halogen, -CN, $-CO_2R^{15}$, and $-C(O)NR^{15}R^{16}$;

R^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl; and

R^2 is hydrogen.

7. The compound of claim 6, or a salt thereof, of the formula (VIII)



(VIII)

where W is NH or O; and n is 0, 1, or 2.

8. The compound of claim 4, or a salt thereof, where

X^1 is halogen;

X^2 is halogen or $-CF_3$;

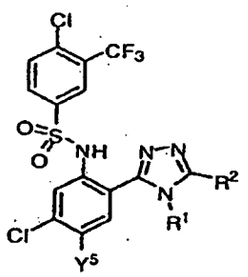
Y^4 is halogen;

Y^5 is hydrogen or halogen;

R^1 is aryl or heteroaryl; and

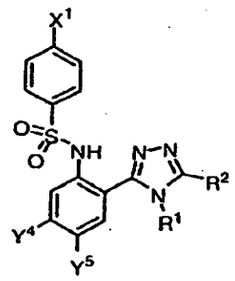
R^2 is hydrogen or substituted or unsubstituted C_{1-8} alkyl.

9. The compound of claim 8, or a salt thereof, of the formula (V):



(V)

10. The compound of claim 2, or a salt thereof, of the formula (IV):



(IV)

where Y^4 is hydrogen or fluoro; and X^1 and Y^5 are other than hydrogen.

11. The compound of claim 10, or a salt thereof, where

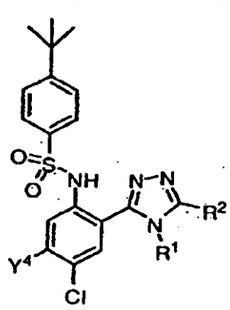
X^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, $-OR^{18}$, $-NR^{18}R^{19}$, and substituted or unsubstituted 3- to 10-membered heterocyclyl;

Y^5 is selected from the group consisting of halogen, -CN, $-CO_2R^{15}$, $-C(O)NR^{15}R^{16}$;

R^1 is selected from the group consisting of substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl; and

R^2 is selected from the group consisting of hydrogen, substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted 3- to 10-membered heterocyclyl, substituted or unsubstituted C_{6-10} aryl, and substituted or unsubstituted 5- to 10-membered heteroaryl.

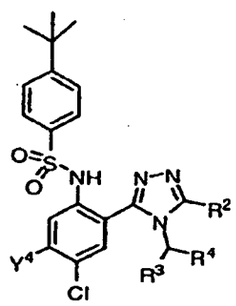
12. The compound of claim 11, or a salt thereof, of the formula (VI):



(VI)

where Y^4 is hydrogen or halogen.

13. The compound of claim 12, or a salt thereof, of the formula (VII):



(VII)

where

Y^4 is hydrogen or halogen; and

R^3 and R^4 are each independently hydrogen, unsubstituted or substituted C_{1-8} alkyl, or R^3 and R^4 together with the carbon which they substitute form a 3-10 member carbocyclic, 4 -10 member heterocyclic, 5-10 member heteroaryl ring or 6-10 membered aryl ring.

14. The compound of claim 13, or salt thereof, where R^2 is hydrogen.

15. The compound of claim 1, selected from the group consisting of

4-tert-butyl-N-(4-chloro-2-(4,5-diisopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-cyclopentyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-cyclopropyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-ethyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-isopropyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(tetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-phenyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-(methoxymethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-isopropyl-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(1H-pyrazol-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(pyridin-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(tetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-methyl-4-phenyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

N-(4-chloro-2-(4-isopropyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)-4-isopropoxybenzenesulfonamide;

N-(2-(3-(2-(4-tert-butylphenylsulfonamido)-5-chlorophenyl)-5-methyl-4H-1,2,4-triazol-4-yl)ethyl)acetamide;

(R)-4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(tetrahydrofuran-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4,5-difluoro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(4-(1-hydroxypropan-2-yl)-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(tetrahydrofuran-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(2-(4-ethyl-4H-1,2,4-triazol-3-yl)-4,5-difluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(2-(4-ethyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4,5-difluoro-2-(4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4,5-diethyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)-3-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-ethyl-4H-1,2,4-triazol-3-yl)-3-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-ethyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-ethyl-5-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-ethyl-5-methyl-4H-1,2,4-triazol-3-yl)-3-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-isobutyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(oxazol-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-((dimethylamino)methyl)-4-methyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-(2-methoxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-(methoxymethyl)-4-(tetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(piperidin-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(piperidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(5-chloro-2-(4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(5-chloro-2-(4-isopropyl-5-(4-methyltetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(5-fluoro-2-(4-isopropyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

N-(4-chloro-2-(4-ethyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)-4-isopropoxybenzenesulfonamide;

ethyl 2-(5-(2-(4-tert-butylphenylsulfonamido)-5-chloro-4-fluorophenyl)-4-methyl-4H-1,2,4-triazol-3-yl)acetate;

5-(2-(4-tert-butylphenylsulfonamido)-5-chloro-4-fluorophenyl)-4-methyl-4H-1,2,4-triazole-3-carboxamide;

5-(2-(4-tert-butylphenylsulfonamido)-5-chloro-4-fluorophenyl)-N,4-dimethyl-4H-1,2,4-triazole-3-carboxamide;

(R)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(1-hydroxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(4-(piperidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(4-(tetrahydro-2H-pyran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(piperidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(piperidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(1-hydroxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-methyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-N-(4-chloro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)-4-isopropoxybenzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-isopropyl-5-(tetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(5-methyloxazol-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-((cyclopropylamino)methyl)-4-methyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-((ethylamino)methyl)-4-methyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(tetrahydro-2H-pyran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-isopropyl-5-(methoxymethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-((methylamino)methyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(methylsulfonylmethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(morpholinomethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(oxazol-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(pyrrolidin-1-ylmethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(tetrahydro-2H-pyran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(tetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-((isopropylamino)methyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(1-hydroxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(2-hydroxy-2-methylpropyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(2-hydroxypropan-2-yl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(2-methoxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(hydroxymethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(methoxymethyl)-4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(methoxymethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

N-(2-(5-(azetidin-1-ylmethyl)-4-methyl-4H-1,2,4-triazol-3-yl)-4-chloro-5-fluorophenyl)-4-tert-butylbenzenesulfonamide;

N-(2-(5-acetyl-4-methyl-4H-1,2,4-triazol-3-yl)-4-chloro-5-fluorophenyl)-4-tert-butylbenzenesulfonamide;

(S)-4-tert-butyl-N-(4,5-difluoro-2-(5-methyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(5-isopropyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(2-(4-ethyl-5-methyl-4H-1,2,4-triazol-3-yl)-4,5-difluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(2-(4-ethyl-5-methyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(piperidin-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-isopropyl-5-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(5-methyloxazol-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-isopropyl-4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-methyl-4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

N-(4-chloro-2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)phenyl)-4-isopropoxybenzenesulfonamide;

N-(4-chloro-2-(4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)-4-isopropoxybenzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(5-ethyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(2-oxopyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-isopropyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-N-(4-chloro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)-4-(4-methyltetrahydro-2H-pyran-4-yl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-cyclobutyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-ethyl-5-isopropyl-4H-1,2,4-triazol-3-yl)-5-fluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-isopropyl-5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(1-methylpiperidin-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(2-(methylsulfonyl)ethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

N-(2-(4-(1-acetylpiperidin-4-yl)-5-methyl-4H-1,2,4-triazol-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide;

N-(2-(4-(2-aminoethyl)-5-methyl-4H-1,2,4-triazol-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide;

N-(2-(4-(azetidin-3-yl)-4H-1,2,4-triazol-3-yl)-4-chloro-5-fluorophenyl)-4-tert-butylbenzenesulfonamide;

(R)-4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)-4,5-difluorophenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-isopropyl-5-(methoxymethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(pyridin-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(tetrahydrofuran-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-((dimethylamino)methyl)-4-isopropyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-(isopropoxymethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-(3-(2-(4-tert-butylphenylsulfonamido)-5-chlorophenyl)-5-methyl-4H-1,2,4-triazol-4-yl)piperidine-1-carboxamide;

4-tert-butyl-N-(4-chloro-2-(4-(2-(dimethylamino)ethyl)-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(1-(methylsulfonyl)piperidin-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-methyl-4-(2-(methylamino)ethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(5-chloro-2-(4-isopropyl-5-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

N-(2-(4-(1-acetylpyrrolidin-3-yl)-5-methyl-4H-1,2,4-triazol-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide;

N-(2-(5-amino-4-isopropyl-4H-1,2,4-triazol-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide;

(R)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(tetrahydrofuran-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(R)-4-tert-butyl-N-(4-chloro-2-(4-(pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-cyano-2-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-(4-tert-butylphenylsulfonamido)-3-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)benzamide;

4-(4-tert-butylphenylsulfonamido)-3-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)benzoic acid;

N-(2-(4-(azetidin-3-yl)-4H-1,2,4-triazol-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-methyl-5-((methylamino)methyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

methyl 4-(4-tert-butylphenylsulfonamido)-3-(5-ethyl-4-methyl-4H-1,2,4-triazol-3-yl)benzoate;

N-(4-chloro-2-(4,5-dimethyl-4H-1,2,4-triazol-3-yl)phenyl)-3-fluoro-4-morpholinobenzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-(2-methoxyethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(2-hydroxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(5-((isopropylamino)methyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(1-methoxyethyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(R)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(pyrrolidin-2-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(4-(1-isopropylpyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-3-(3-(2-(4-tert-butylphenylsulfonamido)-5-chlorophenyl)-4H-1,2,4-triazol-4-yl)pyrrolidine-1-carboxamide;

4-tert-butyl-N-(4-chloro-2-(4-methyl-5-(morpholinomethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(piperidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-(piperazin-1-ylmethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-((tetrahydrofuran-3-ylamino)methyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(5-(((2-methoxyethyl)(methyl)amino)methyl)-4-methyl-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-2-(4-isopropyl-5-(4-methyltetrahydro-2H-pyran-4-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-((4-methylpiperazin-1-yl)methyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-methyl-5-((tetrahydro-2H-pyran-4-ylamino)methyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

(S)-4-tert-butyl-N-(4-chloro-2-(4-(1-(methylsulfonyl)pyrrolidin-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

4-tert-butyl-N-(4-chloro-5-fluoro-2-(4-isopropyl-5-(morpholinomethyl)-4H-1,2,4-triazol-3-yl)phenyl)benzenesulfonamide;

N-(2-(4-(1H-pyrazol-3-yl)-4H-1,2,4-triazol-3-yl)-5-chlorophenyl)-4-chloro-3-(trifluoromethyl)benzenesulfonamide;

4-chloro-N-(5-chloro-2-(5-methyl-4-(1H-pyrazol-3-yl)-4H-1,2,4-triazol-3-yl)phenyl)-3-(trifluoromethyl)benzenesulfonamide;

4-chloro-N-(5-chloro-2-(4-phenyl-4H-1,2,4-triazol-3-yl)phenyl)-3-(trifluoromethyl)benzenesulfonamide;

N-(2-(4-(1H-pyrazol-3-yl)-4H-1,2,4-triazol-3-yl)-5-chloro-4-fluorophenyl)-4-chloro-3-(trifluoromethyl)benzenesulfonamide;

5-(4-chloro-2-(4-chloro-3-(trifluoromethyl)phenylsulfonamido)-5-fluorophenyl)-4-(1H-pyrazol-3-yl)-4H-1,2,4-triazole-3-carboxamide; and

N-(2-([1,2,4]triazolo[4,3-a]pyrimidin-3-yl)-4-chlorophenyl)-4-tert-butylbenzenesulfonamide.

16. A composition comprising a pharmaceutically acceptable carrier and a compound of claim 1.

17. A method for treating a CCR2-mediated condition or disease or a CCR9-mediated condition or disease comprising administering to a subject an effective amount of a compound of any of claims 1-15, or a salt thereof:

18. The method of claim 17, where disease or condition is selected from the group consisting of atherosclerosis, restenosis, multiple sclerosis, inflammatory bowel disease, renal fibrosis, rheumatoid arthritis, obesity, diabetes, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, idiopathic pneumonia syndrome, pulmonary fibrosis, transplantation rejection, graft-versus-host disease, cancer, and neuropathic pain.

19. The method of claim 17, where the administering is oral, parenteral, rectal, transdermal, sublingual, nasal or topical.

20. The method of claim 17, further comprising administering an anti-inflammatory or analgesic agent.

21. A method of modulating CCR2 function in a cell, comprising contacting the cell with a CCR2 modulating amount of the compound of any of claims 1-15.

22. A method of modulating CCR9 function in a cell, comprising contacting the cell with a CCR9 modulating amount of the compound of any of claims 1-15.

23. A method for treating a CCR9-mediated condition or disease comprising administering to a subject an effective amount of the compound of any of claims 1-15.

24. A method for treating a CCR2-mediated condition or disease comprising administering to a subject an effective amount of the compound of any of claims 1-15.

(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL TRATADO DE COOPERACIÓN DE PATENTES (PCT)

(19) Organización Mundial de Propiedad Intelectual
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(57) Resumen: Se proporcionan compuestos (I) que actúan como potentes antagonistas del receptor CCR2 o CCR9. Las pruebas en animales demuestran que estos compuestos son útiles para tratar inflamación, una enfermedad característica para CCR2 y CCR9. Los compuestos son generalmente derivados de aril sulfonamida y son útiles en composiciones farmacéuticas, métodos para el tratamiento de enfermedades mediadas por CCR2, enfermedades mediadas por CCR9, como controles en análisis para la identificación de antagonistas de CCR2 y como controles en análisis para la identificación de antagonistas de CCR9.

TRIAZOLIL FENIL BENCENOSULFONAMIDAS

SOLICITUDES RELACIONADAS

Esta solicitud reivindica prioridad para la solicitud provisional de E.U. Serie No. 60/831,042 presentada en Julio 14 de 2006. La descripción de esta solicitud de prioridad se incorpora en la presente en su totalidad.

INVESTIGACIÓN O DESARROLLO FEDERALMENTE PATROCINADO

La presente invención descrita en la presente se soportó, al menos en parte, por NIH (U19-AI056690-01). El gobierno puede tener ciertos derechos en la invención.

ANTECEDENTES

La presente invención proporciona compuestos, composiciones farmacéuticas que contienen uno o más de esos compuestos o sus sales farmacéuticamente aceptables, que son efectivos para inhibir el enlace o la función de varias quimiocinas a receptores de quimiocina. Como antagonistas o moduladores de receptores de quimiocina, los compuestos y composiciones tienen utilidad en el tratamiento de varias condiciones y enfermedades de trastornos inmunes.

Las quimiocinas, también conocidas como citosinas quimiotácticas, son un grupo de proteínas de bajo peso molecular que se liberan mediante una amplia variedad de células y que tienen una variedad de actividades biológicas. Las quimiocinas atraen varios tipos de células del sistema inmune, tales como macrófagos, células T, eosinófilos,

basófilos y neutrófilos, y hacen que migren desde la sangre hacia varios tejidos linfoides y no linfoides. Median la infiltración de células inflamatorias a sitios de inflamación y son responsables del inicio y perpetuación de muchas enfermedades de inflamación (revisado en Schall, Cytokine, 3:165-183 (1991), Schall et al., Curr. Opin. Immunol., 6:865-873 (1994)).

Además de estimular la quimiotaxis, las quimiocinas pueden inducir otros cambios en células sensibles, incluyendo cambios en la forma de la célula, exocitosis granular, sobre-regulación de integrina, formación de lípidos bioactivos (e.g., leucotrienos), incremento respiratorio repentino asociado con la activación de leucocitos, proliferación celular, resistencia a la inducción de apoptosis y angiogénesis. Por tanto, las quimiocinas son activadores tempranos de la respuesta inflamatoria, ocasionando la liberación del mediador inflamatorio, la quimiotaxis y la extravasación a sitios de infección o inflamación. También son estimulantes de una multitud de procesos celulares que contienen importantes funciones fisiológicas así como consecuencias patológicas.

Las quimiocinas ejercen sus efectos activando los receptores de quimiocina expresados por células sensibles. Los receptores de quimiocina son una clase de receptores acoplados a la proteína G, conocidos también como siete

receptores de transmembrana, encontrados en la superficie de una amplia variedad de tipos celulares tales como leucocitos, células endoteliales, células de músculo liso y células tumorales.

Las quimiocinas y receptores de quimiocina se expresan mediante células renales intrínsecas y células de infiltración durante la inflamación renal (Segerer et al., J. Am. Soc. Nephrol., 11:152-76 (2000); Morii et al., J. Diabetes Complications, 17:11-5 (2003); Lloyd et al., J. Exp. Med., 185:1371-80 (1997); Gonzalez-Cuadrado et al., Clin. Exp. Immunol., 106:518-22 (1996); Eddy & Giachelli, Kidney Int., 47:1546-57 (1995); Diamond et al., Am. J. Physiol., 266:F926-33 (1994)). En humanos, el CCR2 y el ligando MCP-1 se encuentran entre las proteínas expresadas en fibrosis renal y se correlacionan con el grado de infiltración de macrófagos en el intersticio (Yang et al., Zhonghua Yi Xue Za Zhi, 81:73-7 (2001); Stephan et al., J. Urol., 167:1497-502 (2002); Amann et al., Diabetes Care, 26:2421-5 (2003); Dai et al., Chin. Med. J. (Engl), 114:864-8 (2001)). En modelos animales de fibrosis renal, el bloqueo de CCR2 o MCP-1 conduce a una marcada reducción en la severidad de la infamación renal (Kitagawa et al., Am. J. Pathol., 165:237-46 (2004); Wada et al., Am. J. Pathol., 165:237-46 (2004); Shimitzu et al., J. Am. Soc. Nephrol., 14:1496-505 (2003)).

La artritis reumatoide es una enfermedad crónica de

las articulaciones caracterizada por inflamación sinovial que conduce a la destrucción de cartílagos y huesos. Aunque las causas subyacentes de la enfermedad son desconocidas, se cree que los macrófagos y las células T tipo Th-1 juegan un papel clave en el inicio y la perpetuación del proceso inflamatorio crónico (Vervoordeldonk et al., Curr. Rheumatol. Rep., 4:208-17 (2002)).

MCP-1 se encuentra entre las varias quimiocinas, incluyendo MIP-1alfa e IL-8, identificadas en sinovio reumatoide (Villiger et al., J. Immunol., 149:722-7 (1992); Scaife et al., Rheumatology (Oxford), 43:1346-52 (2004); Shadidi et al., Scand. J. Immunol., 57:192-8 (2003); Taylor et al., Arthritis Rheum., 43:38-47 (2000); Tucci et al., Biomed. Sci. Instrum., 34:169-74 (1997)). Los receptores de quimiocina CCR1, CCR2, CCR3 y CCR5 se encuentran sobre-regulados en las articulaciones de ratones artríticos (Plater-Zyberk et al., Immunol. Lett., 57:117-20 (1997). El bloqueo de la actividad de MCP-1 utilizando un antagonista CCR2 o un anticuerpo contra MCP-1 ha mostrado eficacia en la reducción de la inflamación de articulaciones en modelos experimentales de artritis reumatoide (Gong et al., J. Exp. Med., 186:131-7 (1997); Ogata et al., J. Pathol., 182_106-14 (1997)).

La infiltración mediada por el receptor de quimiocina de los macrófagos en los tejidos grasos también

puede contribuir a las complicaciones que surgen de la obesidad, una condición resultante del almacenamiento excesivo de grasa en el cuerpo. La obesidad predispone a los individuos afectados a muchos trastornos, tales como la diabetes no dependiente de insulina, hipertensión, choque y enfermedad de la arteria coronaria. En la obesidad, los tejidos adiposos tienen funciones metabólicas y endocrinas alteradas que conducen a una liberación incrementada de ácidos grasos, hormonas y moléculas pro-inflamatorias. Se cree que los macrófagos en el tejido adiposo son una fuente clave de citosinas pro-inflamatorias incluyendo TNF-alfa, iNOS e IL-6 (Weisberg et al., J. Clin. Invest., 112:1796-808 (2003)). Es probable que la acumulación de macrófagos en el tejido adiposo se encuentre medida por MCP-1 producido por los adipocitos (Christiansen T. et al., Int. J. Obes., (Londres) 2005 Enero 29(1):146-50; Sartipy et al., Proc. Natl. Acad. Sci., EUA., 100:7265-70 (2003)).

El MCP-1 elevado puede inducir la diferenciación de adipocitos y la resistencia a la insulina y contribuye a patologías asociadas con la hiper-insulinemia y la obesidad. MCP-1 se encuentra sobre-expresado en plasma de ratones obesos en comparación con los controles y el adiposo blanco es una fuente principal. El MCP-1 también ha mostrado acelerar la cicatrización de heridas y tiene un efecto angiogénico directo en las células epiteliales y puede jugar

un papel directo en la remodelación del tejido adiposo en la obesidad. (Sartipy P. Loskutoff DJ, Proc. Natl. Acad. Sci., EUA, 100:7265 (2003)).

Los niveles en plasma de MCP-1 se incrementan sustancialmente en ratones con obesidad inducida por la dieta (DIO), y se ha identificado una fuerte correlación entre los niveles de MCP-1 en plasma y el peso corporal. Además, la elevación de MCP-1 inducida por dietas altas en grasas ocasiona cambios en la población de monocitos positiva a CD11b en ratones DIO. (Takahashi K. et al., J. Biol. Chem., 46654 (2003)).

Además, se cree que la inflamación crónica en la grasa juega un papel crucial en el desarrollo de la resistencia a la insulina relacionada con la obesidad (Xu H., et al., J. Clin. Invest., 2003 Diciembre 11 2(12):1821-30). Se ha propuesto que la resistencia a la insulina relacionada con la obesidad es, al menos en parte, una enfermedad inflamatoria crónica iniciada en el tejido adiposo. Muchos genes específicos de la inflamación y macrófagos se encuentran dramáticamente sobre-regulados en tejido adiposo blanco en modelos de ratón de obesidad genética e inducida por dietas altas en grasas (DIO) y esta sobre-regulación precede a un dramático incremento en la insulina circulante.

Se encontraron elevados niveles de expresión de CCR2 y proteína 1 quimioatrayente de monocitos en pacientes

con diabetes mellitus (Biochemical and Biophysical Research Communications, 344(3):780-5 (2206)) en un estudio que involucra pacientes diabéticos. Las concentraciones de MCP-1 en suero y la expresión en superficie de CCR2 en monocitos en pacientes diabéticos fueron significativamente mayores que en no diabéticos y los niveles de MCP-1 en suero se correlacionaron con HbA1c, triglicéridos, BMI, hs-CRP. Los niveles de expresión en superficie de CD36 y CD68 en monocitos se incrementaron significativamente en pacientes diabéticos y más sobre-regulados por MCP-1 en diabéticos, aumentando la absorción de ox-LDL y, por tanto, potencialmente la transformación de célula espumosa. El elevado MCP-1 en suero la expresión incrementada de CCR2, CD36, CD68 en monocitos se correlacionó con bajo control de glucosa en sangre y se correlaciona potencialmente con la acumulación incrementada de monocitos en la pared de vasos.

MCP-1 es un factor potencial en la comunicación cruzada entre el tejido adiposo y el músculo esquelético (Bianco JJ, et al., Endocrinology, 2458 (2006)). El MCP-1 puede reducir significativamente la absorción de glucosa estimulada por insulina y es un inductor prominente de la resistencia a la insulina en la célula de músculo esquelético humano. El tejido adiposo es un órgano activo secretorio y endócrino principal que produce proteínas bioactivas que regulan el metabolismo de la energía y la sensibilidad a la

insulina.

El CCR2 modula los efectos inflamatorios y metabólicos de la alimentación alta en grasas (Weisberg SP, et al., J. Ciln. Invest., 115 (2006)). La deficiencia genética en CCR2 redujo la ingestión de alimentos y atenuó el desarrollo de la obesidad en ratones alimentados con una dieta alta en grasas. En ratones obesos igualados por adiposidad, la deficiencia en CCR2 redujo el contenido de macrófagos y el perfil inflamatorio del tejido adiposo, incrementó la expresión de adiponectina y mejoró la sensibilidad a la homeostasis de glucosa y a la insulina. En animales magros, no se encontró ningún efecto del genotipo CCR2 en pruebas metabólicas. En ratones con dieta alta en grasas, el genotipo CCR2 moduló la alimentación, el desarrollo de la obesidad y la inflamación en tejido adiposo. Una vez establecido, el antagonismo a corto plazo mostró atenuar la acumulación de macrófagos en tejido adiposo y la resistencia a la insulina.

La quimiocina y los receptores de quimiocina son los reguladores clave del tráfico de células inmunes. El MCP-1 es un potente quimioatrayente de monocitos y células T; su expresión se induce bajo condiciones inflamatorias incluyendo estimulaciones de citosina pro-inflamatoria e hipoxia. La interacción entre MCP-1 y CCR2 media la migración de monocitos, macrófagos, así como de células T

activadas, y juega un papel clave en la patogénesis de muchas enfermedades inflamatorias. La inhibición de la función de CCR2 utilizando los antagonistas de molécula pequeña descritos en esta invención representa un nuevo procedimiento para los tratamientos de trastornos inflamatorios.

La psoriasis es una enfermedad inflamatoria crónica caracterizada por la hiperproliferación de queratinocitos y la pronunciada infiltración de leucocitos. Se sabe que los queratinocitos de lesión de psoriasis expresan abundante MCP-1 de ligando CCR2, particularmente cuando se estimulan mediante citosinas pro-inflamatorias tales como THF-alfa (Vestergaard et al., Acta. Derm. Venerreol., 84(5):353-8 (2004); Gillitzer et al., J. Invest. Dermatol., 101(2):127-31 (1993); Deleuran et al., J. Dermatol. Sci., 13(3):228-36 (1996)). Dado que MCP-1 puede atraer la migración tanto de macrófagos como de células dendríticas que expresan CCR2, a la piel, se cree este par de receptor y ligando es importante en la regulación de la interacción entre queratinocitos de proliferación y macrófagos dérmicos durante el desarrollo de la psoriasis. Por tanto, puede ser útil un antagonista de molécula pequeña en el tratamiento de la psoriasis.

Además de las enfermedades inflamatorias, las quimiocinas y los receptores de quimiocina también se han implicado en cánceres (Broek et al., Br. J. Cancer, 88(6):855-62 (2003)). Las células tumòrales estimulan la

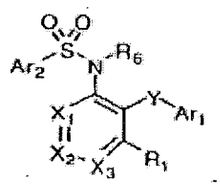
formación de estromas que secretan varios mediadores pivotales para el crecimiento del tumor, incluyendo factores de crecimiento, citosinas y proteasas. Se sabe que el nivel de MCP-1 se asocia significativamente con la acumulación de macrófagos asociada con tumor, y los análisis pronósticos revelan que la alta expresión de MCP-1 es un indicador significativo de la recaída temprana en cáncer de mama (Ueno et al., Clin. Cancer Res., 6(8):3282-9 (2001)). Un antagonista de molécula pequeña de una quimiocina puede, por tanto, ser capaz de reducir la liberación de las citosinas que estimulan el crecimiento bloqueando la acumulación de macrófagos en sitios de formación de tumor.

La infiltración de linfocitos T (células T) en el intestino delgado y el colon se ha vinculado con la patogenesis de enfermedades celiacas, alergias a alimentos, artritis reumatoide, enfermedades intestinales inflamatorias humanas (IBD) que incluyen enfermedad de Crohn y colitis ulcerativa. El bloqueo del tráfico de poblaciones relevantes de célula T al intestino, puede conducir a un procedimiento efectivo para tratar IBD humana. Más recientemente, se ha notado que el receptor 9 de quimiocina (CCR9) se encuentra expresado en células T en callosidades intestinales en sangre periférica, elevado en pacientes con inflamación del intestino delgado tales como enfermedad de Crohn y enfermedad celiaca. El único ligando de CCR9 identificado a la fecha,

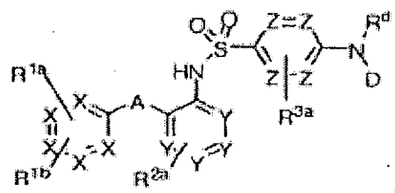
184

TECK (quimiocina expresada en timo) se expresa en el intestino delgado y actualmente se cree que el par de ligando receptor juega un papel pivotal en el desarrollo de IBD. En particular, este par media la migración de la enfermedad que causan las células T al intestino. Ver por ejemplo, Zaballos et al., J. Immunol., 162(10):5671-5675 (1999); Kunkel et al., J. Exp. Med., 192(5):761-768 (2000); Papadakis et al., J. Immunol., 165(9):5069-5076 (2000); Papadakis et al., Gastroenterology, 121(2):246-254 (2001); Campbell et al., J. Exp. Med., 195(1):135-141 (2002); Wurbel et al., Blood, 98(9):2626-2632 (2001); y Uehara et al., J. Immunol., 168(6):2811-2819 (2002). Rivera-Nieves et al., Gastroenterology, 2006 Noviembre; 131 (5):1518-29; y Kontoyiannis et al., J. Exp. Med. Vol. 196, Número 12, Diciembre 16, 2002. Además, los linfocitos portadores de CCR9 han mostrado mediar la patología de filariasis (enfermedad filarial linfática) y la inhibición de CCR9 se ha correlacionado con la reducción de la patología asociada con tales condiciones. Ver por ejemplo, Babu et al., Journal of Infectious Diseases, 191:1018-26, 2005.

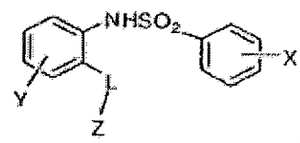
La Solicitud Publicada PCT WO 2003/099773 (Millenium Pharmaceuticals, Inc.) describe compuestos que pueden enlazarse a receptores CCR9 de la fórmula



La Solicitud Publicada PCT WO 2005/004810 (Merck & Co., Inc.) describe antagonistas de brandykinina B1 o agonistas inversos de la fórmula



La Solicitud de Patente Publicada de E.U. 2005/137193 A1 (ChemoCentryx, Inc.) describe moduladores de CCR9 de la fórmula



BREVE SUMARIO

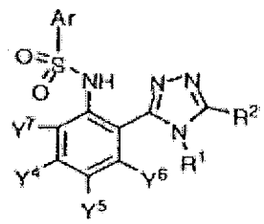
La presente invención se dirige a compuestos y sales farmacéuticamente aceptables de los mismos, composiciones y métodos útiles en la modulación de la actividad de quimiocina. Los compuestos y sus sales, composiciones y métodos descritos en la presente son útiles para tratar o prevenir condiciones o enfermedades mediadas por quimiocina, incluyendo ciertos trastornos y enfermedades inflamatorias e inmunoreguladoras.

Los compuestos de la presente invención han mostrado modular uno o más de CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR3, CXCR4, CXCR5 y CX3CR1. En

186

particular, varios compuestos de la presente invención modulan CCR2 y CCR9 como se muestra en los ejemplos.

En una modalidad, el presente compuesto puede representarse por la fórmula (I) o sus sales:



(I)

en donde Ar, Y^4, Y^5, Y^6, Y^7, R^1 y R^2 son como se define a continuación.

En otro aspecto, la presente invención proporciona composiciones útiles para modular la actividad de quimiocina. En una modalidad, una composición de acuerdo con la presente invención comprende un compuesto de acuerdo con la invención y un vehículo o excipiente farmacéuticamente aceptable.

Aún en otro aspecto, la presente invención proporciona un método para modular la función de quimiocina en una célula, que comprende poner en contacto la célula con una cantidad terapéuticamente efectiva de un compuesto o composición de acuerdo con la invención.

Aún en otro aspecto, la presente invención proporciona un método para modular la función de quimiocina, que comprende poner en contacto un receptor de quimiocina con una cantidad terapéuticamente efectiva de un compuesto o

composición de acuerdo con la invención.

Aún en otro aspecto, la presente invención proporciona un método para tratar una condición o enfermedad mediada por quimiocina, que comprende administrar a un sujeto una cantidad segura y efectiva de un compuesto o composición de acuerdo con la invención.

Además de los compuestos proporcionados en la presente, la presente invención proporciona además composiciones farmacéuticas que contienen uno o más de estos compuestos así como métodos para el uso de estos compuestos en métodos terapéuticos, principalmente para tratar enfermedades asociadas con la actividad de señalización de quimiocina.

DESCRIPCIÓN DETALLADA

General

La presente invención se dirige a compuestos y sales de los mismos, composiciones y métodos útiles en la modulación de la función del receptor que quimiocina, particularmente la función de CCR2 o CCR9. La modulación de la actividad del receptor que quimiocina, como se utiliza en la presente en sus varias formas, pretende abarcar el antagonismo, el agonismo, el antagonismo parcial, el agonismo inverso y/o el agonismo parcial de la actividad asociada con un receptor de quimiocina particular, preferentemente el receptor de CCR2 o CCR9. Por consiguiente, los compuestos de

la presente invención son compuestos que modulan al menos una función o característica de CCR2 o CCR9 de mamífero, por ejemplo, una proteína de CCR2 o de CCR9 humana. La capacidad de un compuesto para modular la función de CCR2 o CCR9 puede demostrarse en un análisis de enlace (e.g., enlace de ligando o enlace de agonista), un análisis de migración, un análisis de señalización (e.g., la activación de una proteína G de mamífero, la inducción de un rápido y transitorio incremento en la concentración de calcio libre citosólico), y/o un análisis de respuesta celular (e.g., estimulación de quimiotaxis, exocitosis o liberación del mediador inflamatorio mediante leucocitos).

Abreviaturas y Definiciones

Al describir los compuestos, composiciones, métodos y procesos de esta invención, los siguientes términos tienen los siguientes significados, a menos que se indique de otra manera.

"Alquilo" por si mismo o como parte de otro sustituyente, se refiere a un grupo de hidrocarburo que puede ser lineal, cíclico o ramificado, o una combinación de los mismos, que tiene el número de átomos de carbono designado (i.e., C_{1-8} significa de uno a ocho carbonos). Ejemplos de grupos de alquilo incluyen metilo, etilo, n-propilo, isopropilo, n-butilo, t-butilo, isobutilo, sec-butilo, ciclohexilo, ciclopentilo, (ciclohexil)metilo,

ciclopropilmetilo, biciclo[2.2.1]heptano, biciclo[2.2.2]octano, etc. Los grupos alquilo pueden encontrarse sustituidos o no sustituidos a menos que se indique de otra manera. Ejemplos de alquilo sustituido incluyen haloalquilo, tioalquilo, aminoalquilo y lo similar.

"Alcoxi" se refiere a -O-alquilo. Ejemplos de un grupo alcoxi incluyen metoxi, etoxi, n-propoxi, etc.

"Alquenilo" se refiere a un grupo de hidrocarburo insaturado que puede ser lineal, cíclico, o ramificado, o una combinación de los mismos. Se prefieren los grupos alquenilo con 2-8 átomos de carbono. El grupo alquenilo puede contener 1, 2 o 3 enlaces dobles de carbono a carbono. Ejemplos de grupos alquenilo incluyen etenilo, n-propenilo, isopropenilo, n-butil-2-enilo, n-hex-3-enilo, ciclohexenilo, ciclopentenilo y lo similar. Los grupos alquenilo pueden ser sustituidos o no sustituidos, a menos que se indique de otra manera.

"Alquinilo", se refiere a un grupo de hidrocarburo insaturado que puede ser lineal, cíclico o ramificado, o una combinación de los mismos. Se prefieren los grupos alquinilo con 2-8 átomos de carbono. El grupo alquenilo puede contener 1, 2 o 3 enlaces triples de carbono a carbono. Ejemplos de grupos alquinilo incluyen etinilo, n-propinilo, n-butil-2-inilo, n-hex-3-inilo, y lo similar. Los grupos alquinilo pueden ser sustituidos o no sustituidos, a menos que se indique de otra manera.

"Arilo" se refiere a un grupo de hidrocarburo poliinsaturado, aromático que tiene un solo anillo (monocíclico) o anillos múltiples (bicíclico), que pueden fusionarse entre sí o enlazarse covalentemente, Se prefieren los grupos arilo con 6-10 átomos de carbono en donde este número de átomos de carbono puede designare por medio de C_{6-10}, por ejemplo. Ejemplos de grupos arilo incluyen fenilo y naftalen-1-ilo, naftalen-2-ilo, bifenilo y lo similar. Los grupos arilo pueden ser sustituidos o no sustituidos a menos que se indique de otra manera.

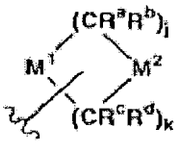
"Halo" o "halógeno", por sí mismos o como parte de otro sustituyente, se refieren a un átomo de cloro, bromo, yodo o flúor.

"Haloalquilo", como un grupo de alquilo sustituido, se refiere a un grupo monohaloalquilo o polihaloalquilo, más típicamente sustituido con de 1-3 átomos de halógeno. Los ejemplos incluyen 1-cloroetilo, 3-bromopropilo, trifluorometilo y lo similar.

"Heterociclilo" se refiere a un anillo no aromático saturado o insaturado que contiene al menos un heteroátomo (típicamente 1 a 5 heteroátomos) seleccionado de nitrógeno, oxígeno o azufre. El anillo heterociclilo puede ser monocíclico o bicíclico. Preferentemente, estos grupos contienen de 0.5 átomos de nitrógeno, 0.2 átomos de azufre y 0.2 átomos de oxígeno. Más preferentemente, estos grupos

contienen de 0.3 átomos de nitrógeno, 0.1 átomos de azufre y de 0.1 átomos de oxígeno. Ejemplos de grupos heterociclo incluyen pirrolidina, piperidina, imidazolina, pirazolidina, butirolactam, valerolactam, imidazolidinona, hindantoína, dioxolano, ftalimida, piperidina, 1,4-dioxano, morfolina, tiomorfolina, tiomorfolina-S-óxido, tiomorfolina-S,S-dióxido, piperazina, pirano, piridona, 3-pirrolina, tiopirano, pirona, tetrahidrofurano, tetrahidrotiofeno, quinuclidina y lo similar. Los grupos heterocíclicos preferidos son monocílicos aunque pueden encontrarse fusionados o covalentemente enlazados a un sistema de anillo arilo o heteroarilo.

En una modalidad preferida, los grupos heterocíclicos pueden representarse por la fórmula (AA) siguiente:



AA

En donde la fórmula (AA) se encuentra unida mediante una valencia libre en ya sea M^1 o M^2; M^1 representa O, NR^e, o $S(O)_1$; M^2 representa CR^fR^g, O, $S(O)_1$, o NR^e; l es 0, 1 o 2; j es 1, 2 o 3 y k es 1, 2 o 3, con la salvedad de que j + k es 3, 4, o 5; y R^a, R^b, R^c, R^d, R^e, R^f y R^g se seleccionan independientemente del grupo que consiste de

hidrógeno, halógeno, alquilo C_{1-8} no sustituido o sustituido, alquenilo C_{2-8} no sustituido o sustituido, alquinilo C_{2-8} no sustituido o sustituido, $-COR^h$, $-CO_2R^h$, $-CONR^hR^i$, $-NR^hCOR^i$, $-SO_2R^h$, $-SO_2NR^hR^i$, $-NSO_2R^hR^i$, $-NR^hR^i$, $-OR^h$, $-Q^1COR^h$, $-Q^1CO_2R^h$, $-Q^1CONR^hR^i$, $-Q^1NR^hCOR^i$, $-Q^1SO_2R^{28}$, $-Q^1SO_2NR^hR^i$, $-Q^1NSO_2R^hR^i$, $-Q^1NR^hR^i$, $-Q^1OR^h$, en donde Q^1 es un miembro seleccionado del grupo que consiste de alquileno C_{1-4}, alquenileno C_{2-4} y alquinileno C_{2-4} y R^h y R^i se seleccionan independientemente del grupo que consiste de hidrógeno y alquilo C_{1-8}, y en donde las porciones alifáticas de cada uno de los sustituyentes R^a, R^b, R^c, R^d, R^e, R^f y R^g se sustituyen independientemente con de uno a tres miembros seleccionados del grupo que consiste de halógeno, $-OH$, $-OR^n$, $-OC(O)NHR^n$, $-OC(O)NR^nR^o$, $-SH$, $-SR^n$, $-S(O)R^n$, $-S(O)_2R^n$, $-SO_2NH_2$, $-S(O)_2NHR^n$, $-S(O)_2NR^nR^o$, $-NHS(O)_2R^n$, $-NR^nS(O)_2R^o$, $-C(O)NH_2$, $-C(O)NHR^n$, $-C(O)NR^nR^o$, $-C(O)R^n$, $-NHC(O)R^o$, $-NR^nC(O)R^o$, $-NHC(O)NH_2$, $-NR^nC(O)NH_2$, $-NR^nC(O)NHR^o$, $-NHC(O)NHR^n$, $-NR^nC(O)NR^oR^p$, $-NHC(O)NR^nR^o$, $-CO_2H$, $-CO_2R^n$, $-NHCO_2R^n$, $-NR^nCO_2R^o$, $-CN$, $-NO_2$, $-NH_2$, $-NHR^n$, $-NR^nR^o$, $-NR^nS(O)NH_2$ y $-NR^nS(O)_2NHR^o$, en donde R^n, R^o y R^p son independientemente un alquilo C_{1-8} no sustituido. Adicionalmente, cualquiera dos de R^a, R^b, R^c, R^d, R^e, R^f y R^g pueden combinarse para formar un sistema de anillo de puente o espirocíclico.

En una modalidad preferida, el número de los grupos $R^a + R^b + R^c + R^d$ que son diferentes a hidrógeno, es de 0, 1 o 2. En una modalidad más preferida, R^a, R^b, R^c, R^d, R^e, R^f y R^g

se seleccionan independientemente del grupo que consiste de hidrógeno, halógeno, alquilo C_{1-8} no sustituido o sustituido, $-COR^h$, $-CO_2R^h$, $-CONR^hR^h$, $-NR^hCOR^h$, $-SO_2R^h$, $-SO_2NR^hR^i$, $-NSO_2R^hR^i$, $-NR^hR^i$ y $-OR^h$, en donde R^h y R^i se seleccionan independientemente del grupo que consiste de hidrógeno y alquilo C_{1-8} no sustituido y en donde las porciones alifáticas de cada uno de los sustituyentes R^a, R^b, R^c, R^d, R^e, R^f y R^g se sustituyen opcionalmente con de uno a tres miembros seleccionados del grupo que consiste de halógeno, $-OH$, $-OR^n$, $-OC(O)NHR^n$, $-OC(O)NR^nR^o$, $-SH$, $-SR^n$, $-S(O)R^n$, $-S(O)_2R^n$, $-SO_2NH_2$, $-S(O)_2NHR^n$, $-S(O)_2NR^nR^o$, $-NHS(O)_2R^n$, $-NR^nS(O)_2R^o$, $-C(O)NH_2$, $-C(O)NHR^n$, $-C(O)NR^nR^o$, $-C(O)R^n$, $-NHC(O)R^o$, $-NR^nC(O)R^o$, $-NHC(O)NH_2$, $-NR^nC(O)NH_2$, $-NR^nC(O)NHR^o$, $-NHC(O)NHR^n$, $-NR^nC(O)NR^oR^p$, $-NHC(O)NR^nR^o$, $-CO_2H$, $-CO_2R^n$, $-NHCO_2R^n$, $-NR^nCO_2R^o$, $-CN$, $-NO_2$, $-NH_2$, $-NHR^n$, $-NR^nR^o$, $-NR^nS(O)NH_2$ y $-NR^nS(O)_2NHR^o$, en donde R^n, R^o y R^p son independientemente un alquilo C_{1-8} no sustituido.

En una modalidad más preferida, R^a, R^b, R^c, R^d, R^e, R^f y R^g son independientemente hidrógeno o alquilo C_{1-4}. En otra modalidad preferida, al menos tres de R^a, R^b, R^c, R^d, R^e, R^f y R^g son hidrógeno.

"Heteroarilo" se refiere a un grupo aromático que contiene al menos un heteroátomo, en donde el grupo heteroarilo puede ser monocíclico o bicílico. Los ejemplos incluyen piridilo, piridazinilo, pirazinilo, pirimidinilo,

triazinilo, quinolinilo, quinoxalinilo, quinazolinilo, cinolinilo, ftalazinilo, benzotriazinilo, purinilo, bencimidazolilo, benzopirazolilo, benzotriazolilo, bencisoxazolilo, isobenzofurilo, isoindolilo, indolizinilo, benzotriazinilo, tienopiridinilo, tienopirimidinilo, pirazolopirimidinilo, imidazopiridinas, benzotiazolilo, benzofuranilo, benzotienilo, indolilo, azaindolilo, azaindeazolilo, quinolilo, isoquinolilo, isotiazolilo, pirazolilo, indazolilo, pteridinilo, imidazolilo, triazolilo, tetrazolilo, oxazolilo, isoxazolilo, oxadiazolilo, tiadiazolilo, pirrolilo, tiazolilo, furilo o tienilo. Los grupos heteroarilo preferidos son aquellos que tienen al menos un átomo de nitrógeno de anillo de arilo, tal como quinolinilo, quinoxalinilo, purinilo, bencimidazolilo, benzopirazolilo, benzotriazolilo, benzotiazolilo, indolilo, quinolilo, isoquinolilo y lo similar. Los sistemas de heteroarilo de 6 anillos preferidos incluyen piridilo, piridazinilo, pirazinilo, pirimidinilo, triazinilo y lo similar. Los sistemas de heteroarilo de 5 anillos preferidos incluyen isotiazolilo, pirazolilo, imidazolilo, tienilo, furilo, triazolilo, tetrazolilo, oxazolilo, isoxazolilo, oxadiazolilo, tiadiazolilo, pirrolilo, tiazolilo y lo similar.

El heterociclilo y el heteroarilo pueden encontrarse unidos en cualquier carbono o heteroátomo de

anillo disponible. Cada heterociclilo y heteroarilo puede tener uno o más anillos. Cuando se encuentran presentes múltiples anillos, éstos pueden encontrarse fusionados entre sí o enlazados covalentemente. Cada heterociclilo y heteroarilo debe contener al menos un heteroátomo (típicamente de 1 a 5 heteroátomos) seleccionados de nitrógeno, oxígeno o azufre. Preferentemente, estos grupos contienen de 0-5 átomos de nitrógeno, de 0.2 átomos de azufre y de 0.2 átomos de oxígeno. Más preferentemente, estos grupos contienen de 0.3 átomos de nitrógeno, de 0.1 átomos de azufre y de 0.1 átomos de oxígeno. Los grupos heterociclilo y heteroarilo pueden encontrarse sustituidos o no sustituidos a menos que se indique de otra manera. Para los grupos sustituidos, la sustitución puede ser en un carbono o heteroátomo. Por ejemplo, cuando la sustitución es oxo (=O o -O), el grupo resultante puede tener ya sea un carbonilo (-C(O)-) o un N-óxido ($-N^+-O$).

Los sustituyentes para alquilo sustituido, alquenilo sustituido y alquinilo sustituido incluyen halógeno, -CN, $-CO_2R'$, -C(O)R', -C(O)NR'R'', oxo, (=O o -O), -OR', -OC(O)R', -OC(O)NR'R'', $-NO_2$, -NR'C(O)R', -NR'''C(O)NR'R'', -NR'R'', $-NR'CO_2R''$, -NR'S(O)R'', $-NR'S(O)_2R'''$, -NR'''S(O)NR'R'', $-NR'''S(O)_2NR'R''$, -SR', -S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R''$, -NR'-C(NHR'')=NR''', -SiR'R''R''', $-N_3$, arilo C_{6-10} sustituido o no sustituido,

heteroarilo de 5 a 10 miembros sustituido o no sustituido, y heterociclilo de 3 a 10 miembros sustituido o no sustituido. El número de posibles sustituyentes varía de cero a (2m'+1), en donde m' es el número total de átomos de carbono en tal radical.

Los sustituyentes adecuados para arilo sustituido, heteroarilo sustituido y heterociclilo sustituido incluyen halógeno, -CN, $-CO_2R'$, -C(O)R', -C(O)NR'R'', oxo, (=O o -O), -OR', -OC(O)R', -OC(O)NR'R'', $-NO_2$, -NR'C(O)R', -NR'''C(O)NR'R'', -NR'R'', $-NR'CO_2R''$, -NR'S(O)R'', $-NR'S(O)_2R'''$, -NR'''S(O)NR'R'', $-NR'''S(O)_2NR'R''$, -SR', -S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R''$, -NR'-C(NHR'')=NR''', -SiR'R''R''', $-N_3$, alquilo C_{1-8} sustituido o no sustituido, alquenilo C_{2-8} sustituido o no sustituido, alquinilo C_{2-8} sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido, heteroarilo de 5 a 10 miembros sustituido o no sustituido, y heterociclilo de 3 a 10 miembros sustituido o no sustituido. El número de posibles sustituyentes varía de cero al número total de valencias abiertas en el sistema de anillo aromático.

Como se utilizaron anteriormente, R', R'' y R''' se refieren cada uno independientemente a una variedad de grupos que incluyen hidrógeno, alquilo C_{1-8} sustituido o no sustituido, alquenilo C_{2-8} sustituido o no sustituido, alquinilo C_{2-8} sustituido o no sustituido, arilo sustituido o

no sustituido, heteroarilo sustituido o no sustituido, heterociclilo sustituido o no sustituido, arilalquilo sustituido o no sustituido, ariloxialquilo sustituido o no sustituido. Cuando R' y R'' se encuentran unidos al mismo átomo de nitrógeno, pueden combinarse con el átomo de nitrógeno para formar un anillo de 3, 4, 5, 6 o 7 miembros (por ejemplo, -NR'R'' incluye 1-pirrolidinilo y 4-morfolinilo). Además R' y R'', R'' y R''' o R' y R''', conjuntamente con el(los) átomo(s) a el(los) cual(es) se encuentran unidos, pueden formar un anillo de 5, 6 o 7 miembros sustituido o no sustituido.

Dos de los sustituyentes en los átomos adyacentes del anillo de arilo o heteroarilo pueden reemplazarse opcionalmente con un sustituyente de la fórmula -T-C(O)-(CH_2)q-U-, en donde T y U son independientemente -NR'''''-, -O-, -CH_2-, o un enlace único, y q es un entero de 0 a 2. Alternativamente, dos de los sustituyentes en los átomos adyacentes del anillo de arilo o heteroarilo pueden reemplazarse opcionalmente con un sustituyente de la fórmula -A'-$(CH_2)_r$-B'-, en donde A' y B' son independientemente -CH_2-, -O-, -NR'''''-. -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$NR'''''- o un enlace único, y r es un entero de 1 a 3. Uno de los enlaces únicos del nuevo anillo así formado puede reemplazarse opcionalmente con un enlace doble. Alternativamente, dos de los sustituyentes en los átomos adyacentes del anillo de

arilo o heteroarilo pueden reemplazarse opcionalmente con un sustituyente de la fórmula $-(CH_2)_s-X-(CH_2)_t-$, en donde s y t son independientemente enteros de desde 0 a 3, y X es -O-, -NR''''-, -S-, -S(O)-, $-S(O)_2-$ o $-S(O)_2NR'-$. R'''' se selecciona de hidrógeno o alquilo C_{1-8} no sustituido.

"Heteroátomo" pretende incluir oxígeno (O), nitrógeno (N), azufre (S) y silicona (Si).

Vehículo, diluyente o excipiente "farmacéuticamente aceptable" es un vehículo, diluyente o excipiente compatible con los otros ingredientes de la formulación y no nocivo para el recipiente del mismo.

"Sal farmacéuticamente aceptable" se refiere a una sal que es aceptable para la administración a un paciente, tal como un mamífero (e.g., sales que tienen seguridad aceptable para mamíferos para un régimen de dosis dado). Tales sales pueden derivarse de bases inorgánicas u orgánicas farmacéuticamente aceptables y de ácidos inorgánicos u orgánicos farmacéuticamente aceptable, dependiendo de los sustituyentes particulares encontrados en los compuestos descritos en la presente. Cuando los compuestos de la presente invención contienen funcionalidades relativamente acídicas, pueden obtenerse sales de adición de base poniendo en contacto la forma neutra de tales compuestos con una cantidad suficiente de la base deseada, ya sea pura o en un solvente inerte adecuado. Las sales derivadas de bases

inorgánicas farmacéuticamente aceptables incluyen sal de aluminio, amonio, calcio, cobre, férricas, ferrosas, litio, magnesio, mangánicas, manganosas, potasio, sodio, zinc y lo similar. Las sales derivadas de bases orgánicas farmacéuticamente aceptables incluyen sales de aminas primarias, secundarias, terciarias y cuaternarias, incluyendo aminas sustituidas, aminas cíclicas, aminas de origen natural y lo similar, tales como arginina, betaína, cafeína, colina, N,N'-dibenciletilenodiamina, dietilamina, 2-dietilaminoetanol, 2-dimetilaminoetanol, etanolamina, etilenodiamina, N-etilmorfolina, N-etilpiperidina, glucamina, glucosamina, histidina, hidrabamina, isopropilamina, lisina, metilglucamina, morfolina, piperazina, piperidina, resinas de poliamina, procaína, purinas, teobromina, trietilamina, trimetilamina, tripropilamina, trometamina y lo similar. Cuando los compuestos de la presente invención contienen funcionalidades relativamente básicas, pueden obtenerse sales de adición de ácido poniendo en contacto la forma neutra de tales compuestos con una cantidad suficiente del ácido deseado, ya sea puro o en un solvente inerte adecuado. Las sales derivadas de ácidos farmacéuticamente aceptables incluyen ácidos acético, ascórbico, bencenosulfónico, canforsulfónico, cítrico, etanosulfónico, fumárico, glucónico, glucurónico, glutámico, hipúrico, bromhídrico, clorhídrico, isetiónico, láctico, lactobiónico, maleico,

málico, mandélico, metanosulfónico, múcico, naftalenosulfónico, nicotínico, nítrico, pamoico, pantoténico, fosfórico, succínico, sulfúrico, tartárico, p-toluenosulfónico y lo similar.

También se encuentran incluidas sales de aminoácidos tales como arginato y lo similar y sales de ácidos orgánicos como ácidos glucurónicos o galacturónicos y lo similar (ver, e.g., Berge S.M. et al., "Pharmaceutical Salts" J. Pharmaceutical Science 1977 66:1-19). Ciertos compuestos específicos de la presente invención contienen funcionalidades tanto básicas como acídicas que permiten convertir los compuestos en sales de adición ya sea de base o de ácido.

Las formas neutras de los compuestos pueden regenerarse poniendo en contacto la sal con una base o ácido y aislando el compuesto de origen de la manera convencional. La forma de origen del compuesto difiere de las varias formas de sal en ciertas propiedades físicas, tales como, la solubilidad en solventes polares, pero, de otra manera, las sales son equivalentes a la forma de origen del compuesto para los propósitos de la invención.

"Sal del mismo" se refiere a un compuesto formado cuando el hidrógeno de un ácido se reemplaza por un catión tal como un catión de metal o un catión orgánico y lo similar. Preferentemente, la sal es una sal

farmacéuticamente aceptable, aunque esto no se requiere para sales de compuestos intermedios que no se destinan a la administración a un paciente.

Además de las formas de sal, la presente invención proporciona compuestos que se encuentran en forma de profármaco. Los profármacos de los compuestos descritos en la presente son aquellos compuestos que experimentan fácilmente los cambios químicos bajo condiciones fisiológicas para proporcionar los compuestos de la presente invención. Adicionalmente, los profármacos pueden convertirse en los compuestos de la presente invención mediante métodos químicos o bioquímicos en un ambiente ex vivo. Por ejemplo, los profármacos pueden convertirse lentamente en los compuestos de la presente invención, cuando se colocan en un depósito de parche transdérmico con una enzima o reactivo químico adecuado.

Los profármacos pueden prepararse modificando los grupos funcionales presentes en los compuestos de tal manera que las modificaciones se desdoblan, ya sea en manipulación de rutina o in vivo, en los compuestos de origen. Los profármacos incluyen compuestos en donde los grupos hidroxilo, amino, sulfhidrilo o carboxilo se encuentran enlazados a cualquier grupo que, al administrarse a un sujeto mamífero, se desdobla para formar un grupo hidroxilo, amino, sulfhidrilo o carboxilo libre, respectivamente. Ejemplos de

profármacos incluyen, pero no se limitan a, derivados de acetato, formato, y benzoato de grupos funcionales de alcohol y amina en los compuestos de la invención. La preparación, selección y el uso de profármacos se trata en T. Higuchi y V. Stella, "Pro-drugs as Novel Delivery Systems" (Profármacos como nuevos sistemas de suministro), Vol. 14 de la A.C.S. Symposium Series; "Design of Prodrugs" (Diseño de profármacos" ed. H. Bundgaard, Elsevier, 1985; y en Bioreversible Carriers in Drug Design, (Vehículos biorreversibles en diseño de fármacos) ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, cada una de las cuales se incorpora en la presente mediante la referencia en su totalidad.

Los compuestos de la invención pueden encontrarse presentes en forma de sus metabolitos farmacéuticamente aceptables. El término "metabolito" significa una forma farmacéuticamente aceptable de un derivado metabólico de un compuesto de la invención (o una sal del mismo). En algunos aspectos, el metabolito puede ser un derivado funcional de un compuesto que se convierte fácilmente in vivo en un compuesto activo. En otros aspectos, el metabolito puede ser un compuesto activo.

"Cantidad terapéuticamente efectiva" se refiere a una cantidad suficiente para efectuar el tratamiento cuando se administra a un paciente que necesita el tratamiento.

"Tratar" o "tratamiento" como se utilizan en la presente, se refieren a tratar o al tratamiento de una enfermedad o condición médica (tal como una infección viral, bacteriana o por hongos u otras enfermedades infecciosas, así como condiciones autoinmunes o inflamatorias) en un paciente, tal como un mamífero (particularmente un humano o un animal de compañía) que incluye mejorar la enfermedad o condición médica, i.e., eliminar u ocasionar la regresión de la enfermedad o condición médica en un paciente; suprimir la enfermedad o condición médica, i.e., retardar o arrestar el desarrollo de la enfermedad o condición médica en un paciente; o aliviar los síntomas de la enfermedad o condición médica en un paciente.

Ciertos compuestos de la presente invención pueden existir en formas no disueltas así como en formas disueltas, incluyendo formas hidratadas. En general, tanto las formas disueltas como las formas no disueltas y pretenden encontrarse abarcadas dentro del alcance de la presente invención. Ciertos compuestos de la presente invención pueden existir en múltiples formas cristalinas o amorfas (i.e., como polimorfos). En general, todas las formas físicas son equivalentes para los usos contemplados por la presente invención y pretenden encontrarse dentro del alcance de la invención.

Será aparente para el experto en la técnica que

ciertos compuestos de la presente invención pueden existir en formas tautoméricas, encontrándose todas tales formas tautoméricas de los compuestos dentro del alcance de la invención. Ciertos compuestos de la presente invención poseen átomos de carbono asimétricos (centros ópticos) o enlaces dobles; los racematos, diastereómeros, isómeros geométricos e isómeros individuales (e.g., enantiómeros separados) pretenden todos encontrarse abarcados dentro del alcance de la invención. Los compuestos de la presente invención también pueden contener proporciones no naturales de isótopos atómicos en uno o más de los átomos que constituyen tales compuestos. Por ejemplo, los compuestos pueden radiomarcarse con isótopos radiactivos, tales como, por ejemplo, tritio (^{3}H), yodo-125 (^{125}I) o carbono-14 (^{14}C). Todas las variaciones isotópicas de los compuestos de la presente invención, ya sea radiactivas o no, pretenden encontrarse abarcadas dentro del alcance de la presente invención.

Los compuestos de la presente invención pueden incluir una marca detectable. Una marca detectable es un grupo que es detectable a bajas concentraciones, comúnmente menores que micromolares, posiblemente menos que nanomolares, y que pueden distinguirse fácilmente de otras moléculas, debido a las diferencias en una propiedad molecular (e.g., peso molecular, proporción de masa a carga, radiactividad,

potencial redox, luminiscencia, fluorescencia, propiedades electromagnéticas, propiedades de enlace y lo similar). Las marcas detectables pueden detectarse mediante medios espectroscópicos, fotoquímicos, bioquímicos, inmunoquímicos, eléctricos, magnéticos, electromagnéticos, ópticos o químicos y lo similar.

Una amplia variedad de marcas detectables se encuentran dentro del alcance de la presente invención, incluyendo marcas de hapteno (e.g., biotina, o marcas utilizadas en conjunción con anticuerpos detectables tales como anticuerpos de peroxidasa de rábano); marcas de etiqueta de masa (e.g., marcas de isótopo estable); marcas radioisotópicas (incluyendo ^{3}H, ^{125}I, ^{35}S, ^{14}C o ^{32}P); marcas de quelado metálico; marcas luminiscentes incluyendo marcas fluorescentes (tales como fluoresceina, isotiocianato, rojo de Texas, rodamina, proteína verde fluorescente y lo similar), marcas fosforescentes, y marcas quimioluminiscentes, que tienen típicamente un rendimiento quantum mayor que 0.1; marcas electroactivas y de transferencia de electrón; marcas de modulador de enzimas incluyendo coenzimas, de peroxidasa de rábano de catalizadores organometálicos, alcalina fosfatasa y otras comúnmente utilizadas en un ELISA; marcas de fotosensibilizador; marcas de microesfera magnética incluyendo Dynabeads; marcas colorimétricas tales como oro

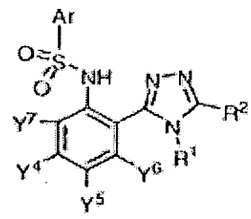
coloidal, plata, selenio u otros metales y marcas de metal solenoide (ver Patente de E.U. No. 5,120,643, que se incorpora en la presente mediante la referencia en su totalidad para todo propósito), o marcas de microesferas de vidrio coloreado o plástico (e.g., poliestireno, polipropileno, látex, etc.); y marcas de negro de carbono. Las patentes que muestran el uso de tales marcas detectables incluyen las Patentes de E.U. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; 4,336,241; 6.312,914; 5,990,479; 6,207,392; 6,423,551; 6,251,303; 6,306,610; 6,322,901; 6,319,426; 6,326,144; y 6,444,143 que se incorporan en la presente mediante la referencia en su totalidad para todo propósito.

Las marcas detectables se encuentran comercialmente disponibles o pueden prepararse como lo conoce el experto en la técnica. Las marcas detectables pueden encontrarse covalentemente unidas a los compuestos utilizando un grupo funcional reactivo, que puede encontrarse ubicado en cualquier posición apropiada. Los métodos para unir una marca detectable son conocidos por el experto en la técnica. Cuando el grupo reactivo se encuentra unido a un alquilo, o cadena de alquilo no sustituido unido a un núcleo de arilo, el grupo reactivo puede ubicarse en una posición terminal de una cadena de alquilo.

Compuestos

211

En una modalidad, los compuestos de la presente invención se representan por la fórmula (I) o sus sales:



(I)

Ar se selecciona del grupo que consiste de arilo C_{6-10} sustituido o no sustituido y un heteroarilo de 5 a 10 miembros sustituido o no sustituido;

Y^4, Y^5, Y^6 y Y^7 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, halógeno, -CN, $-C(O)R^{15}$, $-CO_2R^{15}$, $-C(O)NR^{15}R^{16}$, $-OR^{15}$, $-OC(O)R^{15}$, $-OC(O)NR^{15}R^{16}$, $-SR^{15}$, $-S(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2NR^{15}R^{16}$, $-NO_2$, $-NR^{15}R^{16}$, $-NR^{15}C(O)R^{16}$, $-NR^{15}C(O)OR^{16}$, $-NR^{15}S(O)_2R^{16}$, $-NR^{15}C(O)NR^{16}R^{17}$, alquilo C_{1-8} sustituido o no sustituido, alquenilo C_{2-8} sustituido o no sustituido, alquinilo C_{2-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido, y heteroarilo de 5 a 10 miembros sustituido o no sustituido;

R^{15}, R^{16} y R^{17} se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, alquilo C_{1-8} sustituido o no sustituido, alquenilo C_{2-8} sustituido o no sustituido, alquinilo C_{2-8} sustituido o no

212

sustituido, arilo C_{6-10} sustituido o no sustituido, heteroarilo de 5 a 10 miembros sustituido o no sustituido y heterociclilo de 3 a 10 miembros sustituido o no sustituido;

R^{15} y R^{16}, R^{16} y R^{17} o R^{15} y R^{17} conjuntamente con los átomos a los cuales se encuentran unidos, pueden formar un anillo de 5, 6 o 7 miembros sustituido o no sustituido;

R^1 se selecciona del grupo que consiste de hidrógeno, $-C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2NR^7R^8$, alquilo C_{1-8} sustituido o no sustituido, alquenilo C_{2-8} sustituido o no sustituido, alquinilo C_{2-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido, o heteroarilo de 5 a 10 miembros sustituido o no sustituido;

R^2 se selecciona del grupo que consiste de hidrógeno, halógeno, $-CN$, $-C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$, $-OR^7$, $-OC(O)R^7$, $-OC(O)NR^7R^8$, $-SR^7$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2NR^7R^8$, $-NO_2$, $-NR^7R^8$, $-NR^7C(O)R^8$, $-NR^7C(O)OR^8$, $-NR^7S(O)_2R^8$, $-NR^7C(O)NR^8R^9$, alquilo C_{1-8} sustituido o no sustituido, alquenilo C_{2-8} sustituido o no sustituido, alquinilo C_{2-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido, o heteroarilo de 5 a 10 miembros sustituido o no sustituido;

R^7, R^8 y R^9 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, alquilo C_{1-8} sustituido o no sustituido, alquenilo C_{2-8}

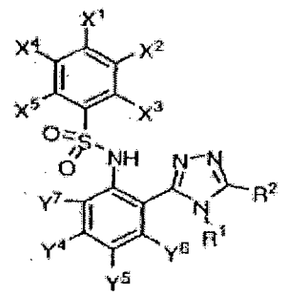
213

sustituido o no sustituido, alquinilo C_{2-8} sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido, heteroarilo de 5 a 10 miembros sustituido o no sustituido y heterociclilo de 3 a 10 miembros sustituido o no sustituido;

R^7 y R^8, R^8 y R^9 o R^7 y R^9 conjuntamente con los átomos a los cuales se encuentran unidos, pueden formar un anillo de 5, 6 o 7 miembros sustituido o no sustituido; y

en donde R^1 y R^2 conjuntamente con los átomos a los cuales se encuentran unidos, pueden formar un anillo de 5, 6 o 7 miembros sustituido o no sustituido.

En una modalidad, los compuestos de la presente invención se representan por la fórmula (II) o sus sales:



(II)

en donde Y^4, Y^5, Y^6, Y^7, R^1 y R^2 son como se define para la fórmula (I);

X^1, X^2, X^3, X^4 y X^5 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, halógeno, alquilo C_{1-8} sustituido o no sustituido, alquenilo C_{2-8} sustituido o no sustituido, alquinilo C_{2-8} sustituido o no sustituido, -CN, $-NO_2$, $-C(O)R^{18}$, $-CO_2R^{18}$, $-C(O)NR^{18}R^{19}$, $-OR^{18}$, -

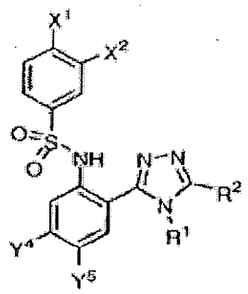
214

$OC(O)R^{19}$, $-OC(O)NR^{18}R^{19}$, $-NO_2$, $-NR^{18}C(O)R^{19}$, $NR^{18}C(O)NR^{19}R^{20}$, $-NR^{18}R^{19}$, $-NR^{18}CO_2R^{19}$, $NR^{18}S(O)_2R^{19}$, $-SR^{18}$, $-S(O)R^{18}$, $-S(O)_2R^{18}$, $-S(O)_2NR^{18}R^{19}$, arilo C_{6-10} sustituido o no sustituido, heteroarilo de 5 a 10 miembros sustituido o no sustituido y heterociclilo de 3 a 10 miembros sustituido o no sustituido;

R^{18}, R^{19} y R^{20} se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, alquilo C_{1-8} sustituido o no sustituido, alquenilo C_{2-8} sustituido o no sustituido, alquinilo C_{2-8} sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido, heteroarilo de 5 a 10 miembros sustituido o no sustituido y heterociclilo de 3 a 10 miembros sustituido o no sustituido; y

R^{18} y R^{19}, R^{19} y R^{20} o R^{18} y R^{20} conjuntamente con los átomos a los cuales se encuentran unidos, pueden formar un anillo de 5, 6 o 7 miembros sustituido o no sustituido.

En otra modalidad, los compuestos se representan por la fórmula (III) o sus sales:



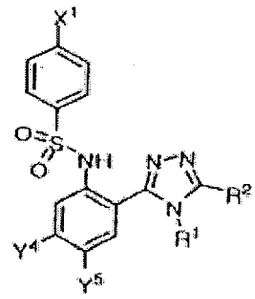
(III)

en donde Y^4, Y^5, R^1 y R^2 son como se definió para la

215

fórmula (I); y X^1 y X^2 son como se definió para la fórmula (II); con la salvedad de que al menos uno de X^1 y X^2 son diferentes a hidrógeno y al menos uno de Y^4 y Y^5 son diferentes a hidrógeno.

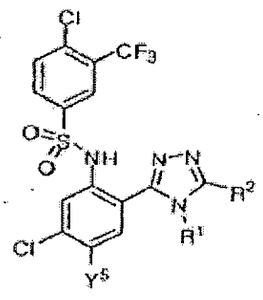
En otra modalidad, los compuestos se representan por la fórmula (IV) o sus sales:



(IV)

en donde Y^4, Y^5, R^1 y R^2 son como se definió para la fórmula (I); y X^1 es como se definió para la fórmula (II); con la salvedad de que X^1 es diferente a hidrógeno y al menos uno de Y^4 y Y^5 son diferentes a hidrógeno.

En otra modalidad, los compuestos de la presente invención se representan por la fórmula (V) o sus sales:

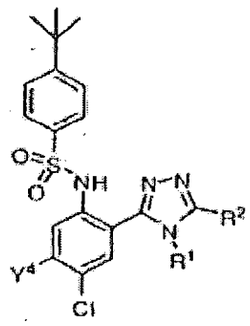


(V)

en donde Y^5 es halógeno o hidrógeno; y R^1 y R^2 son

como se define para la fórmula (I).

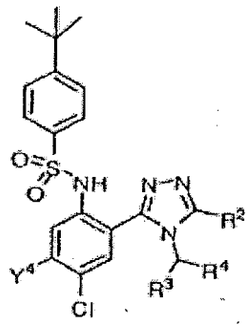
En otra modalidad, los compuestos de la presente invención se representan por la fórmula (VI) o sus sales:



(VI)

en donde Y^4 es hidrógeno o fluoro; R^1 y R^2 son como se definió en la fórmula (I).

En otra modalidad, los compuestos de la presente invención se representan por la fórmula (VIIa) o sus sales:



(VIIa)

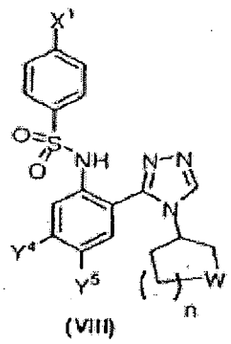
en donde Y^4 es hidrógeno o fluoro; R^2 es como se definió en la fórmula (I); y

R^3 y R^4 son cada uno independientemente hidrógeno, alquilo C_{1-8} no sustituido o sustituido, o R^3 y R^4 conjuntamente con el carbono al cual sustituyen forman un anillo carbocíclico de 3-10 miembros, heterocíclico de 4-10

217

miembros, heteroarilo de 5-10 miembros o un anillo arilo de 6-10 miembros.

En otra modalidad, los compuestos de la presente invención se representan por la fórmula (VIII) o sus sales:



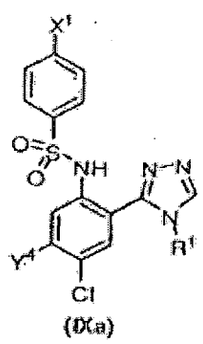
(VIII)

en donde Y^4 y Y^5 son como se definió para la fórmula (I); X^1 es como se definió para la fórmula (II), con la salvedad de que X^1 y Y^5 son diferentes a hidrógeno;

W es NH u O; y

N es 0, 1 o 2.

En otra modalidad, los compuestos de la presente invención se representan por la fórmula (IXa) o sus sales:



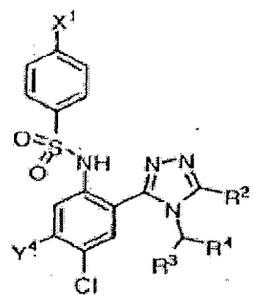
(IXa)

en donde Y^4 es hidrógeno o fluoro; R^1 es como se definió en la Fórmula (I); y

218

X^1 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o no sustituido, $-OR^{18}$, $-NR^{18}R^{19}$ y heterociclilo de 3 a 10 miembros sustituido o no sustituido.

En otra modalidad, los compuestos de la presente invención se representan por la fórmula (IXb) o sus sales:



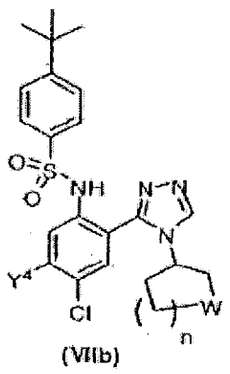
(IXb)

en donde Y^4 es hidrógeno o fluoro; R^2 es como se definió en la fórmula (I);

X^1 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o no sustituido, $-OR^{18}$, $-NR^{18}R^{19}$ y heterociclilo de 3 a 10 miembros sustituido o no sustituido; y

R^3 y R^4 son cada uno independientemente hidrógeno, alquilo C_{1-8} no sustituido o sustituido o R^3 y R^4 conjuntamente con el carbono al cual sustituyen forman un anillo carbocíclico de 3-10 miembros, heterocíclico de 4-10 miembros, heteroarilo de 5-10 miembros o un anillo arilo de 6-10 miembros.

En otra modalidad, los compuestos de la presente invención se representan por la fórmula (VIIb) o sus sales:



(VIIb)

Y^4 es hidrógeno o fluoro;

W es NH u O; y

n es 0, 1 o 2.

Compuestos que modulan la Actividad de CCR2 o CCR9

La presente invención proporciona compuestos que modulan la actividad de al menos uno de CCR2 o CCR9. Los receptores que quimiocina son proteínas de membrana integral que interactúan con un ligando extracelular, tal como una quimiocina, y median una respuesta celular al ligando, e.g., quimiotaxis, la concentración de ion de calcio intracelular incrementada, etc. En consecuencia, la modulación de una función del receptor de quimiocina, e.g., interferencia con una interacción del ligando del receptor de quimiocina, modulará la respuesta mediada por el receptor de quimiocina, y tratará o prevendrá la condición o enfermedad mediada por el receptor de quimiocina. La modulación de una función del receptor de quimiocina incluye tanto la inducción como la inhibición de la función. El tipo de modulación lograda dependerá de las características del compuesto, i.e.,

antagonista o agonista total, parcial o inverso.

Sin pretender vincularse a una teoría en particular, se cree que los compuestos proporcionados en la presente interfieren con la interacción entre un receptor de quimiocina y uno o más ligandos cognado. En particular, se cree que los compuestos interfieren con la interacción entre CCR2 y un ligando CCR2, tal como MCP-1. Los compuestos contemplados por la invención incluyen, pero no se limitan a, los compuestos ejemplares proporcionados en la presente y sus sales.

Por ejemplo, los compuestos de esta invención actúan como potentes antagonistas de CCR2 y esta actividad antagonista se ha confirmado además en pruebas en animales para la inflamación, uno de los característicos estados de enfermedad para CCR2. Por consiguiente, los compuestos proporcionados en la presente son útiles en las composiciones farmacéuticas, métodos de tratamiento de enfermedades mediadas por CCR2 y como controles en análisis para la identificación de antagonistas de CCR2 competitivos.

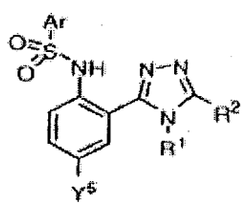
Se cree que los compuestos de la invención interfieren con el inapropiado tráfico de células T modulando o inhibiendo específicamente una función del receptor de quimiocina. Sin pretender vincularse a una teoría en particular, se cree que los compuestos proporcionados en la presente interfieren con la interacción entre un receptor de

quimiocina y uno o más ligandos cognado. En particular, se cree que los compuestos interfieren con la interacción entre CCR9 y un ligando CCR9, tal como TECK. Los compuestos contemplados por la invención incluyen, pero no se limitan a, los compuestos ejemplares proporcionados en la presente y sales de los mismos.

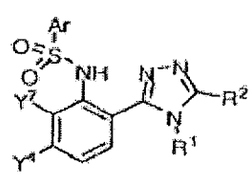
Por ejemplo, los compuestos de esta invención actúan como potentes antagonistas de CCR9, y esta actividad antagonista se ha confirmado además en pruebas en animales para la inflamación, uno de los característicos estados de enfermedad para CCR9. Por consiguiente, los compuestos proporcionados en la presente son útiles en las composiciones farmacéuticas, métodos para el tratamiento de enfermedades mediadas por CCR9 y como controles en análisis para la identificación de antagonistas de CCR9 competitivos.

Compuestos Preferidos

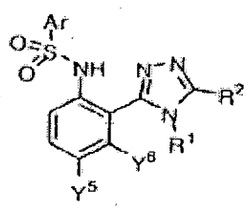
En varias modalidades preferidas, los compuestos pueden representarse por las siguientes fórmulas, o sus sales:



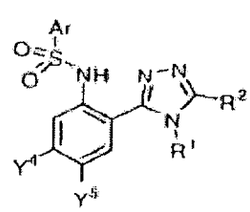
(X)



(XI)

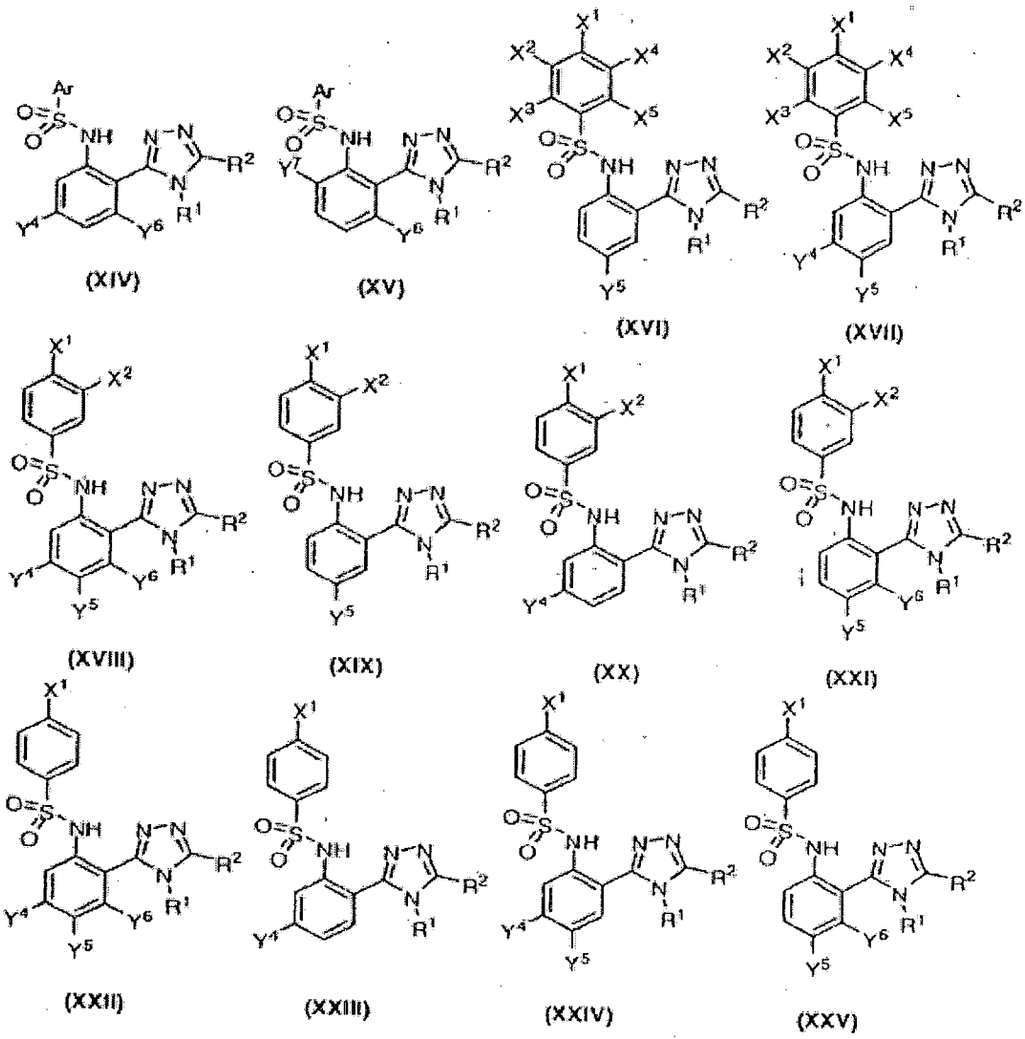


(XII)



(XIII)

222



Las fórmulas X a XXV son ejemplos de la Fórmula I.

En las siguientes descripciones y modalidades, las referencias a sustituyentes específicos solamente corresponden a los números de fórmula en los cuales se encuentran presentes o aparecen esos sustituyentes específicos.

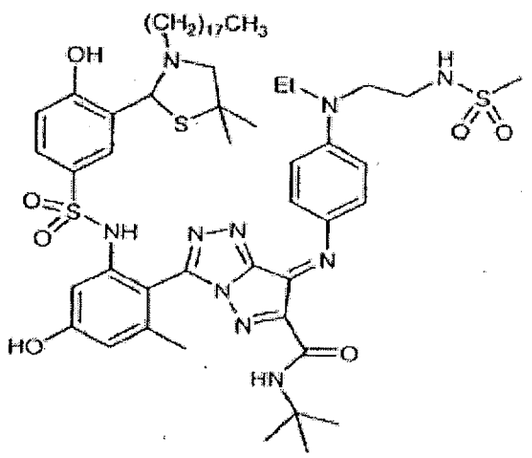
En cada una de las fórmulas (X a XXV), Ar, X^1, X^2,

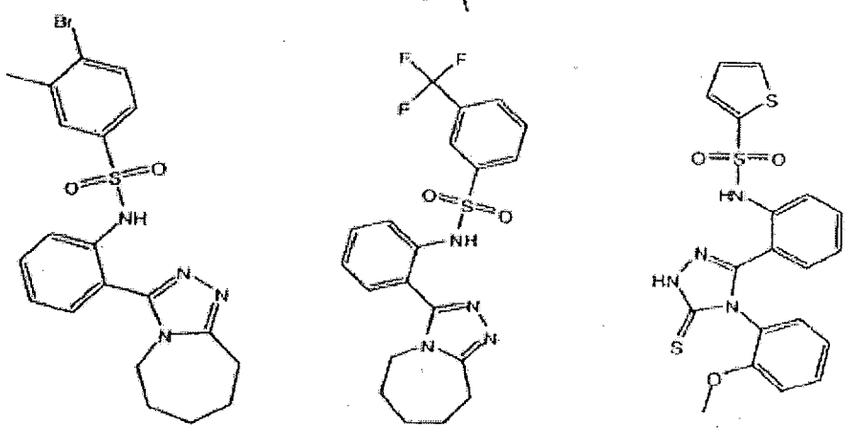
223

X^3, X^4, X^5, Y^4, Y^5, Y^6, Y^7, R^1 y R^2 son como se definió anteriormente.

Compuesto Conocido

El compuesto mostrado abajo:





también referido como

N-(1,1-dimetiletil)-3-[2-[[[3-(5,5-dimetil-3-octadecil-2-tiazolidinil)-4-hidroxifenil]sulfonil]amino]-4-hidroxi-6-metilfenil]-7-[[4-[etil[2-[(metilsulfonil)amino]etil]amino]fenil]imino]-7H-pirazolo[5,1-c]-1,2,4-triazol-6-carboxamida;

224

Bencenosulfonamida, 4-bromo-3-metil-N-[2-(6,7,8,9-tetrahidro-5H-1,2,4-triazolo[4,3-a]azepin-3-il)fenil];

Bencenosulfonamida, N-[2-(6,7,8,9-tetrahidro-5H-1,2,4-triazolo[4,3-a]azepin-3-il)fenil]-3-(trifluorometil); y

2-tiofenosulfonamida, N-[2-[4,5-dihidro-4-(2-metoxifenil)-5-tioxo-1H-1,2,4-triazol-3-il]fenil];

se conoce, pero no como CCR2 o antagonistas de CCR2.

Modalidades Preferidas

En una modalidad de la fórmula (II), X^1 se selecciona del grupo que consiste de halógeno, alquilo C_{1-8} sustituido o no sustituido, $-OR^{18}$, $-NR^{18}R^{19}$ y heterociclilo de 3 a 10 miembros sustituido o no sustituido; Y^7 es hidrógeno; Y^4, Y^5 y Y^6 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, halógeno, -CN, $-CO_2R^{15}$, $-C(O)NR^{15}R^{16}$; R^1 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido y heteroarilo de 5 a 10 miembros sustituido o no sustituido; y R^2 se selecciona del grupo que consiste de hidrógeno, alquilo C_{1-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido y heteroarilo de 5 a 10 miembros sustituido o no sustituido.

En una modalidad de la fórmula (III) X^1 es

225

halógeno; X^2 es halógeno o $-CF_3$; Y^4 es halógeno; Y^5 es hidrógeno o halógeno; R^1 es arilo o heteroarilo; y R^2 es hidrógeno o alquilo C_{1-8} sustituido o no sustituido.

En una modalidad de la fórmula (V), Y^5 es halógeno o hidrógeno; R^1 es arilo C_{6-10} sustituido o no sustituido y heteroarilo de 5 a 10 miembros sustituido o no sustituido; y R^2 es como se definió para la fórmula (I).

En una modalidad de la fórmula (III), X^2 y Y^4 son cada uno independientemente hidrógeno o halógeno; X^1 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o no sustituido, $-OR^{18}$, $-NR^{18}R^{19}$ y heterociclilo de 3 a 10 miembros sustituido o no sustituido; Y^5 se selecciona del grupo que consiste de hidrógeno, halógeno, -CN, $-CO_2R^{15}$, $-C(O)NR^{15}R^{16}$; R^1 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido y heteroarilo de 5 a 10 miembros sustituido o no sustituido; R^2 se selecciona del grupo que consiste de hidrógeno, alquilo C_{1-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido o heteroarilo de 5 a 10 miembros sustituido o no sustituido.

En una modalidad de la fórmula (IV), Y^4 es hidrógeno o halógeno; X^1 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o no sustituido, $-OR^{18}$, $-NR^{18}R^{19}$ y

heterociclilo de 3 a 10 miembros sustituido o no sustituido; Y^5 se selecciona del grupo que consiste de hidrógeno, halógeno, -CN, $-CO_2R^{15}$, $-C(O)NR^{15}R^{16}$; R^1 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido y heteroarilo de 5 a 10 miembros sustituido o no sustituido; R^2 se selecciona del grupo que consiste de hidrógeno, alquilo C_{1-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido o heteroarilo de 5 a 10 miembros sustituido o no sustituido.

En una modalidad de la fórmula (V), Y^5 es halógeno o hidrógeno; R^1 es arilo C_{6-10} sustituido o no sustituido y heteroarilo de 5 a 10 miembros sustituido o no sustituido; y R^2 se selecciona del grupo que consiste de hidrógeno, $C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$ y alquilo C_{1-8} sustituido o no sustituido.

En una modalidad de la fórmula (VI), Y^4 es hidrógeno o fluoro; R^1 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido y heteroarilo de 5 a 10 miembros sustituido o no sustituido; y R^2 se selecciona del grupo que consiste de hidrógeno, alquilo C_{1-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido o

227

heteroarilo de 5 a 10 miembros sustituido o no sustituido.

En una modalidad de la fórmula (VII), Y^4 es hidrógeno o fluoro; R^2 se selecciona del grupo que consiste de hidrógeno, alquilo C_{1-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido y heteroarilo de 5 a 10 miembros sustituido o no sustituido; y R^3 y R^4 son cada uno independientemente hidrógeno, alquilo C_{1-8} sustituido o no sustituido, o R^3 y R^4 conjuntamente con el carbono al cual sustituyen forman un anillo carbocíclico de 3 a 10 miembros un heterociclilo de 4-10 miembros, heteroarilo de 5-10 miembros o un anillo de arilo de 6-10 miembros.

En una modalidad de la fórmula (VIII), X^1 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o no sustituido, $-OR^{18}$, $-NR^{18}R^{19}$ y heterociclilo de 3 a 10 miembros sustituido o no sustituido; Y^4 es hidrógeno o fluoro; Y^5 es cloro; W es NH u O; y n es 0, 1 o 2.

En una modalidad de la fórmula (VIII), Y^4 y Y^5 son como se definió para la fórmula (I); X^1 es ter-butilo, con la salvedad de que al menos uno de Y^4 y Y^5 es diferente a hidrógeno; W es NH u O; y n es 0, 1 o 2.

En una modalidad de la fórmula (VIII), X^1 es ter-butilo; Y^4 es hidrógeno o fluoro; Y^5 es cloro; W es NH u O; y n es 0, 1 o 2.

En una modalidad de la fórmula (XXIV), X^1 es ter-

228

butilo, Y^4 y Y^5 son halógenos; y R^1 y R^2 son como se definió para la fórmula (I).

En una modalidad de la fórmula (XXIV), X^1 es ter-butilo, Y^4 es hidrógeno y Y^5 es -CN; y R^1 y R^2 son como se definió para la fórmula (I).

En una modalidad de la fórmula (XXIV), X^1 es ter-butilo, Y^4 es fluoro y Y^5 es cloro; y R^1 y R^2 son como se definió para la fórmula (I).

En una modalidad de la fórmula (XXIV), X^1 es ter-butilo, Y^4 y Y^5 son halógeno y R^1 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o no sustituido y heterociclilo de 3 a 10 miembros sustituido o no sustituido; y R^2 es como se definió para la fórmula (I).

En una modalidad de la fórmula (XXIV), X^1 es ter-butilo, Y^4 y Y^5 son halógeno, y R^1 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o no sustituido y heterociclilo de 3 a 10 miembros sustituido o no sustituido; y R^2 es alquilo C_{2-8} sustituido o no sustituido y heterociclilo de 3 a 10 miembros sustituido o no sustituido.

En una modalidad de la fórmula (VI), R^1 es heterociclilo, y R^2 es hidrógeno o alquilo C_{1-8} sustituido o no sustituido.

En una modalidad de la fórmula (XXV), X^1 es t-butilo, Y^5 es cloro y Y^6 es fluoro.

En una modalidad de la fórmula (XXIV), X^1 es t-

229

butilo, Y^4 es fluoro y Y^5 es fluoro.

En una modalidad de la fórmula (XXIV), X^1 es t-butilo, Y^4 es fluoro y Y^5 es cloro.

En una modalidad de las fórmulas (IV y XXII-XXV), X^1 es t-Bu o -OiPr; X^2, Y^4, Y^5 y Y^6 son cada uno independientemente hidrógeno o halógeno,

en donde al menos uno de Y^4, Y^5 y Y^6 es halógeno; y R^1 y R^2 se definen como en la fórmula (I).

En una modalidad de las fórmulas (IV y XXII-XXV), X^1 es alquilo C_{1-8} sustituido o no sustituido, $-NR^{18}R^{19}$ o $-OR^{18}$; X^2, Y^4, Y^5 y Y^6 son cada uno independientemente hidrógeno o halógeno, en donde al menos uno de Y^4, Y^5 y Y^6 es halógeno; y R^1 y R^2 se definen como en la fórmula (I).

En una modalidad de las fórmulas (IV y XXII-XXV), X^1 es alquilo C_{1-8} sustituido o no sustituido, $-NR^{18}R^{19}$ o $-OR^{18}$; X^2, Y^4, Y^5 y Y^6 son cada uno independientemente halógeno o hidrógeno, en donde al menos uno de Y^4, Y^5 y Y^6 es halógeno; R^1 es hidrógeno, Me, Et, i-Bu, i-Pr, ciclopropilo, ciclobutilo, ciclopentilo, $-CH(CH_3)CH_2OH$, $-CH_2CH_2NH_2$, $-CH_2CH_2NHC(O)CH_3$, fenilo, 2-piridilo, 4-piridilo, 1H-pirazol-3-ilo, tetrahidrofuran-3-ilo, tetrahidro-2H-piran-3-ilo, tetrahidro-2H-piran-4-ilo, azetidin-3-ilo, pirrolidin-3-ilo, 1-isopreopilpirrolidin-3-ilo, 1-(metilsulfonil)pirrolidin-3-ilo, 1-(carboxamido)pirrolidin-3-ilo, piperidin-3-ilo, piperidin-4-ilo, 1-carboxamido-piperidin-4-ilo, 1-

230

metilsulfonil-piperidin-4-ilo, 1-acetil-piperidin-4-ilo, 1-metil-piperidin-4-ilo, o 3-pirrolidin-2-ilo; R^2 es hidrógeno, Me, Et, i-Pr, $-NH_2$, $-CH_2OH$, $-C(CH_3)_2OH$, $-CH(OH)CH_3$, $-CH_2C(CH_3)_2OH$, $-CH_2C(O)OCH_2CH_3$, $-CH_2OCH_3$, $-CH_2OCH(CH_3)_2$, $-CH_2CH_2OCH_3$, $-CH_2N(CH_3)_2$, $-CH_2NHCH_3$, $-CH_2NHCH_2CH_3$, $-CH_2NHCH(CH_2CH_2)$, $-CH_2NHCH(CH_3)_2$, $-CH_2SO_2CH_3$, $-CH_2CH_2SO_2CH_3$, $-CH(O)CH_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, 2-piridilo, oxazol-4-ilo, 5-metiloxazol-4-ilo, tetrahidro-2H-piran-3-ilo, tetrahidro-2H-piran-4-ilo, tetrahidro-4-metil-2H-piran-4-ilo, tetrahidrofuran-2-ilo, tetrahidrofuran-3-ilo, morfolinometilo, piperidin-4-ilo, (pirrolidin-1-il)metilo, o (azetidin-1-il)metilo).

En una modalidad de las fórmulas (III, y XVIII-XXI), X^2, Y^4, Y^5, y Y^6 son halógeno, y X^1, R^1 y R^2 se definen como en la fórmula (I).

Grupos Ar Preferidos

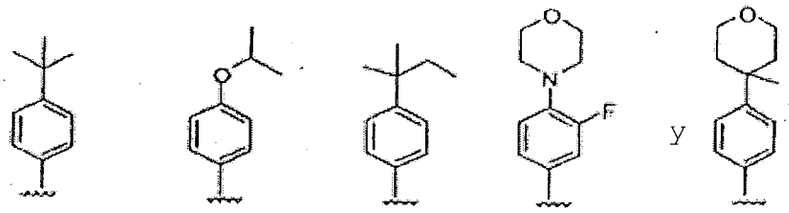
En una modalidad de cualquiera de las fórmulas (I y X-XV), Ar se selecciona del grupo que consiste de arilo C_{6-10} sustituido o no sustituido y heteroarilo de 5 a 10 miembros sustituido o no sustituido.

En una modalidad de cualquiera de las fórmulas (I y X-XV), Ar es un arilo C_{6-10} con al menos 2 sustituyentes diferentes a hidrógeno.

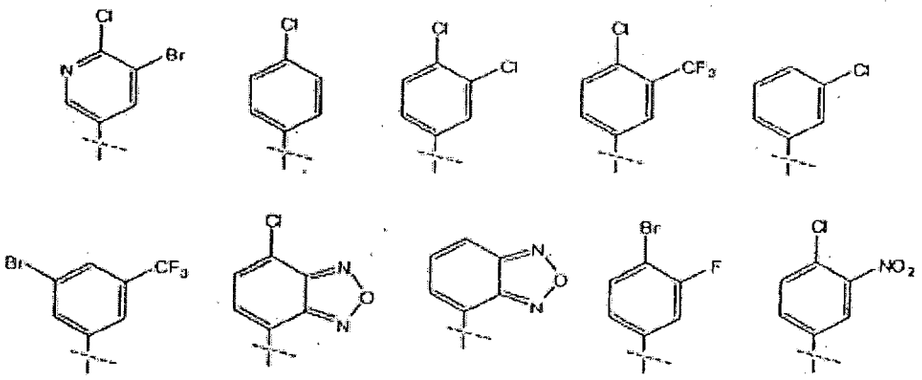
En una modalidad de cualquiera de las fórmulas (I y X-XV), Ar es un arilo bicíclico sustituido o no sustituido o

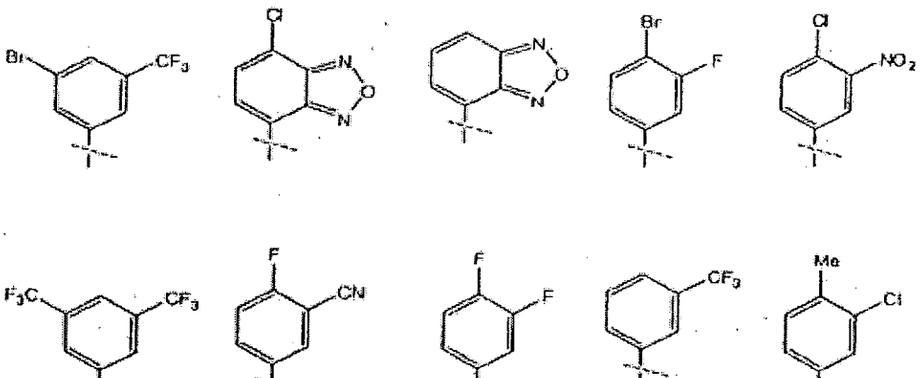
heteroarilo bicíclico sustituido o no sustituido.

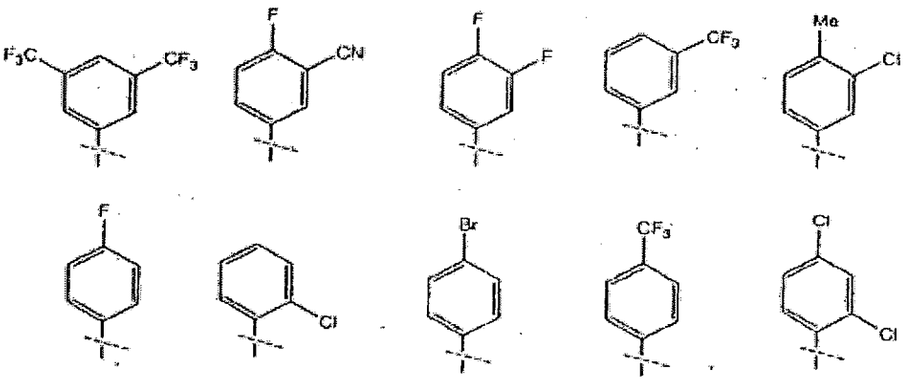
En una modalidad de cualquiera de las fórmulas (I y X-XV), Ar se selecciona del grupo que consiste de:

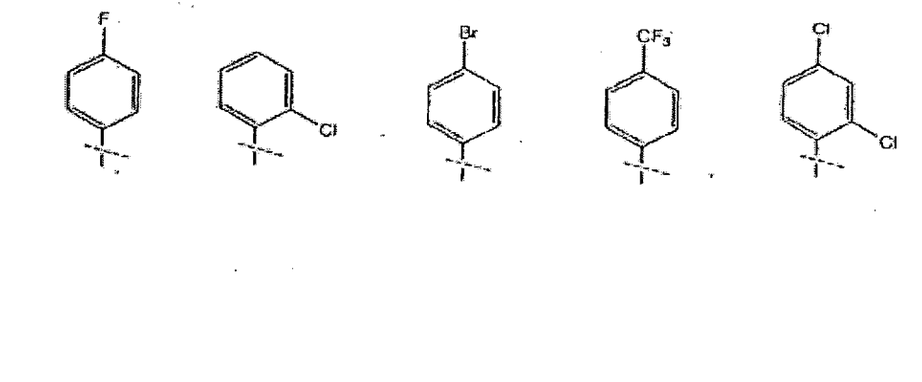


En una modalidad de cualquiera de las fórmulas (I y X-XV), Ar se selecciona del grupo que consiste de:

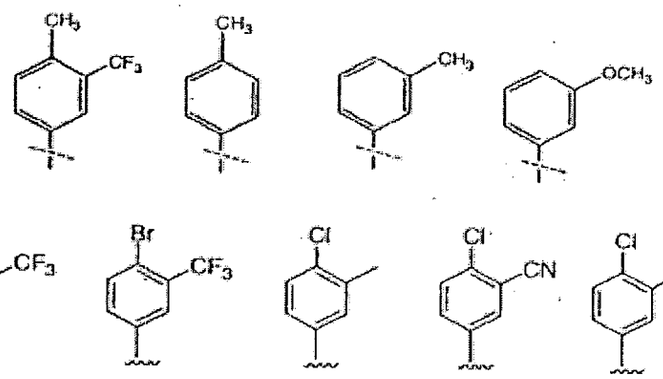


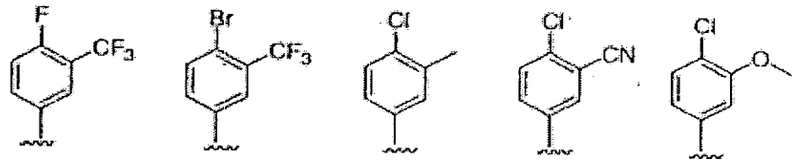






232





Grupos X Preferidos

En una modalidad de las fórmulas (II-IV y XX-XV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es diferente a hidrógeno.

En una modalidad de las fórmulas (II, III, XVI-XXI), al menos dos de X^1, X^2, X^3, X^4 y X^5 son diferentes a hidrógeno.

En una modalidad de las fórmulas (II, III, XVI-XXI), X^1 y X^2 son diferentes a hidrógeno.

En una modalidad de las fórmulas (II, IV, VIII, IX y XX-XV), X^1, X^2, X^3, X^4 y X^6 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, halógeno, -CN, $-NO_2$, $-OR^{18}$, $-C(O)R^{18}$, $-SO_2R^{18}$, $-NR^{18}R^{19}$, alquilo C_{1-8} no sustituido o sustituido, fenilo no sustituido o sustituido, heteroarilo de 5 o 6 miembros no sustituido o sustituido y heterociclilo de 5 o 6 miembros no sustituido o sustituido.

En una modalidad de la fórmula (II-IV, VIII, IX y XX-XV), X^1, X^2, X^3, X^4 y X^5 se seleccionan cada uno

independientemente del grupo que consiste de hidrógeno, halógeno, -CN, $-NO_2$, $-OR^{18}$, $-C(O)R^{18}$, $-SO_2R^{18}$, $-NR^{18}R^{19}$, alquilo C_{2-8} no sustituido, alquilo C_{1-8} sustituido, fenilo no sustituido o sustituido, heteroarilo de 5 o 6 miembros no sustituido o sustituido y heterociclilo de 5 o 6 miembros no sustituido o sustituido.

En una modalidad de la fórmula (II-IV, VIII, IX y XX-XV), X^1, X^2, X^3, X^4 y X^5 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, halógeno, -CN, $-NO_2$, $-OR^{18}$, $-C(O)R^{18}$, $-SO_2R^{18}$, $-NR^{18}R^{19}$, alquilo C_{1-8} no sustituido o sustituido, fenilo no sustituido o sustituido, heteroarilo de 5 o 6 miembros no sustituido o sustituido y heterociclilo de 5 o 6 miembros no sustituido o sustituido; con la salvedad de que al menos dos de X^1, X^2, X^3, X^4 y X^5 son diferentes a hidrógeno; o con la salvedad de que al menos uno de X^1, X^2, X^3, X^4 y X^5 es diferente a hidrógeno.

En otra modalidad de la fórmula (II-IV, VIII, IX y XX-XV), X^1, X^2, X^3, X^4 y X^5 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, halógeno, -CN, $-NO_2$, $-OR^{18}$, $-C(O)R^{18}$, $-SO_2R^{18}$, $-NR^{18}R^{19}$, alquilo C_{1-8} no sustituido o sustituido, fenilo no sustituido o sustituido, heteroarilo de 5 o 6 miembros no sustituido o sustituido y heterociclilo de 5 o 6 miembros no sustituido o sustituido; con la salvedad de que al menos dos de X^1, X^2 y X^4 son diferentes a hidrógeno; o con la salvedad de que al menos

uno de X^1, X^2 y X^4 es diferente a hidrógeno.

En una modalidad adicional de la fórmula (II-IV, VIII, IX y XX-XV), X^1, X^2, X^3, X^4 y X^5 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, halógeno, -CN, $-NO_2$, $-OR^{18}$, $-C(O)R^{18}$, $-SO_2R^{18}$, y $-NR^{18}R^{19}$; con la salvedad de que al menos tres de X^1, X^2, X^3, X^4 y X^5 son diferentes a hidrógeno; o con la salvedad de que al menos dos de X^1, X^2, X^3, X^4 y X^5 son diferente a hidrógeno; o con la salvedad de que al menos uno de X^1, X^2, X^3, X^4 y X^5 es diferente a hidrógeno.

En una modalidad adicional de la fórmula (II-IV, VIII, IX y XX-XV), X^1, X^2, X^3, X^4 y X^5 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, halógeno, alquilo C_{1-8} no sustituido o sustituido, fenilo no sustituido o sustituido, heteroarilo de 5 o 6 miembros no sustituido o sustituido o heterociclilo de 5 o 6 miembros no sustituido o sustituido; con la salvedad de que al menos tres de X^1, X^2, X^3, X^4 y X^5 son diferentes a hidrógeno; o con la salvedad de que al menos dos de X^1, X^2, X^3, X^4 y X^5 son diferente a hidrógeno; o con la salvedad de que al menos uno de X^1, X^2, X^3, X^4 y X^5 es diferente a hidrógeno.

En una modalidad de las fórmulas (II-IV, VIII, IX y XX-XV), cualquiera de las ocurrencias de X^1, X^2, X^3, X^4 y X^5 que se ubican adyacentes entre sí, puede unirse para formar un heterociclilo de 5 o 6 miembros sustituido o no sustituido

o heteroarilo sustituido o no sustituido.

En una modalidad de las fórmulas (II-IV, VIII, IX y XVI-XXV), X^1 es diferente a hidrógeno.

En una modalidad de las fórmulas (II-IV, VIII, IX y XVI-XXV), X^1 es diferente a metilo.

En una modalidad de las fórmulas (II-IV, VIII, IX y XVI-XXV), X^1 se selecciona del grupo que consiste de hidrógeno, halógeno, alquilo C_{1-8} sustituido o no sustituido, alquenilo C_{2-8} sustituido o no sustituido, alquinilo C_{2-8} sustituido o no sustituido, -CN, $-C(O)R^{18}$, $-CO_2R^{18}$, $-C(O)NR^{18}R^{19}$, $-OC(O)R^{19}$, $-OC(O)NR^{18}R^{19}$, $-NO_2$, $-NR^{18}C(O)NR^{19}R^{20}$, $-NR^{18}R^{19}$, $-NR^{18}CO_2R^{19}$, $-NR^{18}S(O)_2R^{19}$, $-SR^{18}$, $-S(O)R^{18}$, $-S(O)_2R^{18}$, $-S(O)_2NR^{18}R^{19}$, arilo C_{6-10} sustituido o no sustituido, heteroarilo de 5 a 10 miembros sustituido o no sustituido, y heterociclilo de 3 a 10 miembros sustituido o no sustituido.

En una modalidad de las fórmulas (II-IV, VIII, IX y XVI-XXV), X^1 se selecciona del grupo que consiste de -CN, $-NO_2$, $-C(O)R^{18}$, $-CO_2R^{18}$, $-C(O)NR^{18}R^{19}$, $-OR^{18}$, $-OC(O)R^{19}$, $-OC(O)NR^{18}R^{19}$, $-NO_2$, $-NR^{18}CO_2R^{19}$, $-NR^{18}C(O)NR^{19}R^{20}$, $-NR^{18}R^{19}$, $-NR^{18}CO_2R^{19}$, $-NR^{18}S(O)_2R^{19}$, $-SR^{18}$, $-S(O)R^{18}$, $-S(O)_2R^{18}$, y $-S(O)_2NR^{18}R^{19}$.

En una modalidad de la fórmula (II-IV, VIII, IX y XVI-XXV), X^1 es $-OR^{18}$.

En una modalidad de la fórmula (II-IV, VIII, IX y XVI-XXV), X^1 es $-NR^{18}R^{19}$.

En una modalidad de la fórmula (II-IV, VIII, IX y XVI-XXV), X^1 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o no sustituido, alquenilo C_{2-8} sustituido o no sustituido, y alquinilo C_{2-8} sustituido o no sustituido.

En una modalidad de la fórmula (II-IV, VIII, IX y XVI-XXV), X^1 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o alquilo C_{2-8} no sustituido, alquenilo C_{2-8} sustituido o no sustituido, y alquinilo C_{2-8} sustituido o no sustituido.

En una modalidad de las fórmulas (II-IV, VIII, IX y XVI-XXV), X^1 es un alquilo C_{2-8} no sustituido.

En una modalidad de las fórmulas (II-IV, VIII, IX y XVI-XXV), X^1 es ter-butilo.

En una modalidad de las fórmulas (II-IV, VIII, IX y XVI-XXV), X^1 es iso-propoxi.

En una modalidad de las fórmulas (II-IV, VIII, IX y XVI-XXV), X^1 es morfolinilo.

En una modalidad de las fórmulas (II-IV, VIII, IX y XVI-XXV), X^1 se selecciona del grupo que consiste de arilo C_{6-10} sustituido o no sustituido, heteroarilo de 5 a 10 miembros sustituido o no sustituido y heterociclilo de 3 a 10 miembros sustituido o no sustituido.

En una modalidad de las fórmulas (II-IV, VIII, IX y XVI-XXV), X^1 se selecciona del grupo que consiste de fenilo sustituido o no sustituido, heteroarilo de 5 a 6 miembros

sustituido o no sustituido, y heterociclilo de 5 a 6 miembros sustituido o no sustituido.

En una modalidad de las fórmulas (II-IV, VIII, IX y XVI-XXV), X^1 es fenilo sustituido o no sustituido.

En una modalidad de las fórmulas (II-IV, VIII, IX y XVI-XXV), X^1 es heteroarilo de 5 a 6 miembros sustituido o no sustituido.

En una modalidad de las fórmulas (II-IV, VIII, IX y XVI-XXV), X^1 es heterociclilo de 5 a 6 miembros sustituido o no sustituido.

En una modalidad de las fórmulas (II-IV, VIII, IX y XVI-XXV), cuando X^2, X^3, X^4 y X^5 son hidrógeno, X^1 es diferente a -Cl, $-NO_2$, $-OCH_3$, $-CH_3$, $-NHC(O)CH_3$ o $-CH_2CH_2$-(fenilo).

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), X^1 es un anillo heterocíclico de 5 o 6 miembros sustituido o no sustituido, y el heterociclo se selecciona del grupo que consiste de pirrolidina, piperidina, imidazolidina, pirazolidina, butirolactam, valerolactam, imidazolidinona, hindantoína, dioxolano, ftalimida, piperidina, 1,4-dioxano, morfolina, tiomorfolina, tiomorfolina-S-óxido, tiomorfolina-S,S-dióxido, piperazina, pirano, piridona, 3-pirrolina, tiopirano, pirona, tetrahidrofurano y tetrahidrotiofeno.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), X^1 es un anillo heteroarilo de 5 o 6

miembros sustituido o no sustituido seleccionado del grupo que consiste de piridilo, piridazinilo, pirazinilo, pirimidinilo, triazinilo, isotiazolilo, pirazolilo, imidazolilo, tienilo, furilo, triazolilo, tetrazolilo, oxazolilo, isoxazolilo, oxadiazolilo, tiadiazolilo, pirrolilo y tiazolilo.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), X^1 es un grupo heterocíclico sustituido o no sustituido seleccionado del grupo que consiste de pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, 1,3-dioxalanilo, tiomorfolinilo, tiomorfolinil-S,S-dióxido, piperazinilo y piranilo.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), X^1 es alquilo C_{1-8} sustituido. Preferentemente, el sustituyente es un grupo heterociclilo sustituido o no sustituido de la fórmula (AA) como se define en el párrafo [0044], [0045] y [0046]. Más preferentemente, el sustituyente se selecciona del grupo que incluye pirrolidina, piperidina, imidazolidina, pirazolidina, butirolactam, valerolactam, imidazolidinona, hindantoína, dioxolano, ftalimida, piperidina, 1,4-dioxano, morfolina, tiomorfolina, tiomorfolina-S-óxido, tiomorfolina-S,S-dióxido, piperazina, pirano, piridona, 3-pirrolina, tiopirano, pirona, tetrahidrofurano y tetrahidrotiofeno.

En una modalidad de cada una de las fórmulas (II-

IV, VIII, IX y XVI-XXV), un sustituyente adecuado para el alquilo C_{1-8} sustituido (X^1, X^2, X^3, X^4 o X^5) puede seleccionarse del grupo que consiste de -CN, $-OR^{18}$, $-C(O)R^{18}$, $-CO_2R^{18}$, $-O(CO)R^{18}$, $-SO_2R^{18}$ y halógeno. En una modalidad, X^1, X^2, X^3, X^4 y X^5 son hidrógeno.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es halógeno, particularmente cloro.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es un alquilo C_{1-8} no sustituido.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es un alquilo C_{2-8} no sustituido.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es t-butilo.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es oxazolilo.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es trifluorometoxi.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es

240

$-SO_2R^{18}$. En una modalidad particular, R^{18} es metilo.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es $-OR^{18}$. En una modalidad particular, R^{18} es metilo.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es $-SR^{18}$. En una modalidad particular, R^{18} es metilo.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es alquilo C_{1-6} no sustituido (en particular metilo) o haloalquilo C_{1-6} (en particular $-CF_3$).

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es alquilo C_{1-6} sustituido (preferentemente no haloalquilo C_{1-6}).

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es isopropilo.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es un ciano.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es un grupo ciano, halógeno o trifluorometilo.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es

241

$-C(Me)_2CH_2OH$.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es $-C(O)Me$.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es $-(CH_2)_2CO_2Me$.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es isoamilo.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es 1,3-dioxalanilo.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es furilo.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es pirazolilo.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), al menos uno de X^1, X^2, X^3, X^4 y X^5 es tienilo.

En una modalidad de cada una de las fórmulas (II-IV, VIII, IX y XVI-XXV), X^1 es un alquilo C_{1-8} sustituido, en donde los sustituyentes adecuados son como se definió para la

fórmula (II). En una modalidad preferida, el alquilo C_{1-8} sustituido se sustituye con un heteroarilo de 5 a 6 miembros seleccionado del grupo que consiste de piridilo, piridazinilo, pirazinilo, pirimidinilo, triazinilo, isotiazolilo, pirazolilo, imidazolilo, tienilo, furilo, triazolilo, tetrazolilo, oxazolilo, isoxazolilo, oxadiazolilo, tiadiazolilo, pirrolilo y tiazolilo. Más preferentemente, el alquilo C_{1-8} sustituido se sustituye con oxazolilo.

En una modalidad de la fórmula (II-IV, VIII y XVI-XXV), X^1 y X^2 son diferentes a hidrógeno.

En una modalidad de la fórmula (II-IV, VIII y XVI-XXV), X^1 y X^2 se seleccionan del grupo que consiste de halógeno, alquilo C_{1-8} sustituido o no sustituido, OR^{18}, $-NO_2$, -CN y $-CO_2R^{18}$.

En una modalidad de las fórmulas (II, III, XVI-XXI), al menos uno de X^1 y X^2 se selecciona del grupo que consiste de halógeno, -CN y $-CF_3$.

En una modalidad de las fórmulas (II, III, XVI-XXI), tanto X^1 como X^2 se seleccionan del grupo que consiste de halógeno, -CN y $-CF_3$.

En una modalidad adicional de las fórmulas (II, III, XVI-XXI), uno de X^1 y X^2 es halógeno y uno de X^1 y X^2 se selecciona del grupo que consiste de halógeno, -CN y $-CF_3$.

En una modalidad adicional de las fórmulas (II,

III, XVI-XXI), uno de X^1 y X^2 es halógeno y uno de X^1 y X^2 se selecciona del grupo que consiste de halógeno, -CN, $-CH_3$ y $-CF_3$.

En una modalidad adicional de las fórmulas (II, III, XVI-XXI), X^1 se selecciona del grupo que consiste de halógeno y $-CH_3$ y X^2 se selecciona del grupo que consiste de halógeno, -CN, $-CH_3$, $-OCH_3$, $-OCF_3$ y $-CF_3$.

En una modalidad de la fórmula (II, III, XVI-XXI), X^1 se selecciona del grupo que consiste de halógeno y $-CH_3$, y X^2 se selecciona del grupo que consiste de halógeno, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCF_3$, $-CF_2H$ y CF_2R^{10}, en donde R^{10} es alquilo C_{1-8} sustituido o no sustituido.

En una modalidad de la fórmula (II, III, XVI-XXI), X^1 y X^2 se seleccionan del grupo que consiste de -Cl, -F, -Br, $-CF_3$, $-CONHCH_3$, $-OCF_3$, $-CH_3$, $-OCH_3$, $-NO_2$, -CN y $-CO_2H$.

En una modalidad de la fórmula (II, III, XVI-XXI), X^1 se selecciona del grupo que consiste de halógeno y $-CH_3$ y X^2 se selecciona del grupo que consiste de halógeno, $-CH_3$, $-CF_3$, $-OCH_3$ y $-OCF_3$.

En una modalidad de la fórmula (II, III, XVI-XXI), X^1 es cloro y X^2 es $-CF_3$.

En una modalidad de la fórmula (II, III, XVI-XXI), X^2 es diferente a hidrógeno.

En una modalidad de las fórmulas (II, III, XVI-XXI), X^2 es diferente a hidrógeno.

En una modalidad de la fórmula (II, III, XVI-XXI), X^2 se selecciona del grupo que consiste de halógeno, alquilo C_{1-8} sustituido o no sustituido, $-OR^{18}$, $-NO_2$, -CN y $-CO_2R^{18}$.

En una modalidad de la fórmula (II, III, XVI-XXI), X^2 se selecciona del grupo que consiste de -Cl, -F, -Br, $-CF_3$, $-CONHCH_3$, $-OCF_3$, $-CH_3$, $-OCH_3$, $-NO_2$, -CN y $-CO_2H$.

En una modalidad de las fórmulas (II, III, XVI-XXI), X^2 es fluoro.

Grupos Y Preferidos

En una modalidad de cualquiera de las fórmulas (I-IX y X-XXV), Y^4, Y^5, Y^6 y Y^7 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, halógeno, -CN, $-CO_2R^{15}$, $-OR^{15}$ y alquilo C_{1-8} sustituido o no sustituido, en donde de 1 a 2 de Y^4, Y^5, Y^6 y Y^7 son diferentes a hidrógeno.

En una modalidad de cualquiera de las fórmulas (I-IX y X-XXV), Y^4, Y^5, Y^6 y Y^7 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, -CN, flúor, cloro, y bromo, en donde de 1 a 2 de Y^4, Y^5, Y^6 y Y^7 son diferentes a hidrógeno.

En una modalidad de cualquiera de las fórmulas (I-IX y X-XXV), al menos uno de Y^4, Y^5, Y^6 y Y^7 es diferente a hidrógeno; preferentemente Y^4 es halógeno.

En otra modalidad de cualquiera de las fórmulas (I-VIII y X-XXV), al menos uno de Y^4, Y^5, Y^6 y Y^7 es diferente a

hidrógeno; preferentemente Y^5 es halógeno.

En otra modalidad de cualquiera de las fórmulas (I-VIII y X-XXV), Y^5 y Y^7 son hidrógeno y Y^4 es halógeno.

En otra modalidad de cualquiera de las fórmulas (I-VIII y X-XXV), Y^5 y Y^7 son hidrógeno y Y^4 es cloro.

En una modalidad de cualquiera de las fórmulas (I-II y X-XXV), Y^7 y Y^6 son hidrógeno y Y^4 y Y^5 son fluoro.

En una modalidad de cualquiera de las fórmulas (I-II y X-XXV), Y^7 y Y^6 son hidrógeno y Y^4 es cloro y Y^5 es $-CH_3$.

En una modalidad de cualquiera de las fórmulas (I-IX y X-XXV), Y^4 y Y^5 se seleccionan del grupo que consiste de halógeno, -CN, $-OR^{15}$ y alquilo C_{1-8} sustituido o no sustituido.

En una modalidad de cualquiera de las fórmulas (I-IX y X-XXV), Y^4 y Y^5 se seleccionan del grupo que consiste de -Cl, -Br, -F, $-OCH_3$, $-CH_3$, $-CF_3$ y -CN.

En una modalidad de cualquiera de las fórmulas (I-IV, VI-IX y X-XXV), Y^4 se selecciona del grupo que consiste de -Cl, -Br, -F y $-OCH_3$.

En una modalidad de cualquiera de las fórmulas (I-IV, VI-IX, XI, XIII, XIV, XVII, XVIII, XX, XXII-XXIV), Y^4 es halógeno.

En una modalidad de cualquiera de las fórmulas (I-IV, VI-IX, XI, XIII, XIV, XVII, XVIII, XX, XXII-XXIV), Y^4 es fluoro.

En una modalidad de cualquiera de las fórmulas (I-

IV, VI-IX, XI, XIII, XIV, XVII, XVIII, XX, XXII-XXIV), Y^4 es cloro.

En una modalidad de cualquiera de las fórmulas (I-V, VIII, X, XII, XIII, XVI-XIX, XXI, XXII, XXIV, XXV), Y^5 se selecciona del grupo que consiste de -Cl, -Br, -F, $-CH_3$, $-CF_3$ y -CN.

En una modalidad de cualquiera de las fórmulas (I-V, VIII, X, XII, XIII, XVI-XIX, XXI, XXII, XXIV, XXV), Y^5 es halógeno.

En una modalidad de cualquiera de las fórmulas (I-V, VIII, X, XII, XIII, XVI-XIX, XXI, XXII, XXIV, XXV), Y^5 es cloro.

En una modalidad de cualquiera de las fórmulas (I-V, VIII, X, XII, XIII, XVI-XIX, XXI, XXII, XXIV, XXV), Y^5 es fluoro.

En una modalidad de cualquiera de las fórmulas (I-V, VIII, X, XII, XIII, XVI-XIX, XXI, XXII, XXIV, XXV), Y^5 es -CN.

En una modalidad de cualquiera de las fórmulas (I, II, XII, XIV, XV, XVIII, XXI, XXII, XXV), Y^6 es fluoro.

En una modalidad de cualquiera de las fórmulas (I, II, XII, XIV, XV, XVIII, XXI, XXII, XXV), Y^5 es cloro y Y^6 es fluoro.

En una modalidad de cualquiera de las fórmulas (I-IV VIII, XIII, XVII, XVIII, XXII, XXIV), Y^5 es cloro y Y^4 es

fluoro.

En una modalidad de cualquiera de las fórmulas (I-IV VIII, XIII, XVII, XVIII, XXII, XXIV), Y^5 y Y^4 son fluoro.

En una modalidad de cualquiera de las fórmulas (I-IV VIII, XIII, XVII, XVIII, XXII, XXIV), Y^5 es -CN y Y^4 es fluoro.

En una modalidad de cualquiera de las fórmulas (I-IV VIII, XIII, XVII, XVIII, XXII, XXIV), Y^5 es -CN y Y^4 es hidrógeno.

Grupos R^1 y R^2 preferidos

En una modalidad de las fórmulas (I-VI, IXa y X-XXV), R^1 es diferente a hidrógeno.

En una modalidad de las fórmulas (I-VI, IXa y X-XXV), R^1 se selecciona del grupo que consiste de $-C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$, $-S(O)R^7$, $-S(O)_2R^7$ y $-S(O)_2NR^7R^8$.

En una modalidad de las fórmulas (I-VI, IXa y X-XXV), R^1 y R^2 conjuntamente con los átomos a los cuales sustituyen forman un anillo carbocíclico o heterocíclico.

En una modalidad de las fórmulas (I-VI, IXa y X-XXV), R^1 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o no sustituido, alquenilo C_{2-8} sustituido o no sustituido, alquinilo C_{2-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido, y heteroarilo de 5 a 10 miembros sustituido o no sustituido.

En una modalidad de las fórmulas (I-VI, IXa y X-XXV), R^1 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o no sustituido, alquenilo C_{2-8} sustituido o no sustituido, alquinilo C_{2-8} sustituido o no sustituido, heterociclilo de 5 o 6 miembros sustituido o no sustituido, fenilo sustituido o no sustituido, y heteroarilo de 5 a 6 miembros sustituido o no sustituido.

En una modalidad de las fórmulas (I-VI, IXa y X-XXV), R^1 es alquilo C_{1-8} sustituido o no sustituido.

En una modalidad de las fórmulas (I-VI, IXa y X-XXV), R^1 es fenilo sustituido o no sustituido.

En una modalidad de las fórmulas (I-VI, IXa y X-XXV), R^1 es heteroarilo de 5 a 6 miembros sustituido o no sustituido.

En una modalidad de las fórmulas (I-VI, IXa y X-XXV), R^1 es heterociclilo de 5 a 6 miembros sustituido o no sustituido.

En una modalidad de las fórmulas (I-VI, IXa y X-XXV), R^1 es metilo, etilo o isopropilo.

En una modalidad de las fórmulas (I-VI, IXa y X-XXV), R^1 se selecciona del grupo que consiste de fenilo no sustituido o sustituido, piridilo no sustituido o sustituido, y pirazolilo no sustituido o sustituido.

En una modalidad de las fórmulas (I-VI, IXa y X-XXV), R^1 es metilo, etilo, isopropilo o isobutilo.

En una modalidad de las fórmulas (I-VI, IXa y X-XXV), R^1 es ciclopropilo, ciclobutilo o ciclopentilo.

En una modalidad de las fórmulas (I-VI, IXa y X-XXV), R^1 es heterociclilo.

En una modalidad de las fórmulas (I-VII, IXb y X-XXV), R^2 es hidrógeno.

En una modalidad de las fórmulas (I-VII, IXb y X-XXV), R^2 es diferente a hidrógeno.

En una modalidad de las fórmulas (I-VII, IXb y X-XXV), R^2 se selecciona del grupo que consiste de halógeno, -CN, $-C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$, $-OR^7$, $-OC(O)R^7$, $-OC(O)NR^7R^8$, $-SR^7$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2NR^7R^8$, $-NO_2$, $-NR^7R^8$, $-NR^7C(O)R^8$, $-NR^7C(O)OR^8$, $-NR^7S(O)_2R^8$, y $-NR^7C(O)NR^8R^9$.

En una modalidad de las fórmulas (I-VII, IXb y X-XXV), R^2 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o no sustituido, alquenilo C_{2-8} sustituido o no sustituido, alquinilo C_{2-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido, y heteroarilo de 5 a 10 miembros sustituido o no sustituido.

En una modalidad de las fórmulas (I-VII, IXb y X-XXV), R^2 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o no sustituido, alquenilo C_{2-8} sustituido o no sustituido, alquinilo C_{2-8} sustituido o no sustituido, heterociclilo de 5 a 6 miembros sustituido o no sustituido,

fenilo sustituido o no sustituido, y heteroarilo de 5 a 6 miembros sustituido o no sustituido.

En una modalidad de las fórmulas (I-VII, IXb y X-XXV), R^2 es alquilo C_{1-8} sustituido o no sustituido.

En una modalidad de las fórmulas (I-VII, IXb y X-XXV), R^2 es fenilo sustituido o no sustituido.

En una modalidad de las fórmulas (I-VII, IXb y X-XXV), R^2 es heterociclilo de 5 a 6 miembros sustituido o no sustituido.

En una modalidad de las fórmulas (I-VII, IXb y X-XXV), R^2 es heteroarilo de 5 a 6 miembros sustituido o no sustituido.

En una modalidad de las fórmulas (I-VII, IXb y X-XXV), R^2 es metilo.

En una modalidad de las fórmulas (I-VII, IXb y X-XXV), R^2 se selecciona del grupo que consiste de metilo, etilo, isopropilo y 4-tetrahidro-4H-piranilo.

En una modalidad de las fórmulas (I-VII, IXb y X-XXV), R^2 es metilo, etilo o isopropilo.

En una modalidad de las fórmulas (I-VII, IXb y X-XXV), R^2 es alquilo C_{1-8} sustituido.

En una modalidad de las fórmulas (I-VII, IXb y X-XXV), R^2 es $-CH_2OR^7$ o $-CH_2NR^7R^8$.

En una modalidad de las fórmulas (I-VII, y X-XXV), R^1 y R^2 se combinan para formar un anillo de 6 miembros.

Grupos R^3 y R^4 Preferidos

En una modalidad de la fórmula (VII y IXb), R^3 y R^4 son cada uno hidrógeno.

En una modalidad de la fórmula (VII y IXb), uno de R^3 y R^4 es hidrógeno y el otro es alquilo C_{1-8} no sustituido o sustituido.

En una modalidad de la fórmula (VII y IXb), tanto R^3 como R^4 son alquilo C_{1-8} no sustituido o sustituido.

En una modalidad de la fórmula (VII y IXb), R^3 y R^4 conjuntamente con el átomo de carbono al cual sustituyen forman un anillo carboxílico de 3-10 miembros.

En una modalidad de la fórmula (VII y IXb), R^3 y R^4 conjuntamente con el carbono al cual sustituyen forman un anillo heterocíclico de 4-10 miembros.

En una modalidad de la fórmula (VII y IXb), R^3 y R^4 conjuntamente con el carbono al cual sustituyen forman un anillo heteroarilo de 5-10 miembros.

Grupos W Preferidos

En una modalidad de la fórmula (VIII y VIIb), W es NH.

En una modalidad de la fórmula (VIII y VIIb), W es O.

Compuestos Ejemplares

Los siguientes compuestos se encuentran dentro del alcance de la fórmula (I):

4-ter-butil-N-(4-cloro-2-(4,5-diisopropil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4,5-dimetil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-ciclopentil-5-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-ciclopropil-5-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-etil-5-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-isopropil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-isopropil-5-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-metil-5-(tetrahidro-2H-piran-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-fenil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-(metoximetil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-etil-4-isopropil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-isopropil-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-(1H-pirazol-3-

il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-(piridin-2-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-(piridin-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-(tetrahidro-2H-piran-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-fenil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

N-(4-cloro-2-(4-isopropil-5-metil-4H-1,2,4-triazol-3-il)fenil)-4-isopropoxibencenosulfonamida;

N-(2-(3-(2-(4-ter-butilfenilsulfonamido)-5-clorofenil)-5-metil-4H-1,2,4-triazol-4-il)etil)acetamida;

(R)-4-ter-butil-N-(4-cloro-2-(4-metil-5-(tetrahidrofuran-2-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4,5-difluoro-2-(4-pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(4-(1-hidroxipropan-2-il)-5-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(4-metil-5-

(tetrahidrofuran-2-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(2-(4-etil-4H-1,2,4-triazol-3-il)-4,5-difluorofenil)bencenosulfonamida;

4-ter-butil-N-(2-(4-etil-4H-1,2,4-triazol-3-il)-5-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4,5-difluoro-2-(4-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4,5-dietil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4,5-dimetil-4H-1,2,4-triazol-3-il)-3-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4,5-dimetil-4H-1,2,4-triazol-3-il)-5-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-etil-4H-1,2,4-triazol-3-il)-3-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-etil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-etil-5-isopropil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-etil-5-metil-4H-1,2,4-triazol-3-il)-3-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-isobutil-5-metil-4H-

1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-metil-5-(oxazol-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-(dimetilamino)metil)-4-metil-4H-1,2,4-triazol-3-il)-5-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-(2-metoxietil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-(metoximetil)-4-(tetrahidro-2H-piran-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-(piperidin-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-(piperidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(5-cloro-2-(4-isopropil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(5-cloro-2-(4-isopropil-5-(4-metiltetrahidro-2H-piran-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(5-fluoro-2-(4-isopropil-5-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

N-(4-cloro-2-(4-etil-5-metil-4H-1,2,4-triazol-3-

il)fenil)-4-isopropoxibencenosulfonamida;

etil 2-(5-(2-(4-ter-butilfenilsulfonamido)-5-cloro-4-fluorofenil)-4-metil-4H-1,2,4-triazol-3-il)acetato;

5-(2-(4-ter-butilfenilsulfonamido)-5-cloro-4-fluorofenil)-4-metil-4H-1,2,4-triazol-3-carboxamida;

5-(2-(4-ter-butilfenilsulfonamido)-5-cloro-4-fluorofenil)-N,4-dimetil-4H-1,2,4-triazol-3-carboxamida;

(R)-4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(1-hidroxietil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(4-(piperidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(4-(tetrahidro-2H-piran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(5-metil-4-(piperidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-5-fluoro-2-(4-(piperidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-5-fluoro-2-(4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-5-fluoro-2-(4-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(1-hidroxietil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-5-fluoro-2-(5-metil-4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-N-(4-cloro-2-(4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)-4-isopropoxibencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-isopropil-5-(tetrahidro-2H-piran-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-metil-5-(5-metiloxazol-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-((ciclopropilamino)metil)-4-metil-4H-1,2,4-triazol-3-il)-5-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-((etilamino)metil)-4-metil-4H-1,2,4-triazol-3-il)-5-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-etil-4-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)-5-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-etil-4-metil-4H-1,2,4-triazol-3-il)-5-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-etil-4-metil-4H-1,2,4-

triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-(tetrahidro-2H-piran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-isopropil-5-(metoximetil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-((metilamino)metil))-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-(metilsulfonilmetil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-(morfolinometil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-(oxazol-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-(pirrolidin-1-ilmetil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-(tetrahidro-2H-piran-3-il)-4H-1,2,4-triazol-3-

il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-(tetrahidro-2H-piran-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-((isopropilamino)metil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(1-hidroxietil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(2-hidroxi-2-metilpropil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(2-hidroxipropan-2-il)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(2-metoxietil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(hidroximetil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(metoximetil)-4-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(metoximetil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

N-(2-(5-(azetidin-1-ilmetil)-4-metil-4H-1,2,4-triazol-3-il)-4-cloro-5-fluorofenil)-4-ter-butilbencenosulfonamida;

N-(2-(5-acetil-4-metil-4H-1,2,4-triazol-3-il)-4-cloro-5-fluorofenil)-4-ter-butilbencenosulfonamida;

(S)-4-ter-butil-N-(4,5-difluoro-2-(5-(metil-4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(5-etil-4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(5-isopropil-4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(5-metil-4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(2-(4,5-dimetil-4H-1,2,4-triazol-3-il)-5-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(2-(4-etil-5-metil-4H-1,2,4-triazol-3-il)-4,5-difluorofenil)bencenosulfonamida;

4-ter-butil-N-(2-(4-etil-5-metil-4H-1,2,4-triazol-3-il)-5-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-metil-5-(piperidin-4-il)-4H-1,2,4-triazol-3-il)-5-fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-isopropil-4H-1,2,4-triazol-3-il)-5-fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-isopropil—5-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil—5-(metiloxazol-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-isopropil—4-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-metil—4-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

N-(4-cloro-2-(4,5-dimetil-4H-1,2,4-triazol-3-il)fenil)-4-isopropoxibencenosulfonamida;

N-(4-cloro-2-(4-isopropil-4H-1,2,4-triazol-3-il)fenil)-4-isopropoxibencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(5-etil-4-(pirrolidin-

3-il)-4H-1,2,4-triazol-3-il)-5-fluorofenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-5-fluoro-2-(oxopirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-5-fluoro-2-(5-isopropil-4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-N-(4-cloro-2-(4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)-4-(4-metilterahidro-2H-piran-4-il)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-ciclobutil-5-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-etil-5-isopropil-4H-1,2,4-triazol-3-il)-5-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-isopropil-5-(trifluorometil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-(1-metilpiperidin-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-(2-metilsulfonil)etil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

N-(2-(4-(1-acetilpiperidin-4-il)-5-metil-4H-1,2,4-

triazol-3-il)-4-clorofenil)-4-ter-butilbencenosulfonamida;

N-(2-(4-(2-aminoetil)-5-metil-4H-1,2,4-triazol-3-il)-4-clorofenil)-4-ter-butilbencenosulfonamida;

N-(2-(4-(1-acetidin-3-il)-4H-1,2,4-triazol-3-il)-4-cloro-5-fluorofenil)-4-ter-butilbencenosulfonamida;

(R)-4-ter-butil-N-(4-cloro-2-(5-metil-4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(2-(4,5-dimetil-4H-1,2,4-triazol-3-il)-4,5-difluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-isopropil-5-(metoximetil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-metil-5-(piridin-2-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-metil-5-(tetrahidrofuran-2-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-((dimetilamino)metil)-4-isopropil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-(isopropoximetil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-

il)fenil)bencenosulfonamida;

4-(3-(2-(4-ter-butilfenilsulfonamido)-5-clorofenil)-5-metil-4H-1,2,4-triazol-3-il)piperidina-1-carboxamida;

4-ter-butil-N-(4-cloro-2-(4-(2-(dimetilamino)etil)-5-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-(1-(metilsulfonil)piperidin-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-(2-(metilamino)etil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(5-cloro-2-(4-isopropil-5-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

N-(2-(4-(1-acetilpirrolidin-3-il)-5-metil-4H-1,2,4-triazol-3-il)-4-clorofenil)-4-ter-butilbencenosulfonamida;

N-(2-(5-amino-4-isopropil-4H-1,2,4-triazol-3-il)-4-clorofenil)-4-ter-butilbencenosulfonamida;

(R)-4-ter-butil-N-(4-cloro-5-fluoro-2-(4-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(R)-4-ter-butil-N-(4-cloro-2-(4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-ciano-2-(5-etil-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-(4-ter-butilfenilsulfonamido)-3-(5-etil-4-metil-4H-1,2,4-triazol-3-il)benzamida;

ácido 4-(4-ter-butilfenilsulfonamido)-3-(5-etil-4-metil-4H-1,2,4-triazol-3-il)benzoico;

N-(2-(4-(azetidin-3-il)-4H-1,2,4-triazol-3-il)-4-clorofenil)-4-ter-butilbencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-metil-5-((metilamino)metil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

metil 4-(4-ter-butilfenilsulfonamido)-3-(5-etil-4-metil-4H-1,2,4-triazol-3-il)benzoato;

N-(4-cloro-2-(4,5-dimetil-4H-1,2,4-triazol-3-il)fenil)-3-fluoro-4-morfolinobencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-(2-metoxietil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(2-hidroxietil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-(isopropilamino)metil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(1-metoxietil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(R)-4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-(pirrolidin-2-il)-4H-1,2,4-triazol-3-

il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(4-(1-isopropilpirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-3-(3-(2-(4-ter-butilfenilsulfonamido)-5-clorofenil)-4H-1,2,4-triazol-4-il)pirrolidina-1-carboxamida;

4-ter-butil-N-(4-cloro-2-(4-metil-5-(morfolinometil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-(piperidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-(piperazin-1-ilmetil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-((tetrahidrofuran-3-ilamino)metil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(((2-metoxietil)metil)amino)metil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-isopropil-5-(4-metiltetrahidro-2H-piran-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-((4-

metilpiperazin-1-il)metil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-((tetrahidro-2H-piran-4-ilamino)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(4-(1-(metilsulfonil)pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-isopropil-5-(morfolinometil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

N-(2-(1H-pirazol-3-il)-4H-1,2,4-triazol-3-il)-5-clorofenil)-4-cloro-3-(trifluorometil)bencenosulfonamida;

4-cloro-N-(5-cloro-2-(5-metil-4-(1H-pirazol-3-il)-4H-1,2,4-triazol-3-il)fenil)-3-(trifluorometil)bencenosulfonamida;

4-cloro-N-(5-cloro-2-(5-fenil-4H-1,2,4-triazol-3-il)fenil)-3-(trifluorometil)bencenosulfonamida;

N-(2-(4-(1H-pirazol-3-il)-4H-1,2,4-triazol-3-il)-5-cloro-4-fluorofenil)-4-cloro-3-(trifluorometil)bencenosulfonamida;

5-(4-cloro-2-(4-cloro-3-(trifluorometil)fenilsulfonamido)-5-fluorofenil)-4-(1H-pirazol-3-il)-4H-1,2,4-triazol-3-carboxamida; y

N-(2-([1,2,4]triazol[4,3-a]pirimidin-3-il)-4-

clorofenil)-4-ter-butilbencenosulfonamida.

Composiciones que modulan la Actividad de Quimiocina

En otro aspecto, la presente invención proporciona composiciones que modulan la actividad de quimiocina, específicamente la actividad de CCR2 o la actividad de CCR9. Generalmente, las composiciones para modular la actividad del receptor de quimiocina en humanos y animales comprenderá un excipiente o diluyente farmacéuticamente aceptable y un compuesto que tiene la fórmula proporcionada anteriormente como la fórmula (I).

El término "composición", como se utiliza en la presente pretende abarcar un producto que comprende los ingredientes especificados en las cantidades especificadas, así como cualquier producto que resulte, directa o indirectamente de la combinación de los ingredientes especificados en las cantidades especificadas. Por "farmacéuticamente aceptable" se entiende que el vehículo, diluyente o excipiente debe ser compatible con los otros ingredientes de la formulación y no nocivo al recipiente del mismo.

Las composiciones farmacéuticas para la administración de los compuestos de esta invención pueden presentarse convenientemente en forma de dosis unitaria y pueden prepararse mediante cualquiera de los métodos muy

conocidos en la técnica farmacéutica. Todos los métodos incluyen la etapa de poner el ingrediente activo en asociación con el vehículo que constituye uno o más ingredientes accesorios. En general, las composiciones farmacéuticas se preparan poniendo el ingrediente activo uniformemente e íntimamente en asociación con un vehículo líquido o un vehículo sólido finamente dividido o ambos, y después, si es necesario, dando forma al producto en la formulación deseada. En la composición farmacéutica el compuesto activo objetivo se incluye en una cantidad suficiente para producir el efecto deseado al proceso o condición de las enfermedades.

Las composiciones farmacéuticas que contienen el ingrediente activo pueden encontrarse en una forma adecuada para uso oral, por ejemplo, como tabletas, pastillas, comprimidos, suspensiones acuosas u oleosas, polvos o gránulos dispersables, emulsiones y auto emulsiones como se describe en la Patente de E.U. No. 6,451,339, cápsulas duras o blandas o jarabes o elíxires. Las composiciones destinadas a uso oral pueden prepararse de acuerdo con cualquier método conocido por la técnica para la fabricación de composiciones farmacéuticas. Tales composiciones pueden contener uno o más agentes seleccionados de agentes edulcorantes, agentes saborizantes, agentes colorantes y agentes conservadores, a fin de proporcionar preparaciones farmacéuticamente elegantes

y paladeables. Las tabletas contienen el ingrediente activo en mezcla con otros excipientes no tóxicos farmacéuticamente aceptables que son adecuados para la fabricación de tabletas. Estos excipientes, por ejemplo, pueden ser diluyentes inertes, tales como celulosa, dióxido de silicona, óxido de aluminio, carbonato de calcio, carbonato de sodio, glucosa, manitol, sorbitol, lactosa, fosfato de calcio o fosfato de sodio; agentes de granulado y desintegración, por ejemplo, almidón de maíz, o ácido algínico; agentes aglomerantes, por ejemplo PVP, celulosa, PEG, almidón, gelatina o acacia, y agentes lubricantes, por ejemplo, estearato de magnesio, ácido esteárico o talco. Las tabletas pueden ser no recubiertas o pueden recubrirse entéricamente o de otra manera mediante técnicas conocidas para retardar la desintegración y la absorción en el tracto gastrointestinal y, en consecuencia, proporcionar una acción sostenida durante un período más largo. Por ejemplo, puede emplearse un material de retraso de tiempo tal como monoestearato de glicerilo o diestearato de glicerilo. También pueden recubrirse mediante las técnicas descritas en las Patentes de E.U. Nos. 4,256,108; 4,166,452 y 4,265,874 para formar tabletas terapéuticas osmóticas para liberación controlada.

Las formulaciones para uso oral también pueden presentarse como cápsulas de gelatina duras, en donde el ingrediente activo se mezcla con un diluyente sólido inerte,

por ejemplo, carbonato de calcio, fosfato de calcio o caolina, o como cápsulas de gelatina blandas, en donde el ingrediente activo se mezcla con agua o un medio oleoso, por ejemplo, aceite de maní, parafina líquida o aceite de oliva. Adicionalmente, las emulsiones pueden prepararse con un ingrediente no mezclable en agua tal como aceites y estabilizarse con surfactantes tales como mono-diglicéridos, ésteres de PEG y lo similar.

Las suspensiones acuosas contienen los materiales activos en mezcla con excipientes adecuados para la fabricación de suspensiones acuosas. Tales excipientes son agentes de suspensión, por ejemplo, carboximetilcelulosa de sodio, metilcelulosa, hidroxi-propilmetilcelulosa, alginato de sodio, polivinil-pirrolidona, goma tragacanto y goma acacia; los agentes de dispersión o humectación pueden ser una fosfatida de origen natural, por ejemplo, lecitina, o productos de condensación de un óxido de alquileno con ácidos grasos, por ejemplo, estearato de polioxi-etileno, o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo, heptadecaetilenoxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol tal como monooleato de polioxietileno sorbitol o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y anhídridos de

hexitol, por ejemplo, monooleato de polietileno sorbitán. Las suspensiones acuosas también pueden contener uno o más conservadores, por ejemplo, etilo, o n-propilo, p-hidroxibenzoato, uno o más agentes colorantes, uno o más agentes saborizantes y uno o más agentes edulcorantes tales como sacarosa o sacarina.

Las suspensiones oleosas pueden formularse suspendiendo el ingrediente activo en un aceite vegetal, por ejemplo aceite de arachis, aceite de oliva, aceite de ajonjolí o aceite de coco, o en un aceite mineral tal como parafina líquida. Las suspensiones oleosas pueden contener un agente espesante, por ejemplo, cera de abejas, parafina dura o alcohol cetílico. Los agentes edulcorantes tales como los expuestos anteriormente, y los agentes saborizantes pueden agregarse para proporcionar una preparación oral paladeable. Estas composiciones pueden preservarse mediante la adición de un anti-oxidante tal como ácido ascórbico.

Los polvos y gránulos dispersables adecuados para la preparación de una suspensión acuosa mediante la adición de agua, proporcionan el ingrediente activo en mezcla con un agente de dispersión o de humectación, un agente de suspensión y uno o más conservadores. Los agentes de dispersión o de humectación adecuados y los agentes de suspensión se ejemplifican por aquellos ya mencionados anteriormente. También pueden encontrarse presentes

excipientes adicionales, por ejemplo, agentes edulcorantes, saborizantes y colorantes.

Las composiciones farmacéuticas de la invención pueden encontrarse también en forma de emulsiones de aceite en agua. La fase oleosa puede ser un aceite vegetal, por ejemplo aceite de oliva o aceite de arachis o un aceite mineral, por ejemplo, parafina líquida o mezclas de éstos. Los agentes emulsificantes adecuados pueden ser gomas de origen natural, por ejemplo goma acacia o goma tragacanto, fosfatidas de origen natural por ejemplo, semilla de soja, lecitina y ésteres o ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo, monooleato de sorbitan, y productos de condensación de dichos ésteres parciales con óxido de etileno, por ejemplo monooleato de polioxietileno sorbitan. Las emulsiones también pueden contener agentes edulcorantes y saborizantes.

Los jarabes y elíxires pueden formularse con agentes edulcorantes, por ejemplo, glicerol, propileno glicol, sorbitol o sacarosa. Tales formulaciones también pueden contener un emoliente un conservador y agentes saborizantes y colorantes. Las soluciones orales pueden prepararse en combinación con, por ejemplo, ciclodextrina, PEG y surfactantes.

Las composiciones farmacéuticas pueden encontrarse en forma de una suspensión acuosa u oleosa estéril

inyectable. Esta suspensión puede formularse de acuerdo con la técnica conocida utilizando aquellos agentes de dispersión o de humectación adecuados y agentes de suspensión que se han mencionado anteriormente. La preparación inyectable estéril también puede ser una solución o suspensión estéril inyectable en un diluyente o solvente no tóxico parenteralmente aceptable, por ejemplo, como una solución en 1,3-butano diol. Entre los vehículos y solventes aceptables que pueden emplearse, se encuentran agua, solución de Ringer y solución isotónica de cloruro de sodio. Además, se emplean convencionalmente aceites fijados estériles como un medio solvente o de suspensión. Para este propósito, puede emplearse cualquier aceite blando fijado incluyendo mono o diglicéridos sintéticos. Además los ácidos grasos tales como ácido oleico encuentran su uso en la preparación de inyectables.

Las composiciones farmacéuticas también pueden administrarse en forma de supositorios para administración rectal del fármaco. Estas composiciones pueden prepararse mezclado el fármaco con un excipiente adecuado no irritante que es sólido a temperaturas ordinarias pero es líquido a la temperatura rectal y, en consecuencia, se fundirá en el recto para liberar el fármaco. Tales materiales son manteca de cacao y polietileno glicoles. Adicionalmente, los compuestos pueden administrarse mediante suministro ocular por medio de

soluciones o ungüentos. Aún adicionalmente, el suministro transdérmico de los compuestos sujeto puede lograrse por medio de parches iontoforéticos y lo similar.

Para uso tópico, se emplean cremas, ungüentos, jaleas, soluciones o suspensiones que contienen los compuestos de la invención. Como se utiliza en la presente, la aplicación tópica también pretende incluir el uso de enjuagues bucales y gárgaras.

Las composiciones farmacéuticas y los métodos de la presente invención pueden comprender además otros compuestos terapéuticamente activos, como se anota en la presente, tales como los aplicados en el tratamiento de las condiciones patológicas antes mencionadas.

En una modalidad, la presente invención proporciona una composición que consiste de un vehículo farmacéuticamente aceptable y un compuesto de la invención.

Métodos de Tratamiento

Dependiendo de la enfermedad que va a tratarse y de la condición del sujeto, los compuestos y composiciones de la presente invención pueden administrarse mediante vías de administración oral, parenteral (e.g., inyección o infusión intramuscular, intraperitoneal, intravenosa, ICV, intracisternal, inyección subcutánea o implante) inhalación, nasal, vaginal, rectal, sublingual o tópicas y pueden formularse, solos o conjuntamente, en formulaciones unitarias

en dosis adecuadas que contienen portadores, adyuvantes o vehículos no tóxicos farmacéuticamente aceptables, apropiados para cada vía de administración. La presente invención también contempla la administración de los compuestos y composiciones de la presente invención en una formulación de depósito.

En el tratamiento o prevención de las condiciones que requieren la modulación del receptor de quimiocina, un nivel de dosis apropiado sería generalmente de aproximadamente 0.001 a 100 mg por kg del peso corporal del paciente por día, que pueden administrarse en dosis únicas o múltiples. Preferentemente, el nivel de dosis será de aproximadamente 0.01 a aproximadamente 25 mg/kg por día; más preferentemente de aproximadamente 0.05 a aproximadamente 10 mg/kg por día. Un nivel de dosis adecuado puede ser de aproximadamente 0.01 a 25 mg/kg por día, de aproximadamente 0.05 a 10 mg/kg por día o de aproximadamente 0.1 a 5 mg/kg por día. Dentro de este rango, la dosis puede ser de 0.005 a 0.05, de 0.05 a 0.5, de 0.5 a 5.0 o de 5.0 a 50 mg/kg por día. Para administración oral, las composiciones se proporcionan preferentemente en forma de tabletas que contienen de 1.0 a 1000 miligramos del ingrediente activo, particularmente 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0 y 1000.0 miligramos del ingrediente

activo para el ajuste sintomático de la dosis al paciente que se trata. Los compuestos pueden administrarse en un régimen de 1 a 4 veces por día, preferentemente una o dos veces al día.

Sin embargo, se entenderá que el nivel de dosis específico y la frecuencia de la dosis para cualquier paciente particular puede variar y dependerá de una variedad de factores que incluyen la actividad del compuesto específico empleado, la estabilidad metabólica y la longitud de acción de ese compuesto, la edad, peso corporal, características hereditarias, salud general, sexo, dieta, modo y tiempo de administración, tasa de excreción, combinación de fármacos, la severidad de la condición particular y del huésped que experimenta la terapia.

Aún en otras modalidades, los presentes métodos se dirigen al tratamiento de enfermedades alérgicas, en donde un compuesto o composición de la invención se administra ya sea solo o en combinación con un segundo agente terapéutico, en donde dicho segundo agente terapéutico es una antihistamina. Cuando se utiliza en combinación, el médico puede administrar una combinación del compuesto o composición de la presente invención y un segundo agente terapéutico. También el compuesto o composición y el segundo agente terapéutico pueden administrarse secuencialmente en cualquier orden.

Los compuestos y composiciones de la presente

invención pueden combinarse con otros compuestos y composiciones que tienen utilidades relacionadas para prevenir y tratar la condición o enfermedad de interés, tal como condiciones y enfermedades inflamatorias incluyendo enfermedad inflamatoria del intestino, enfermedades alérgicas, psoriasis, dermatitis atópica y asma, y aquellas patologías anotadas anteriormente. La selección de los agentes apropiados para su uso en terapias de combinación, puede efectuarse por el de experiencia ordinaria en la técnica. La combinación de los agentes terapéuticos puede actuar de manera sinérgica para efectuar el tratamiento o prevención de los varios trastornos. Al utilizar este procedimiento, se puede ser capaz de lograr la eficacia terapéutica con dosis menores de cada agente, reduciendo así el potencial para efectos secundarios adversos.

Para tratar, prevenir, mejorar, controlar o reducir el riesgo de inflamación, los compuestos de la presente invención pueden utilizarse en conjunción con un agente anti-inflamatorio o analgésico tal como un agonista opiato, un inhibidor de ciclooxigenasa, tal como el inhibidor de ciclooxigenasa 2, un inhibidor de interleucina tal como el inhibidor de interleucina 1, un antagonista de NMDA, un inhibidor de óxido nítrico o un inhibidor de la síntesis de óxido nítrico, un agente anti-inflamatorio no esteroidal, o un agente anti-inflamatorio supresor de citosina, por

ejemplo, con un compuesto tal como acetaminofén, aspirina, codeína, secuestrantes de TNF biológicos, fentanilo, ibuprofeno, indometacina, cetorolac, morfina, naproxeno, fenacetina, piroxicam, un analgésico esteroidal, sufentanilo, sunlindac, tenidap y lo similar.

De manera similar, los compuestos de la presente invención pueden administrarse con un aliviador del dolor; un potenciador tal como cafeína, un antagonista de H2, simeticona, hidróxido de aluminio o magnesio; un descongestivo tal como pseudoefedrina; un antitusivo tal como codeína; un diurético; una antihistamina sedante o no sedante; un antagonista de antígeno muy posterior (VLA-4); un inmunosupresor tal como ciclosporina, tacrolimus, rapamicina, agonistas del receptor EDG u otros inmunosupresores tipo FK-506; un esteroide; un agente anti-asmático no esteroidal tal como un agonista beta-2, antagonista de leucotrieno, o inhibidor de biosíntesis de leucotrieno; un inhibidor de fosfodiesterasa tipo IV (PDE-IV); un agente de disminución de colesterol tal como un inhibidor de HMG-CoA reductasa, secuestrante, o inhibidor de absorción de colesterol; y un agente anti-diabético tal como insulina, inhibidores de alfa-glucosidasa o glitazonas.

La proporción en peso del compuesto de la presente invención al segundo ingrediente activo puede variar y dependerá de la dosis efectiva de cada ingrediente.

Generalmente, se utilizará una dosis efectiva de cada uno. Por tanto, por ejemplo, cuando un compuesto de la presente invención se combina con un NSAID, la proporción en peso del compuesto de la presente invención al NSAID variará generalmente de aproximadamente 1000:1 a aproximadamente 1:1000, preferentemente de aproximadamente 200:1 a aproximadamente 1:200. Las combinaciones de un compuesto de la presente invención y otros ingredientes activos también se encontrarán dentro del rango antes mencionado, pero en cada caso, debe utilizarse una dosis efectiva de cada ingrediente activo.

Métodos para Tratar o Prevenir Condiciones o Enfermedades mediadas por CCR2

Condiciones y Enfermedades

Aún en otro aspecto, la presente invención proporciona métodos para tratar o prevenir una condición o enfermedad mediada por CCR2 administrando a un sujeto que tiene tal condición o enfermedad, una cantidad terapéuticamente activa de cualquier compuesto de la fórmula (I) anterior. Los compuestos para su uso en la presente invención incluyen aquellos compuestos de acuerdo con la fórmula (I), aquellos proporcionados anteriormente como modalidades, aquellos específicamente ejemplificados en los Ejemplos siguientes y aquellos proporcionados con estructuras específicas en la presente. El "sujeto" se define en la

presente incluyendo animales tales como mamíferos, incluyendo, pero sin limitarse a primates (e.g., humanos, vacas, ovejas, cabras, caballos, perros, gatos, conejos, ratas, ratones y lo similar. En modalidades preferidas, el sujeto es un humano.

Como se utiliza en la presente, la frase "condición o enfermedad mediada por CCR2" y frases y términos relacionados, se refiere a una condición o enfermedad caracterizada por la inapropiada actividad funcional de CCR2, i.e., menor que o mayor que la normal. la actividad funcional de CCR2 inapropiada puede surgir como resultado de la expresión de CCR2 en células que normalmente no expresan CCR2, de la expresión de CCR2 incrementada (que conduce, e.g., a trastornos y enfermedades inflamatorias e inmunorreguladoras) o de la expresión de CCR2 disminuida. La actividad funcional de CCR2 inapropiada también puede surgir como resultado de la secreción de MCP-1 por células que normalmente no secretan MCP-1, de la expresión de MCP-1 incrementada (que conduce a, e.g., trastornos y enfermedades inflamatorias e inmunorreguladoras o de la expresión de MCP-1 disminuida. Una condición o enfermedad mediada por CCR2 puede encontrarse mediada completa o parcialmente por la inapropiada actividad funcional de CCR2. Sin embargo, una condición o enfermedad mediada por CCR2 es una en la cual la modulación de CCR2 da como resultado algún efecto en la

condición o enfermedad subyacente (e.g., un antagonista de CCR2 da como resultado alguna mejoría en el bienestar del paciente en al menos algunos pacientes). Además, MCP-2, 3 y 4 también son ligandos de CCR2.

En una modalidad, la presente invención proporciona un método para tratar una condición o enfermedad mediada por CCR2 que implica administrar a un sujeto una cantidad segura y efectiva del compuesto o composición de la invención.

En una modalidad, la presente invención proporciona un método para tratar una condición o enfermedad mediada por CCR2 que implica administrar a un sujeto una cantidad segura y efectiva del compuesto o composición de la invención, en donde la condición o enfermedad mediada por CCR2 es aterosclerosis.

En una modalidad, la presente invención proporciona un método para tratar una condición o enfermedad mediada por CCR2 que implica administrar a un sujeto una cantidad segura y efectiva del compuesto o composición de la invención, en donde la condición o enfermedad mediada por CCR2 es restenosis.

En una modalidad, la presente invención proporciona un método para tratar una condición o enfermedad mediada por CCR2 que implica administrar a un sujeto una cantidad segura y efectiva del compuesto o composición de la invención, en donde la condición o enfermedad mediada por CCR2 es

esclerosis múltiple.

En una modalidad, la presente invención proporciona un método para tratar una condición o enfermedad mediada por CCR2 que implica administrar a un sujeto una cantidad segura y efectiva del compuesto o composición de la invención, en donde la condición o enfermedad mediada por CCR2 se selecciona del grupo que consiste de enfermedad inflamatoria intestinal, fibrosis renal, artritis reumatoide y diabetes no dependiente de insulina.

En una modalidad, la presente invención proporciona un método para tratar una condición o enfermedad mediada por CCR2 que implica administrar a un sujeto una cantidad segura y efectiva del compuesto o composición de la invención, en donde la condición o enfermedad mediada por CCR2 es diabetes tipo 2.

En una modalidad, la presente invención proporciona un método para tratar una condición o enfermedad mediada por CCR2 que implica administrar a un sujeto una cantidad segura y efectiva del compuesto o composición de la invención, en donde la condición o enfermedad mediada por CCR2 se selecciona del grupo que consiste de enfermedad pulmonar obstructiva crónica, fibrosis pulmonar idiopática y síndrome de neumonía idiopática.

En una modalidad, la presente invención proporciona un método para tratar una condición o enfermedad mediada por

CCR2 que implica administrar a un sujeto una cantidad segura y efectiva del compuesto o composición de la invención, en donde la administración es oral, parenteral, rectal, transdérmica, sublingual, nasal o tópica.

En una modalidad, la presente invención proporciona un método para tratar una condición o enfermedad mediada por CCR2 que implica administrar a un sujeto una cantidad segura y efectiva del compuesto o composición de la invención, en donde el compuesto se administra en combinación con un agente anti-inflamatorio o analgésico.

En una modalidad, la presente invención proporciona un método para tratar una condición o enfermedad mediada por CCR2 que implica administrar a un sujeto una cantidad segura y efectiva del compuesto o composición de la invención, en donde también se administra un agente anti-inflamatorio o analgésico.

En una modalidad, la presente invención proporciona un método para modular la función de CCR2 en una célula, en donde la función de CCR2 en la célula se modula poniendo en contacto la célula con una cantidad moduladora de CCR2 del compuesto de la presente invención.

En una modalidad, la presente invención proporciona un método para tratar una condición o enfermedad mediada por CCR2 que implica administrar a un sujeto una cantidad segura y efectiva del compuesto o composición de la invención, en

donde la enfermedad se selecciona del grupo que consiste de fibrosis pulmonar, rechazo al transplante, enfermedad de injerto contra huésped y cáncer.

Aún en otras modalidades, los presentes métodos se dirigen al tratamiento de psoriasis, en donde un compuesto o composición de la invención se utiliza solo o en combinación con un segundo agente terapéutico tal como un corticoesteroide, un lubricante, un agente queratolítico, un derivado de vitamina D3, PUVA y antralina.

En otras modalidades, los presentes métodos se dirigen al tratamiento de dermatitis atópica utilizando un compuesto o composición de la invención ya sea solo o en combinación con un segundo agente terapéutico tal como un lubricante y un corticoesteroide.

En modalidades adicionales, los presentes métodos se dirigen al tratamiento del asma utilizando un compuesto o composición de la invención ya sea solo o en combinación con un segundo agente terapéutico tal como un agonista beta-2 y un corticoesteroide.

Métodos para Tratar o Prevenir Condiciones o Enfermedades mediadas por CCR9

Condiciones o Enfermedades

Aún en otro aspecto, la presente invención proporciona métodos para tratar o prevenir una condición o enfermedad mediada por CCR9 administrando a un sujeto que

tiene tal condición o enfermedad, una cantidad terapéuticamente activa de cualquier compuesto de la fórmula (I) anterior. Los compuestos para su uso en la presente invención incluyen aquellos compuestos de acuerdo con la fórmula (I), aquellos proporcionados anteriormente como modalidades, aquellos específicamente ejemplificados en los Ejemplos siguientes y aquellos proporcionados con estructuras específicas en la presente. El "sujeto" se define en la presente incluyendo animales tales como mamíferos, incluyendo, pero sin limitarse a primates (e.g., humanos, vacas, ovejas, cabras, caballos, perros, gatos, conejos, ratas, ratones y lo similar. En modalidades preferidas, el sujeto es un humano.

Como se utiliza en la presente, la frase "condición o enfermedad mediada por CCR9" y frases y términos relacionados, se refiere a una condición o enfermedad caracterizada por la inapropiada actividad funcional de CCR9, i.e., menor que o mayor que la normal. La actividad funcional de CCR9 inapropiada puede surgir como resultado de la expresión de CCR9 en células que normalmente no expresan CCR9, de la expresión de CCR9 incrementada (que conduce, e.g., a trastornos y enfermedades inflamatorias e inmunorreguladoras) o de la expresión de CCR9 disminuida. La actividad funcional de CCR9 inapropiada también puede surgir como resultado de la secreción de TECK por células que

normalmente no secretan TECK, de la expresión de TECK incrementada (que conduce a, e.g., trastornos y enfermedades inflamatorias e inmunorreguladoras o de la expresión de TECK disminuida. Una condición o enfermedad mediada por CCR9 puede encontrarse mediada completa o parcialmente por la inapropiada actividad funcional de CCR9. Sin embargo, una condición o enfermedad mediada por CCR9 es una en la cual la modulación de CCR9 da como resultado algún efecto en la condición o enfermedad subyacente (e.g., un antagonista de CCR9 da como resultado alguna mejoría en el bienestar del paciente en al menos algunos pacientes).

El término "cantidad terapéuticamente efectiva" significa la cantidad del compuesto sujeto que emitirá la respuesta biológica o médica de una célula, tejido, sistema, o animal, tal como un humano, que se busca por el investigador, veterinario, médico u otro proveedor del tratamiento.

Las enfermedades y condiciones asociadas con inflamación, trastornos inmunes, infección y cáncer, pueden tratarse o prevenirse con los presentes compuestos, composiciones y métodos. En un grupo de modalidades, las enfermedades o condiciones, incluyendo enfermedades crónicas, de humanos u otras especies, pueden tratarse con inhibidores de la función de CCR9. Estas enfermedades o condiciones incluyen: (1) enfermedades alérgicas tales como anafilaxis

sistémica o respuestas de hipersensibilidad, alergias a fármacos, alergias a picaduras de insectos y alergias a alimentos, (2) enfermedades inflamatorias intestinales tales como enfermedad de Crohn, colitis ulcerativa, ileítis y enteritis, (3) vaginitis, (4) psoriasis y dermatosis inflamatorias tales como dermatitis, eczema, dermatitis atópica, dermatitis alérgica por contacto, urticaria y prurito, (5) vasculitis, (6) espondiloartropatías, (7) escleroderma, (8) asma y enfermedades alérgicas respiratorias tales como asma alérgica, rinitis alérgica, enfermedades de hipersensibilidad pulmonar y lo similar, (9) enfermedades autoinmunes, tales como fibromialgia, escleroderma, espondilitis anquilosante, RA juvenil, enfermedad de Still, RA juvenil poliarticular, RA juvenil pauciarticular, polimialgia reumática, artritis reumatoide, artritis psoriática, osteoartritis, artritis poliarticular, esclerosis múltiple, lupus eritematoso sistémico, diabetes tipo I, diabetes tipo II, glomerulonefritis y lo similar, (10) rechazo al transplante (incluyendo rechazo a alotransplante), (11) enfermedad de injerto contra huésped (incluyendo tanto aguda como crónica), (12) otras enfermedades en las cuales van a inhibirse las respuestas inflamatorias no deseadas, tales como aterosclerosis, miositis, enfermedades neurodegenerativas (e.g., enfermedad de Alzheimer), encefalitis, meningitis, hepatitis, nefritis, sepsis,

sarcoidosis, conjuntivitis alérgica, otitis, enfermedad pulmonar obstructiva crónica, síndrome de Behcet y gota, (13) alergias a alimentos mediadas por inmunidad tales como enfermedad Coeliac (Celiac), (14) fibrosis pulmonar y otras enfermedades fibróticas y (15) síndrome de intestino irritable.

En otro grupo de modalidades, las enfermedades o condiciones pueden tratarse con moduladores y agonistas de la función de CCR9. Ejemplos de enfermedades que van a tratarse modulando la función de CCR9 incluyen cánceres, enfermedades cardiovasculares, enfermedades en las cuales juega un papel la angiogénesis o la neovascularización, (enfermedades neoplásicas, retinopatía y degeneración macular), enfermedades infecciosas (infecciones virales, e.g., infección VIH e infecciones bacterianas) y enfermedades inmunosupresoras tales como condiciones de transplante de órganos y condiciones de transplante de piel. El término "condiciones de transplante de órganos" pretende incluir condiciones de transplante de médula ósea y condiciones de transplante de órganos sólidos (e.g., riñón, hígado, pulmón, páncreas o combinaciones de los mismos).

Preferentemente, los métodos presentes se dirigen al tratamiento de enfermedades o condiciones seleccionadas de enfermedad inflamatoria intestinal incluyendo enfermedad de Crohn y colitis ulcerativa, enfermedades alérgicas,

psoriasis, dermatitis atópica y asma, enfermedad autoinmune tal como artritis reumatoide y alergias a alimentos mediadas por inmunidad tales como enfermedad Coeliac.

Aún en otras modalidades, los presentes métodos se dirigen al tratamiento de psoriasis en donde un compuesto o composición de la invención se utiliza solo o en combinación con un segundo agente terapéutico tal como un corticoesteroide, un lubricante, un agente queratolítico, un derivado de vitamina D3, PUVA y antralina.

En otras modalidades, los presentes métodos se dirigen al tratamiento de dermatitis atópica utilizando un compuesto o composición de la invención ya sea solo o en combinación con un segundo agente terapéutico tal como un lubricante y un corticoesteroide.

En modalidades adicionales, los presentes métodos se dirigen al tratamiento del asma utilizando un compuesto o composición de la invención ya sea solo o en combinación con un segundo agente terapéutico tal como un agonista beta-2 y un corticoesteroide.

Preparación de Moduladores

Los siguientes ejemplos se ofrecen para ilustrar, pero no limitar, la invención reivindicada.

Adicionalmente, los expertos en la técnica reconocerán que las moléculas reivindicadas en esta patente pueden sintetizarse utilizando una variedad de

transformaciones estándar de química orgánica.

Ciertos tipos de reacción generales empleados ampliamente para sintetizar los compuestos en esta invención, se resumen en los ejemplos. Específicamente, se proporcionan procedimientos genéricos para la formación de sulfonamida, la formación de N-óxido de piridina y la síntesis de 2-aminofenil-arilmetanona mediante procedimientos tipo Friedel-Crafts, pero se describen otras numerosas químicas estándar y se emplearon rutinariamente.

Aunque no se pretende ser exhaustivo, se incluyen abajo las transformaciones representativas sintéticas orgánicas que pueden utilizarse para preparar los compuestos de la invención.

Estas transformaciones representativas incluyen; manipulaciones funcionales estándar; reducciones tales como de nitro a amino; oxidaciones de grupos funcionales incluyendo alcoholes y piridinas; sustituciones de arilo mediante IPSO u otros mecanismos para la introducción de una variedad de grupos incluyendo nitrilo, metilo y halógeno; introducciones y retiros del grupo de protección; formación Grignard y reacción con un electrófilo; acoplamientos cruzados mediados por metal incluyendo, pero sin limitarse a reacciones Buckwald, Suzuki y Sonigashira; halogenaciones y otras reacciones electrófilas de sustitución aromática; formaciones de sal de diazonio y reacciones de estas

especies; eterificaciones; condensaciones ciclativas, deshidrataciones, oxidaciones y reducciones que conducen a grupos heteroarilo; metalaciones de arilo y transmetalaciones y reacción de las especies de aril-metal siguientes con un electrófilo tal como un cloruro de ácido o amida Weinreb; amidaciones; esterificaciones; reacciones de sustitución nucleófila; alquilaciones; acilaciones; formación de sulfonamida; clorosulfonilaciones; hidrólisis de éster y relacionadas y lo similar.

Ciertas moléculas reivindicadas en esta patente pueden existir en diferentes formas enantioméricas y diastereoméricas y todas esas variantes de estos compuestos se encuentran dentro del alcance de la invención.

En la descripción de las síntesis siguientes, se obtuvieron algunos precursores a partir de fuentes comerciales. Estas fuentes comerciales incluyen Aldrich Chemical Co., Acros Organics, Ryan Scientific Incorporated, Oakwood Products Incorporated, Lancaster Chemicals, Sigma Chemical Co., Lancaster Chemical Co, TCI-America, Alfa Aesar, Davos Chemicals y GFS Chemicals.

Los compuestos de la invención, incluyendo aquellos listados en la tabla de actividades, pueden elaborarse mediante los métodos y procedimientos descritos en la siguiente sección experimental y mediante el uso de transformaciones de química orgánica estándar que son muy

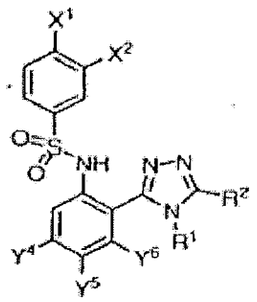
conocidas por los expertos en la técnica.

Ejemplos

Los compuestos anteriores y otros dentro del alcance de esta invención pueden elaborarse y probarse por su actividad utilizando los siguientes procedimientos.

Los compuestos ejemplares utilizados en el método de la invención y en las composiciones farmacéuticas de la invención incluyen, pero no se limitan a los compuestos listados en la Tabla 1. Las sales farmacéuticamente aceptables de los compuestos listados en la Tabla 1 son también útiles en el método de la invención y en las composiciones farmacéuticas de la invención.

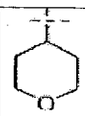
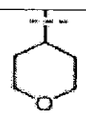
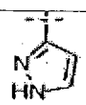
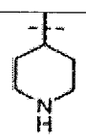
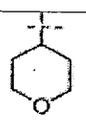
Tabla 1: Compuestos Ejemplares

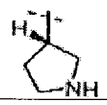
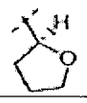
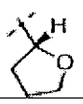
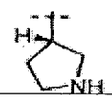
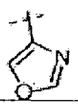
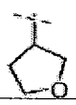


(I)

	X^1	X^2	Y^4	Y^5	Y^5	R^1	R^2
1	t-Bu	H	H	Cl	H	i-Pr	H
2	t-Bu	H	H	Cl	H	Ph	H
3	t-Bu	H	H	Cl	H	i-Pr	Me
4	t-Bu	H	H	Cl	H	Ph	Me
5	t-Bu	H	H	Cl	H	Et	Me
6	t-Bu	H	H	Cl	H	Me	Me

295

7	t-Bu	H	H	Cl	H	Ciclopropilo	Me
8	t-Bu	H	H	Cl	H	Me	*i*-Pr
9	t-Bu	H	H	Cl	H	Me	
10	t-Bu	H	H	Cl	H	Me	$-CH_2OCH_3$
11	t-Bu	H	H	Cl	H	i-Pr	i-Pr
12	t-Bu	H	H	Cl	H		Me
13	t-Bu	H	H	Cl	H	i-Pr	Et
14	t-Bu	H	H	Cl	H	Ciclopentilo	Me
15	Oi-Pr	H	H	Cl	H	i-Pr	Me
16	t-Bu	H	H	Cl	H		Me
17	Oi-Pr	H	H	Cl	H	Et	Me
18	t-Bu	H	Cl	H	H	i-Pr	H
19	t-Bu	H	H	Cl	H	i-Bu	Me
20	t-Bu	H	H	Cl	H		Me
21	t-Bu	H	H	Cl	H		$-CH_2OCH_3$
22	t-Bu	H	F	F	H	Et	H
23	t-Bu	H	F	H	H	Et	H
24	t-Bu	H	F	H	H	i-Pr	Me

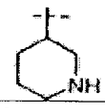
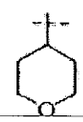
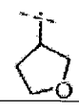
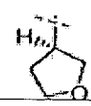
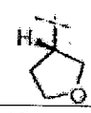
25	t-Bu	H	H	Cl	F	Et	H
26	t-Bu	H	H	Cl	H		Me
27	t-Bu	H	H	Cl	H	$-CH_2CH_2NHC(O)CH_3$	Me
28	t-Bu	H	H	Cl	F	Me	Me
29	t-Bu	H	H	Cl	F	Et	Me
30	t-Bu	H	H	Cl	H	Me	H
31	t-Bu	H	H	Cl	H	Et	H
32	t-Bu	H	H	Cl	H		H
33	t-Bu	H	H	Cl	H	Me	
34	t-Bu	H	H	Cl	H	Me	
35	t-Bu	H	H	Cl	H		H
36	t-Bu	H	F	Cl	H	Me	Me
37	t-Bu	H	F	F	H		H
38	t-Bu	H	H	Cl	H	Et	Et
39	t-Bu	H	F	Cl	H	Me	$-CH_2N(CH_3)_2$
40	t-Bu	H	H	Cl	H	Me	
41	t-Bu	H	H	Cl	H	Me	$-CH_2CH_2OCH_3$
42	t-Bu	H	F	F	H		H

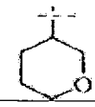
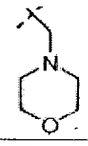
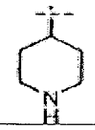
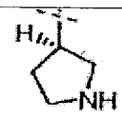
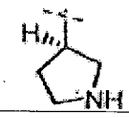
Organizacion y
Digitalizacion CSA Ltda

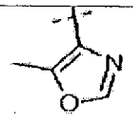
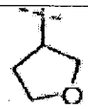
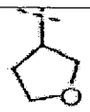
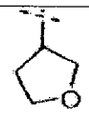
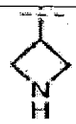
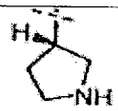
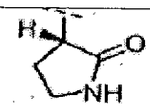
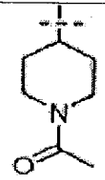
PATENTE DE INVENCIÓN

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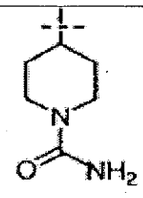
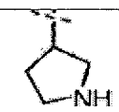
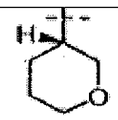
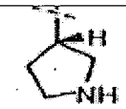
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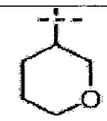
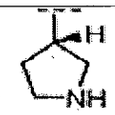
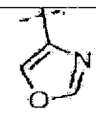
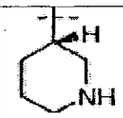
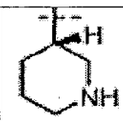
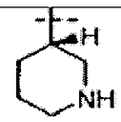
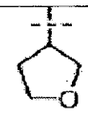
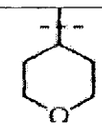
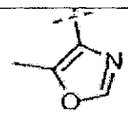
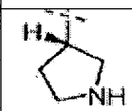
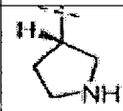
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45	t-Bu	H	F	Cl	H	Me	$-CH_2NHCH_3$
46	t-Bu	H	H	Cl	H	i-Pr	
47	t-Bu	H	F	Cl	H		Et
48	t-Bu	H	F	Cl	H	Me	$-CH_2NHCH_2CH_3$
49	t-Bu	H	F	Cl	H	Me	$-CH_2NHCH(CH_3)_2$
50	t-Bu	H	F	Cl	H	Me	$-CH_2CHCH(CH_2CH_2)$
51	t-Bu	H	F	Cl	H	i-Pr	$-CH_2OCH_3$
52	t-Bu	H	F	Cl	H		$-CH_2OCH_3$
53	t-Bu	H	F	Cl	H		H
54	t-Bu	H	F	Cl	H		H
55	t-Bu	H	F	Cl	H	Me	$-C(O)NH_2$
56	t-Bu	H	F	Cl	H	Me	$-C(O)NHCH_3$
57	t-Bu	H	F	Cl	H	Me	$-C(CH_3)_2OH$
58	t-Bu	H	F	Cl	H	Me	$-C(O)CH_3$
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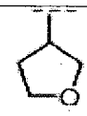
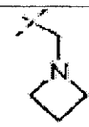
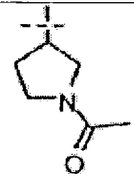
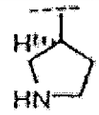
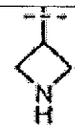
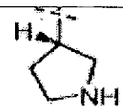
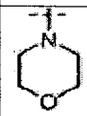
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64	t-Bu	H	F	Cl	H	Me	$-CH_2C(O)OCH_2CH_3$
65	t-Bu	H	F	Cl	H	Me	$-CH_2C(CH_3)_2OH$
66	t-Bu	H	F	Cl	H	Me	
67	t-Bu	H	F	Cl	H	Me	$-CH_2SO_2CH_3$
68	Oi-Pr	H	H	Cl	H	Me	Me
69	Oi-Pr	H	H	Cl	H	i-Pr	H
70	t-Bu	H	H	Cl	H	Me	
71	t-Bu	H	F	F	H	Et	Me
72	t-Bu	H	F	H	H	Me	Me
73	t-Bu	H	H	Cl	H		Me
74	t-Bu	H	F	H	H	Et	Me
75	t-Bu	H	H	Cl	H		H
76	t-Bu	H	F	Cl	H	Me	H

77	t-Bu	H	F	F	H		Me
78	t-Bu	H	F	Cl	H	i-Pr	H
79	t-Bu	H	F	Cl	H	Me	
80	t-Bu	H	F	Cl	H		Me
81	t-Bu	H	F	Cl	H		i-Pr
82	t-Bu	H	F	Cl	H	i-Pr	
83	t-Bu	H	H	Cl	H	$-CH_2H_2NH_2$	Me
84	t-Bu	H	H	Cl	H	Ciclobutilo	Me
85	t-Bu	H	F	Cl	H		H
86	t-Bu	H	H	Cl	H	i-Pr	$-CF_3$
87	t-Bu	H	F	Cl	H	Et	*i*-Pr
88	t-Bu	H	F	Cl	H		Et
89	t-Bu	H	F	Cl	H	Me	$-CH_2CH_2SO2CH_3$
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91	t-Bu	H	H	Cl	H		Me

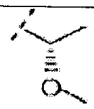
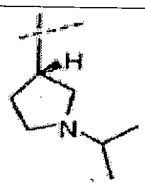
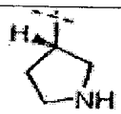
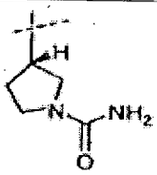
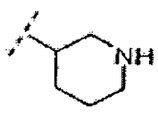
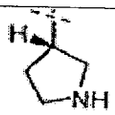
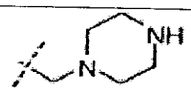
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94	t-Bu	H	H	Cl	H		Me
95	t-Bu	H	Cl	H	H	i-Pr	Me
96	t-Bu	H	H	Cl	H	i-Pr	$-CH_2OCH_3$
97	t-Bu	H	H	Cl	H	Me	2-piridilo
98	t-Bu	H	H	Cl	H	i-Pr	$-CH_2N(CH_3)_2$
99	t-Bu	H	H	Cl	H		Me
100	t-Bu	H	F	F	H	Me	Me
101	t-Bu	H	H	Cl	H		Me
102	t-Bu	H	H	Cl	H	Me	
103	t-Bu	H	H	Cl	H	Me	$-CH_2OCH(CH_3)_2$
104	t-Bu	H	H	Cl	H		H
105	t-Bu	H	H	Cl	H	Me	Et
106	t-Bu	H	F	Cl	H		Me

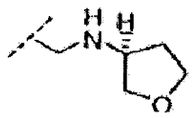
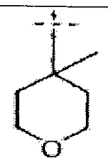
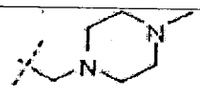
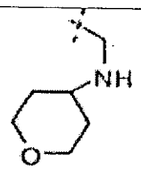
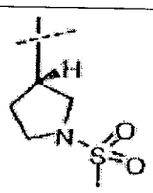
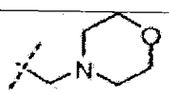
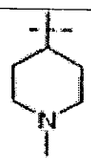
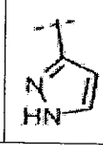
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110	t-Bu	H	F	Cl	H	Me	Et
111	t-Bu	H	F	Cl	H	Me	
112	t-Bu	H	F	Cl	H		H
113	t-Bu	H	H	Cl	H		H
114	t-Bu	H	H	Cl	H		Me
115	t-Bu	H	F	Cl	H	Me	
116	t-Bu	H	F	Cl	H	Me	
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118	t-Bu	H	H	Cl	H		i-Pr
119	t-Bu	H	H	Cl	H		Et

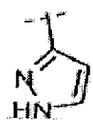
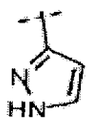
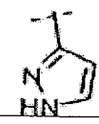
120	t-Bu	H	F	Cl	H		H
121	t-Bu	H	F	Cl	H	Me	
122	t-Bu	H	F	Cl	H	Me	
123	t-Bu	H	F	Cl	H	Me	-CH2OH
124	t-Bu	H	H	Cl	H		Me
125	t-Bu	H	H	Cl	H	-CH2CH2N(CH3)2	Me
126	t-Bu	H	H	Cl	H	-CH2CH2NHCH3	Me
127	t-Bu	H	H	Cl	H		Me
128	t-Bu	H	H	CN	H	Me	Et
129	t-Bu	H	H		H	Me	Et
130	t-Bu	H	H		H	Me	Et
131	t-Bu	H	H	Cl	H		H
132	t-Bu	H	H	Cl	H	Me	-CH2NHCH3
133	t-Bu	H	H		H	Me	Et
134	O-*i*Pr	H	H	Cl	H		H
135		F	H	Cl	H	Me	Me

304

136	t-Bu	H	F	Cl	H	$-CH_2CH_2OCH_3$	H
137	t-Bu	H	F	Cl	H	Me	$-CH_2CH_2OH$
138	t-Bu	H	H	Cl	H	Me	$-CH_2NHCH(CH_3)_2$
139	t-Bu	H	F	Cl	H	Me	
140	t-Bu	H	F	Cl	H	Me	
141	t-Bu	H	H	Cl	H		H
142		H	H	Cl	H		H
143	t-Bu	H	H	Cl	H		H
144	t-Bu	H	H	Cl	H	Me	
145	t-Bu	H	F	Cl	H	Me	
146	t-Bu	H	F	Cl	H		i-Pr
147	t-Bu	H	F	Cl	H	Me	

305

148	t-Bu	H	F	Cl	H	Me	
149	t-Bu	H	F	Cl	H	Me	– $CH_2N(CH_3)CH_2CH_2OCH_3$
150	t-Bu	H	F	Cl	H	i-Pr	
151	t-Bu	H	F	Cl	H	Me	
152	t-Bu	H	F	Cl	H	Me	
153	t-Bu	H	H	Cl	H		H
154	t-Bu	H	F	Cl	H	i-Pr	
155	t-Bu	H	H	Cl	H		Me
156	t-Bu	H	Cl	H	H	CH=CH-CH=N-	
157	Cl	CF_3	Cl	H	H		H

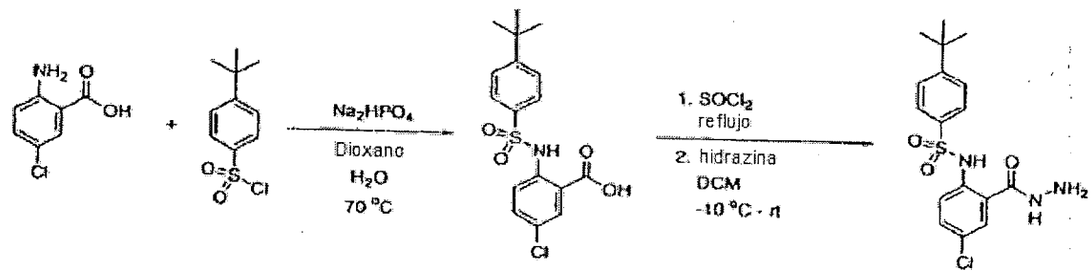
158	Cl	CF_3	Cl	H	H		H
159	Cl	CF_3	Cl	H	H	Ph	H
160	Cl	CF_3	Cl	F	H		H
161	Cl	CF_3	Cl	F	H		$-CONH_2$

Los compuestos anteriores y otros dentro del alcance de esta invención pueden elaborarse y probarse por su actividad utilizando los siguientes procedimientos.

Los reactivos y solventes utilizados abajo pueden obtenerse de fuentes comerciales tales como Aldrich Chemical Co., (Milwaukee, Wisconsin, EUA). Los ^1H NMR se registraron en un espectrómetro Varian Mercury 400 MHz NMR. Los picos significativos se tabulan en el orden: multiplicidad (br, amplia; s, única; d, doble; t, triple; q, cuádruple; m, múltiple) y el número de protones. Los resultados de la espectrometría de masa se reportan como la proporción de masa sobre carga, seguidos por la relativa abundancia de cada ion (en paréntesis). En las tablas, se reporta un solo valor m/e para el ion M + H (o, como se anota M - H) que contiene los isótopos atómicos más comunes. Los patrones de isótopo

corresponden a la fórmula esperada en todos los casos. El análisis de masa de ionización por electroaspersión (ESI) se condujo en un espectrómetro de masa por electroaspersión Hewlett-Packard MSD utilizando el HP 1100 HPLC para el suministro de muestras. Normalmente, el analito se disolvió en metanol a 0.1 mg/ml y 1 microlitro se infundió con el solvente de suministro en el espectrómetro de masa, que escaneó de 100 a 1500 daltons. Todos los compuestos pudieron analizarse en el modo ESI positivo, utilizando acetonitrilo/agua con ácido fórmico al 1% como el solvente de suministro. Los compuestos proporcionados abajo podrían también analizarse en el modo ESI negativo, utilizando 2 mM de NH_4Oac en acetonitrilo/agua como sistema de suministro.

Procedimiento General A - ejemplificado para 4-ter-butil-N-(4-cloro-2-hidrazinocarbonil-fenil)bencenosulfonilamida



Etapa 1: Se agregó ácido 2-amino-5-clorobenzoico (200 g, 1.17 mol) a una solución de hidrogen fosfato de sodio (497 g, 3.50 mol) en agua (2.4 l) a 70°C y se agitó hasta homogeneidad (-10 min.). Se agregó cloruro de 4-ter-

butilbencenosulfonilo (353 g, 1.52 mol) disuelto en 800 ml de p-dioxano, a la solución de anilina en agitación en una corriente en reposo durante un período de ½ hora mediante un embudo de adición de 1 litro. La mezcla resultante se agitó a 70°C durante la noche. Al día siguiente, al verificar por LCMS el consumo de anilina, la mezcla de reacción se dividió en dos porciones iguales para facilitar el manejo. Cada porción se vació en una corriente lenta en dos litros de 2M de HCl/H_2O en agitación rápida en un matraz Erlenmeyer de cuatro litros. El precipitado se recolectó mediante filtración al vacío y se lavó bien con agua. Los precipitados de cada porción se combinaron subsecuentemente y se secaron in vacuo para producir 320 g de ácido 2-(4-ter-butil-bencenosulfonilamino)-5-cloro-benzoico como un sólido blanquecino (rendimiento 87%): Tiempo de retención de HPLC = 2.76 minutos (Agilent Zorbax SB-C18, 2.1 x 50 mm, 5u, 35°C, utilizando una proporción de flujo de 1 ml/min, un gradiente de 2.5 minutos de 20-100% B con un lavado de 1.1 minutos a 100% B (A = 0.1% ácido fórmico/5% acetonitrilo/agua 94.9%, B = 0.08% ácido fórmico/5% agua/94.9% acetonitrilo)); MS (ES) M + H esperado 368.0, encontrado 368.0.

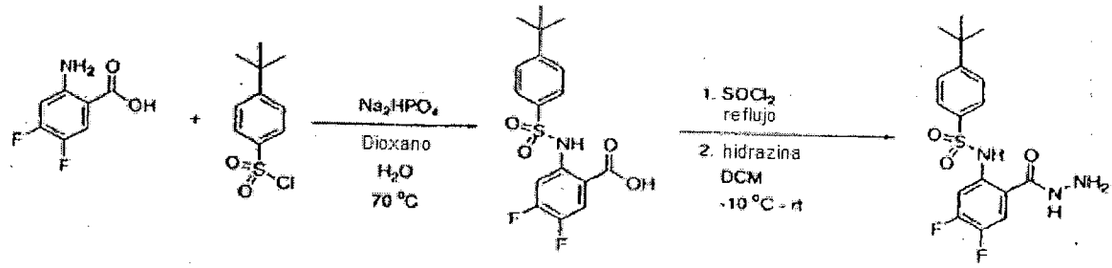
Etapa 2: Se introdujo cloruro de tionilo (300 ml, 4.11 mol) a un matraz de fondo redondo de 1 litro adaptado con una barra de agitación magnética. Se agregó ácido 2-(4-ter-butil-bencenosulfonilamino)-5-cloro-benzoico (80 g, 218

mol) bajo agitación rápida y la mezcla se calentó a reflujo bajo una atmósfera de nitrógeno. Se monitoreó el progreso de la reacción mediante la adición de algunas gotas de la mezcla de reacción en ~1 ml de 2.0 M de dimetilamina en THF seguido por análisis LCMS. La conversión completa en la dimetil amida se observó a 1.25 horas. La mezcla cruda se concentró subsecuentemente in vacuo para producir un aceite amarillo espeso que después se disolvió en 100 ml de tolueno y se concentró de nuevo para generar cloruro de 2-(4-ter-butil-bencenosulfonilamino)-5-cloro-benzoilo como un sólido amarillo pálido que se utilizó directamente en la siguiente etapa.

Etapa 3: El cloruro de 2-(4-ter-butil-bencenosulfonilamino)-5-clorobenzoilo crudo se disolvió en diclorometano (300 ml) y se transfirió a un embudo de adición. Se enfrió hidrato de hidrazina (212 ml, 4.35 mol) disuelto en 1.2 l de diclorometano en un matraz Erlenmeyer de 4 l, a 10°C en un baño de hielo seco-acetona y la solución de cloruro de acilo se agregó en una corriente lenta a la solución de hidrazina en agitación durante un período de 15 minutos. El baño frío se retiró subsecuentemente después de la adición y el análisis LCMS a los 15 minutos indicó que la reacción fue completa. La mezcla de reacción resultante se templó con agua (500 ml), dando como resultado un precipitado blanco voluminoso que se recolectó mediante filtración al

vacío. El precipitado se mezcló en 800 ml de etil acetato y se agregó ácido acético mientras se agitó hasta formar una solución homogénea. La solución se transfirió a un embudo de separación y se extrajo con 3 x 100 ml de agua. Las fases acuosas se descartaron y la fase orgánica se secó sobre sulfato de sodio, se filtró y se concentró in vacuo para producir 4-ter-butil-N-(4-cloro-2-hidrazinocarbonil-fenil)bencenosulfonamida (71 g) en un rendimiento de 85%: Tiempo de retención de HPLC = 2.49 minutos; MS (ES) M + H esperado 382.0, encontrado 382.0.

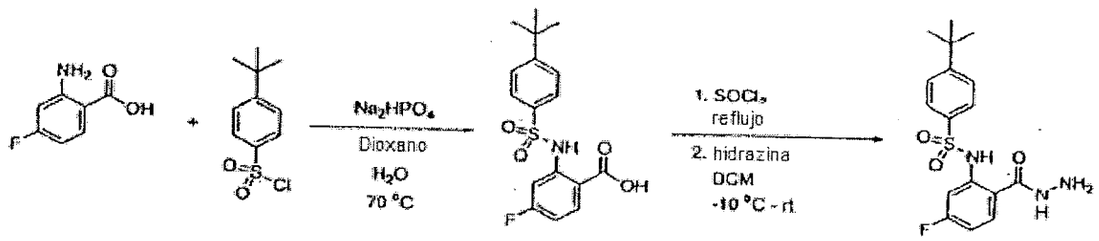
4-ter-butil-N-(4,5-difluoro-2-hidrazinocarbonil-fenil)bencenosulfonamida



Se sintetizó 4-ter-butil-N-(4,5-difluoro-2-hidrazinocarbonil-fenil)bencenosulfonamida a partir de ácido 2-amino-4,5-difluorobenzoico de acuerdo con el procedimiento general A.

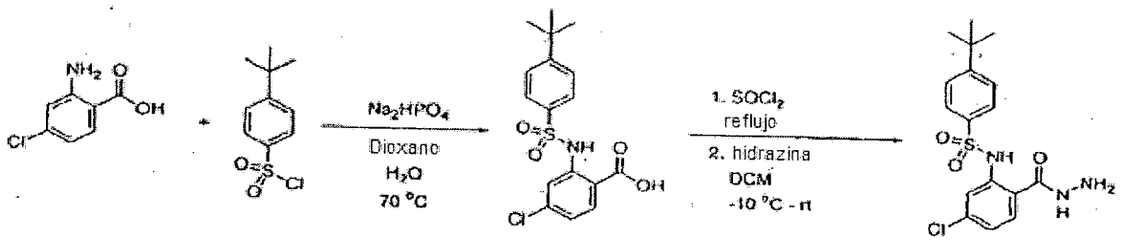
4-ter-butil-N-(5-fluoro-2-hidrazinocarbonil-fenil)bencenosulfonamida

312



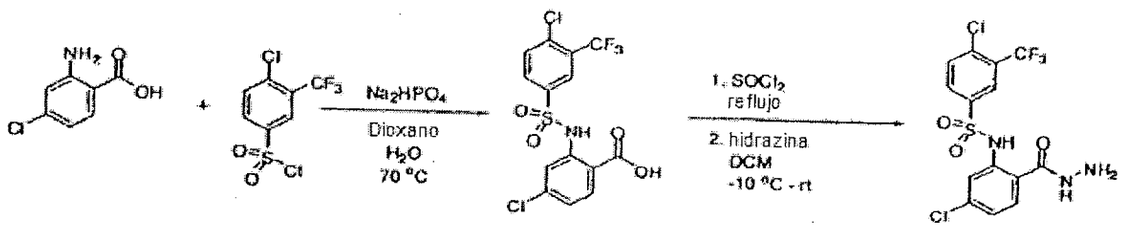
Se sintetizó 4-ter-butil-N-(5-fluoro-2-hidrazinocarbonil-fenil)bencenosulfonamida a partir de ácido 2-amino-4-fluorobenzoico de acuerdo con el procedimiento general A.

4-ter-butil-N-(5-cloro-2-hidrazinocarbonil-fenil)bencenosulfonamida



Se sintetizó 4-ter-butil-N-(5-fluoro-2-hidrazinocarbonil-fenil)bencenosulfonamida a partir de ácido 2-amino-4-clorobenzoico de acuerdo con el procedimiento general A.

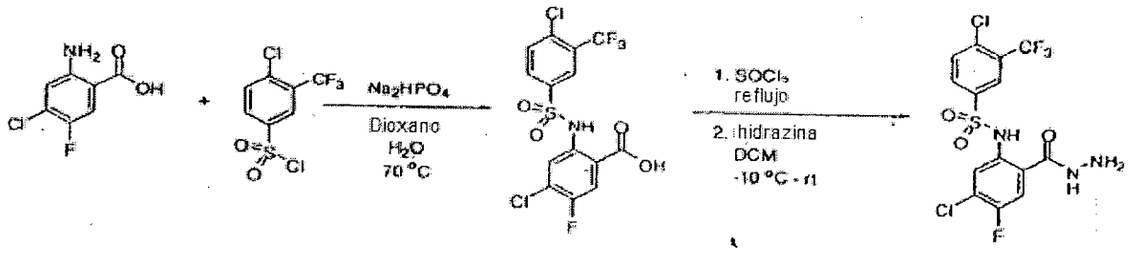
4-cloro-N-(5-cloro-2-hidrazinocarbonil-fenil)-3-trifluorometil-bencenosulfonamida



313

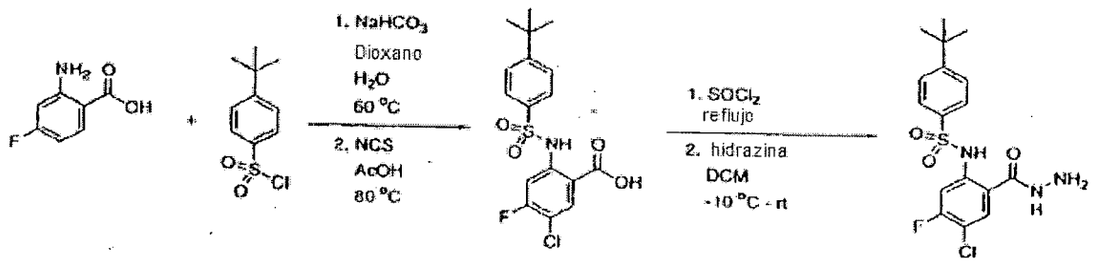
Se sintetizó 4-cloro-N-(5-cloro-2-hidrazinocarbonil-fenil)-3-trifluorometil-bencenosulfonamida a partir de ácido 2-amino-4-clorobenzoico de acuerdo con el procedimiento general A.

4-cloro-N-(5-cloro-4-fluoro-2-hidrazinocarbonil-fenil)-3-trifluorometil-bencenosulfonamida



Se sintetizó 4-cloro-N-(5-cloro-4-fluoro-2-hidrazinocarbonil-fenil)-3-trifluorometil-bencenosulfonamida a partir de ácido 2-amino-4-cloro-5-fluorobenzoico de acuerdo con el procedimiento general A.

Procedimiento General B ejemplificado para 4-ter-butil-N-(4-cloro-5-fluoro-2-hidrazinocarbonil-fenil)bencenosulfonamida



Etapa 1: Se agregó ácido 2-amino-4-fluorobenzoico (25 g, 161 mol) a una solución de bicarbonato de sodio (54.1

g, 645 mol) en agua (2.4 l) a temperatura ambiente y se agitó hasta homogeneidad. La solución resultante se calentó a 60°C en un baño de aceite. Se agregó subsecuentemente por goteo cloruro de 4-ter-butilbencenosulfonilo (45.0 g, 193 mol), disuelto en 200 ml de p-dioxano, a la solución de anilina en agitación en una corriente en reposo durante un período de 30 minutos. La mezcla de reacción se agitó a 60°C durante la noche. Al día siguiente, al verificar con LCMS el consumo de anilina, la solución se vació en una corriente lenta en un litro de 2M de HCl/H_2O en agitación rápida. El precipitado resultante se recolectó mediante filtración al vacío y se lavó completamente con agua y se secó in vacuo para producir 46 g de ácido 2-(4-ter-butil-bencenosulfonilamino)-4-fluoro-benzoico como un sólido blanquecino (rendimiento 82%): Tiempo de retención de HPLC = 2.68; MS (ES) M + H esperado 352.0, encontrado 352.0.

Etapa 2: Se agregó el ácido 2-(4-ter-butil-bencenosulfonilamino)-4-fluoro-benzoico (23 g, 65.5 mol) a 230 ml de ácido acético en agitación en un matraz de fondo redondo de 500 ml. Se agregó entonces N-clorosuccinimida (17.5 g, 131 mol) y la mezcla se calentó a 80°C bajo una atmósfera de N_2. La reacción se determinó completa en siete horas de acuerdo con el análisis LCMS. El baño caliente se retiró subsecuentemente y la reacción se templó mediante la adición de 250 ml de una solución al 50% de metabisulfito de

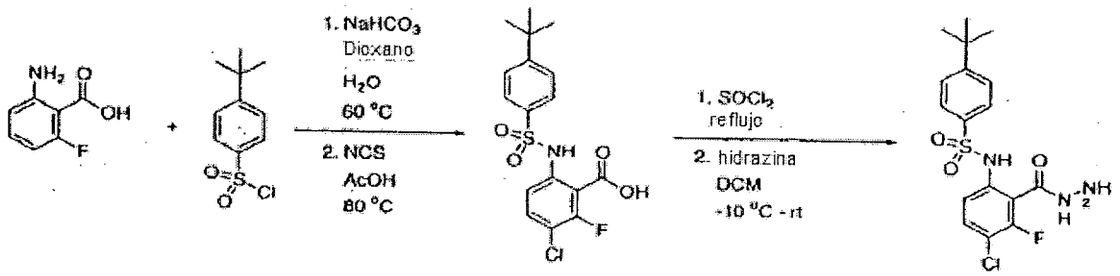
sodio. La mezcla formó inmediatamente una mezcla blanca espesa que se dejó agitar durante aproximadamente 15 minutos. la filtración al vacío de la mezcla dio como resultando un sólido blanco que se lavó con una pequeña cantidad de agua y se secó in vacuo para generar 22 g de ácido 2-(4-ter-butil-bencenosulfonilamino)-5-cloro-4-fluoro-benzoico (sólido blanco, rendimiento 87%): Tiempo de retención de HPLC = 2.87 minutos; MS (ES) M + H esperado 386.0, encontrado 386.0.

Etapa 3: Se introdujo cloruro de tionilo (220 ml, 3.02 mol) a un matraz de fondo redondo de 1 litro adaptado con una barra de agitación magnética. Se agregó ácido 2-(4-ter-butil-bencenosulfonilamino)-5-cloro-4-fluoro-benzoico (22 g, 57.0 mol) bajo agitación rápida y la mezcla se calentó a reflujo bajo una atmósfera de nitrógeno. Se monitoreó el progreso de la reacción mediante la adición de algunas gotas de la mezcla de reacción en ~1 ml de 2.0 M de dimetilamina en THF seguido por análisis LCMS. La conversión completa en la dimetil amida se observó a 1.25 horas. La mezcla cruda se concentró subsecuentemente in vacuo para producir un aceite naranja. Se agregó hexano (50 ml) al matraz y la mezcla se concentró de nuevo para producir cloruro de 2-(4-ter-butil-bencenosulfonilamino)-5-cloro-benzoilo como un sólido naranja cristalino que se utilizó directamente en la siguiente etapa.

Etapa 4: El cloruro de 2-(4-ter-butil-bencenosulfonilamino)-5-cloro-4-fluoro-benzoilo crudo (57.0

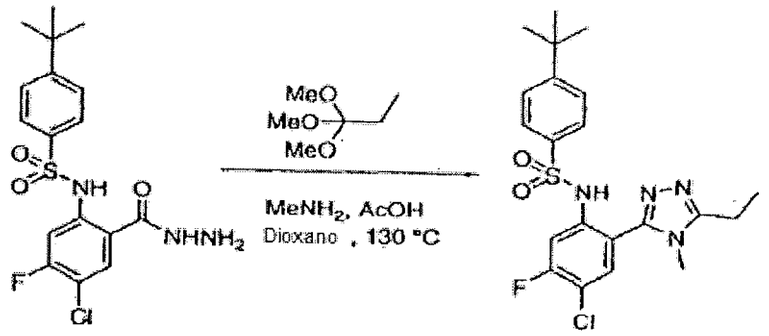
mol) se disolvió en diclorometano (100 ml) y se transfirió a un embudo de adición. Se enfrió hidrazina anhidrosa (44 ml, 1.38 mol) disuelto en 300 ml de diclorometano en un matraz Erlenmeyer de un litro, a -10°C en un baño de hielo seco-acetona y la solución de cloruro de acilo se agregó en una corriente lenta a la solución de hidrazina en agitación durante un período de 15 minutos. El baño frío se retiró subsecuentemente después de la adición y el análisis LCMS a los 15 minutos indicó que la reacción fue completa. La mezcla de reacción resultante se templó con agua (200 ml), dando como resultado un precipitado blanco voluminoso que se recolectó mediante filtración al vacío. El precipitado se mezcló en 500 ml de etil acetato y se agregó ácido acético mientras se agitó hasta formar una solución homogénea. La solución se transfirió a un embudo de separación y se extrajo con 2 x 50 ml de agua. Las fases acuosas se descartaron y la fase orgánica se secó sobre sulfato de sodio, se filtró y se concentró in vacuo para producir 4-ter-butil-N-(4-cloro-5-fluoro-2-hidrazinocarbonil-fenil)bencenosulfonamida (16 g) en un rendimiento de 71%: Tiempo de retención de HPLC = 2.63 minutos; MS (ES) M + H esperado 400.0, encontrado 400.0.

4-ter-butil-N-(4-cloro-3-fluoro-2-hidrazinocarbonil-fenil)bencenosulfonamida



Se sintetizó 4-ter-butil-N-(4-cloro-3-fluoro-2-hidrazinocarbonil-fenil)bencenosulfonamida a partir de ácido 2-amino-6-fluorobenzoico de acuerdo con el procedimiento general B.

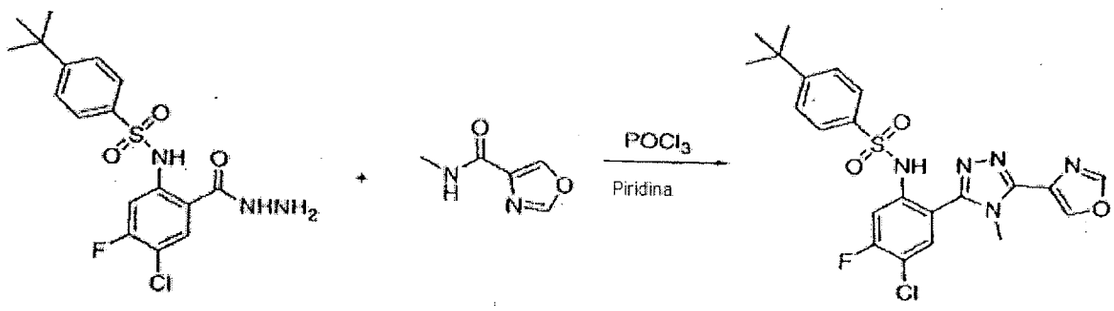
Procedimiento General C ejemplificado para 4-ter-butil-N-[4-cloro-2-(5-etil-4-metil-4H-[1,2,4]triazol-3-il)-5-fluoro-fenil]-bencenosulfonamida



Un vial de escintilación de 25 ml se cargó con 4-ter-butil-N-(4-cloro-3-fluoro-2-hidrazinocarbonil-fenil)-bencenosulfonamida (1.0 g, 2.51 mol) y trimetil ortopropionato (0.534 ml, 3.76 mol) y después se agitó durante 1 hora a 45°C. A la mezcla de reacción anterior se agregó metilamina (3.75 ml, 2.0 M en THF), AcOH (0.125 ml), y dioxano (10 ml). El vial se selló, se calentó a 130°C y se

agitó durante la noche. Al siguiente día la mezcla de reacción se enfrió a 0°C para inducir la precipitación del producto. El sólido blanco resultante se filtró y se disolvió en EtOAc (50 ml). Los orgánicos se lavaron subsecuentemente con solución de $NaHCO_3$ saturado (25 ml), solución de NH_4Cl saturado (25 ml), agua (25 ml) y salmuera (25 ml); se secaron con Na_2SO_4 y se concentraron in vacuo para producir el compuesto del título como un sólido blanco (0.3 g) en un rendimiento de 27%: ^1H NMR (400 MHz, $CDCl_3$) delta 7.62-7.57 (m, 3H), 7.36 (d, 2H), 7.25 (d, 1H), 3.32 (s, 3H), 2.75 (q, 2H), 1.45 (t, 3H), 1.30 (s, 9H), MS (ES) M + H esperado 451.0, encontrado 451.0.

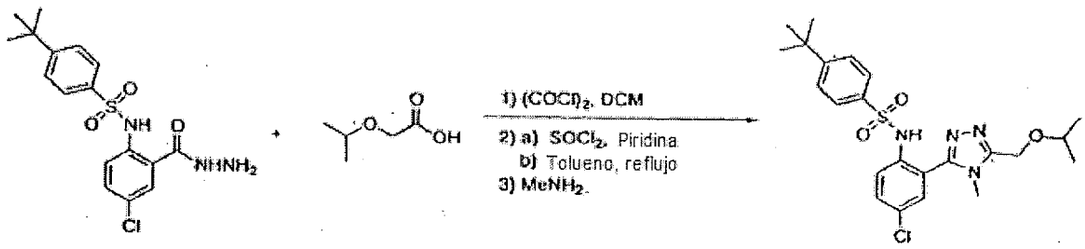
Procedimiento General D ejemplificado para 4-ter-butil-N-[4-cloro-5-fluoro-2-(4-metil-5-oxazol-4-il-4H-[1,2,4]triazol-3-il)-fenil]-bencenosulfonamida



Un vial de escintilación de 25 ml se cargó con metilamida de ácido oxazol-4-carboxílico (132 mg, 1.0 mol), $POCl_3$ (0.27 ml, 3 mol), piridina (0.48 ml, 6 mol) y CH_3CN (10 ml). El vial se selló, se calentó a 40°C y se agitó durante

cuatro horas. Los volátiles se evacuaron entonces in vacuo y al residuo se agregó 4-ter-butil-N-(4-cloro-5-fluoro-2-hidrazinocarbonil-fenil)-bencenosulfonamida (400 mg, 1.0 mol), diisopropilamina (2.0 ml) y dioxano (2.0 ml). El vial se selló, se calentó a 130°C y se agitó durante dos horas. Los volátiles se retiraron entonces in vacuo y el residuo se purificó mediante cromatografía automatizada de gel de sílice y después HPLC para producir 4-ter-butil-N-[4-cloro-5-fluoro-2-(4-metil-5-oxazol-4-il-4H-[1,2,4]triazol-3-il)-fenil]bencenosulfonamida como un polvo blanco: ^{1}H NMR (400 MHz, $CDCl_3$) delta 9.72 (s, 1H), 8.48 (d, 1H), 8.04 (d, 1H), 7.67 (d, 1H), 7.50 (d, 2H), 7.33 (d, 1H), 7.3 (d, 2H), 3.59 (s, 3H), 1.23 (s, 9H). MS (ES) M + H esperado 490.1, encontrado 490.0.

Procedimiento General E ejemplificado para 4-ter-butil-N-[4-cloro-2-[5-isopropilmetil-4-metil-4H-[1,2,4]triazol-3-il)-fenil]-bencenosulfonilamida



Etapa 1: Cloruro de oxalilo (0.19 ml, 2.20 mol) se agregó a una solución de ácido isopropoxiacético (200 mg, 1.69 mol) en diclorometano (17 ml) y se agitó a temperatura

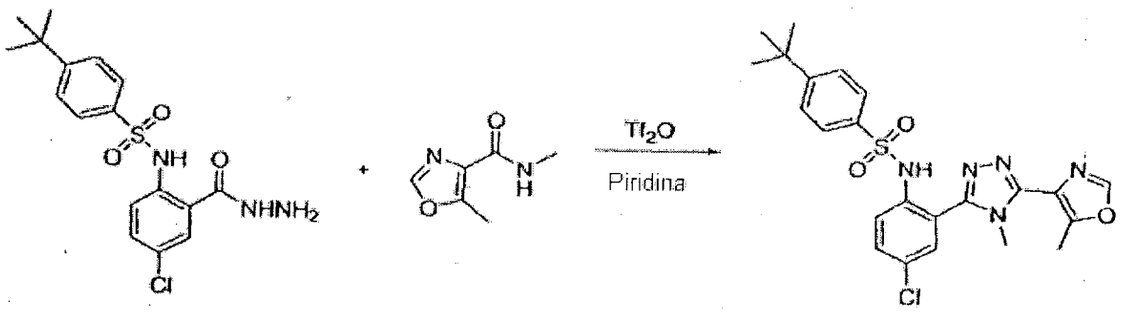
ambiente durante 2 horas. La reacción se concentró y se agregaron 3 ml de THF. La solución de cloruro de ácido se agregó subsecuentemente lentamente a una solución de 4-ter-butil-N-(4-cloro-2-hidrazinocarbonil-fenil)bencenosulfonilamida (645 mg, 1.69 mol) en 10 ml de THF a 0°C. después de agitar la reacción durante 1 hora, se templó con agua y se diluyó con etil acetato. La fase acuosa se extrajo con etil acetato (3 x) y diclorometano (2 x), y las capas orgánicas combinadas se secaron sobre sulfato de magnesio y se concentraron in vacuo. El residuo crudo se purificó mediante cromatografía de columna instantánea (0-100% etil acetato en hexano) para producir 4-ter-butil-N-[4-cloro-2-[N'-(2-isopropoxi-acetil)-hidrazinocarbonil]-fenil]bencenosulfonamida como un sólido amarillo.

Etapa 2: Se agregó cloruro de tionilo a una solución de 4-ter-butil-N-[4-cloro-2-[N'-(2-isopropoxi-acetil)-hidrazinocarbonil]-fenil]bencenosulfonamida (150 mg, 0.312 mol) y piridina (66 ul, 0.811 mol) en dietil éter (3 ml). La solución resultante se agitó durante 18 horas a temperatura ambiente seguido por el retiro de los volátiles in vacuo. Se agregaron subsecuentemente 2 ml de tolueno y la reacción se calentó a reflujo durante 5 horas. La solución resultante se concentró a presión reducida y el residuo se purificó mediante cromatografía de columna instantánea (0.50% etil acetato en hexano) para producir 4-ter-butil-N-[4-cloro-

2-(5-isopropoximetil-[1,3,4]oxadiazol-2-il)-fenil]bencenosulfonamida como un sólido blanco.

Etapa 3: En un recipiente a presión se calentó 4-ter-butil-N-[4-cloro-2-(5-isopropoximetil-[1,3,4]oxadiazol-2-il)-fenil]bencenosulfonamida (71 mg, 0.15 mol) y metil amina (40% en H_2O, 1.5 ml, 0.6 mol) a 135°C durante 18 horas. La reacción se enfrió a temperatura ambiente, se concentró in vacuo y el residuo se purificó mediante cromatografía de columna instantánea (0.50% etil acetato en hexano) para producir el compuesto del título como un sólido blanco: MS (ES) M + H esperado 477.2, encontrado 477.1.

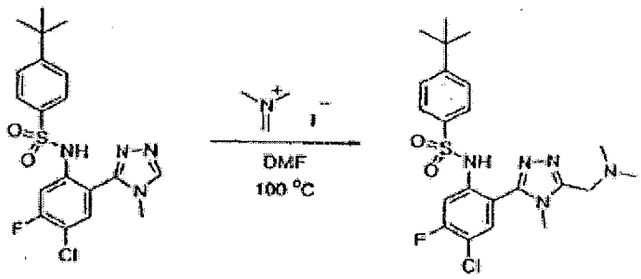
Procedimiento General F ejemplificado para 4-ter-butil-N-[4-cloro-2-[4-metil-5-(5-metil-oxazol-4-il)-4H-[1,2,4]triazol-3-il]-fenil]bencenosulfonamida



Un vial se cargó con metilamida de ácido 5-metil-oxazol-4-carboxílico (71 mg, 0.5 mol), piridina (0.12 ml, 1.5 mol) y diclorometano anhidroso (2.5 ml). El recipiente de reacción se enfrió a -40°C y se agregó trifluorometanosulfonil anhídrido (0.11 ml, 0.65 mol). La reacción se calentó subsecuentemente a -10°C durante 2.5

horas y después se agregó 4-ter-butil-N-(4-cloro-2-hidrazinocarbonil-fenil)bencenosulfonamida (191 mg, 0.5 mol). La reacción se calentó a temperatura ambiente agitando 2 horas adicionales. El solvente se concentró in vacuo y se agregó etanol (5 ml) y diisopropilamina (0.5 ml) y la solución se agitó a 90°C durante la noche. Al siguiente día, la reacción se concentró in vacuo y el material crudo se purificó mediante cromatografía de columna instantánea (10 - 100% etil acetato y hexano), seguido por HPLC de preparación (10-90% gradiente de MeCN-agua) para producir el compuesto del título: MS (ES) M + H esperado 486.1, encontrado 486.0.

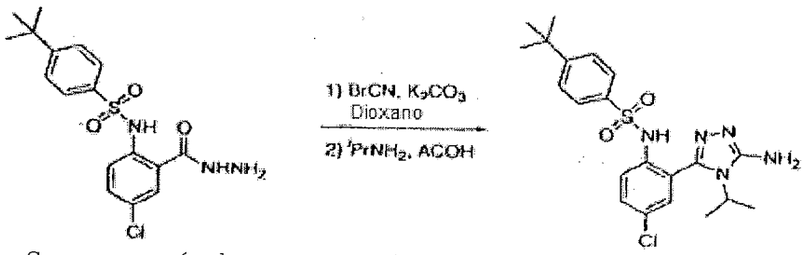
Procedimiento General G ejemplificado para 4-ter-butil-N-[4-cloro-2-[5-dimetilaminometil-4-metil-4H-[1,2,4]triazol-3-il)-5-fluoro-fenil]bencenosulfonamida



Se cargó un matraz de 25 ml en forma de pera con 4-ter-butil-N-[4-cloro-5-fluoro-2-(4-metil-4H-[1,2,4]triazol-3-il)-fenil]bencenosulfonamida (preparada de acuerdo con el procedimiento general C) (75 mg, 0.18 mol), yoduro de N,N-dimetilmetilenoiminio (43 mg, 0.23 mol) y DMF (0.44 ml). El matraz se calentó a 100°C y se agitó durante la noche. Al

día siguiente, el solvente se evacuó in vacuo y el residuo se purificó mediante HPLC para producir 4-ter-butil-N-[4-cloro-2-(5-dimetilaminometil-4-metil-4H-[1,2,4]triazol-3-il)-5-fluoro-fenil]bencenosulfonamida como un polvo blanco: ^{1}H NMR (400 MHz, CD_3OD) delta 7.60 (d, 1H), 7.48-7.54 (m, 4H), 7.28 (d, 1H), 3.70 (s, 2H), 3.46 (s, 3H), 3.45 (s, 3H), 2.36 (s, 6H), 1.33 (s, 9H), MS (ES) M + H esperado 480.2, encontrado 480.1.

Procedimiento General H ejemplificado para N-[2-(5-amino-4-isopropil-4H-[1,2,4]triazol-3-il)-4-cloro-fenil)-4-ter-butil-bencenosulfonamida

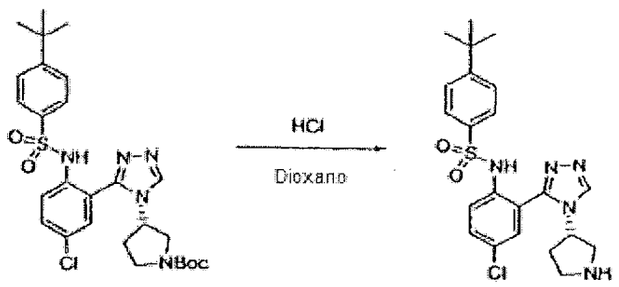


Se agregó bromuro cianógeno (111 mg, 1.05 mol) a una solución de 4-ter-butil-N-(4-cloro-2-hidrazinocarbonil-fenil)-bencenosulfonamida (200 mg, 0.524 mol) y carbonato de potasio (145 mg, 1.05 mol) en dioxano (2 ml) y la reacción se agitó durante 18 horas a temperatura ambiente. Se agregó isopropil amina (0.18 ml, 2.09 mol) y ácido acético (0.15 ml) y la reacción se calentó a 135°C durante 18 horas adicionales. La solución resultante se dividió entre etil acetato/agua y la fase orgánica se lavó con 1N de HCl, bicarbonato de sodio saturado, y salmuera; se secó sobre

326

sulfato de magnesio y se concentró in vacuo. El producto crudo se purificó finalmente mediante cromatografía de columna instantánea (10-100% etil acetato y hexano) después HPLC de preparación (10-90% gradiente de MeCN-agua) para proporcionar el compuesto del título como un sólido blanco;: MS (ES) M + H esperado 448.2, encontrado 448.1.

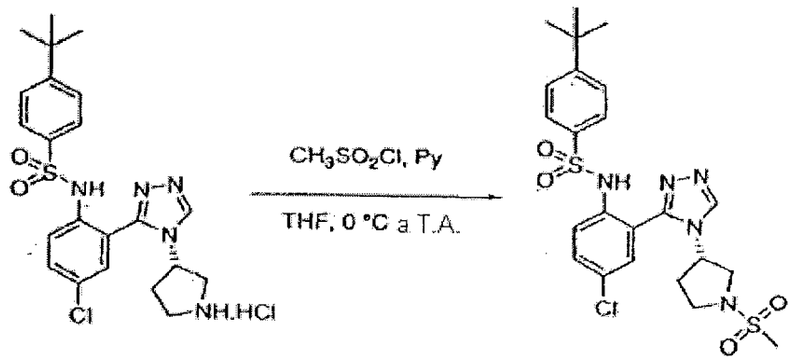
Procedimiento General I ejemplificado para 4-ter-butil-N-[4-cloro-2-(4-pirrolidin-3-il-4H-[1,2,4]triazol-3-il)-fenil]bencenosulfonamida



Se cargó un matraz de fondo redondo de 50 ml con ter-butil-éster de ácido 3-[3-[2-(4-ter-butil-bencenosulfonilamino)-5-cloro-fenil]-[1,2,4]triazol-4-il)pirrolidina-1-carboxílico (preparado de acuerdo con el procedimiento general C, 750 mg, 1.34 mol), seguido por la adición de HCl en dioxano (13 ml, 4.0 M). la solución homogénea se agitó durante la noche, el solvente se evacuó in vacuo, y el residuo se purificó mediante HPLC para producir 4-ter-butil-N-[4-cloro-5-fluoro-2-(4-pirrolidin-3-il-4H-[1,2,4]triazol-3-il)-fenil]bencenosulfonamida como un polvo blanco: ^{1}H NMR (400 MHz, $(CD_3)_2SO$) delta 10.02 (s, 1H), 9.67

(bs, 1H), 9.17 (s, 1H), 9.12 (bs, 1H), 7.71 (s, 2H), 7.51-7.61 (m, 4H), 7.20 (d, 1H), 4.72 (quint, 1H), 3.35-3.62 (m, 3H), 3.18-3.28 (m, 1H), 2.38-2.49 (m, 1H), 2.16-2.28 (m, 1H), 1.29 (s, 9H), MS (ES) M + H esperado 460.2, encontrado 460.1.

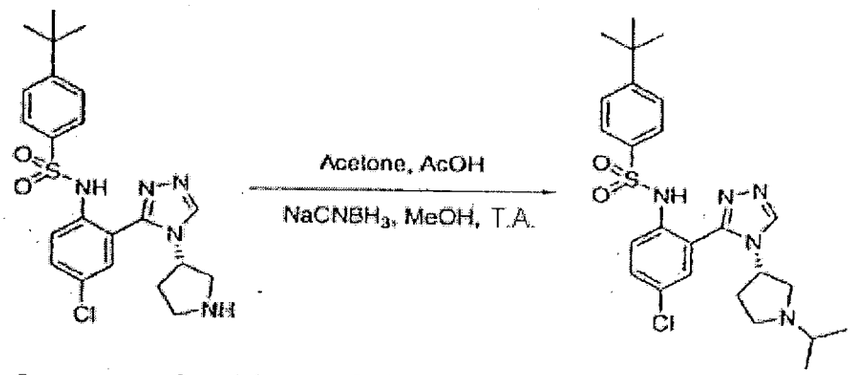
Procedimiento General J ejemplificado para 4-ter-butil-N-[4-cloro-2-[(S)-4-(1-metanosulfonil-pirrolidin-3-il)-4H-[1,2,4]triazol-3-il]fenil]bencenosulfonamida



Al 4-ter-butil-N-[4-cloro-2-((S)-4-pirrolidin-3-il-4H-[1,2,4]triazol-3-il)fenil]bencenosulfonamida (0.25 g, 0.505 mol) en THF (8 ml) se agregó piridina (0.60 ml, 7.4 mol). La solución resultante se agitó durante 20 minutos a temperatura ambiente. La mezcla de reacción se enfrió subsecuentemente a 0°C, se agregó cloruro de metanosulfonilo (0.595 ml, 7.6 mol) y la mezcla se agitó durante la noche a temperatura ambiente. Al día siguiente, los volátiles se evaporaron y el residuo resultante se absorbió sobre gel de sílice y se purificó mediante cromatografía automatizada en fase normal (utilizando 50 - 100% EtOAc en hexanos) para obtener el compuesto del título (0.183 g) en un rendimiento

de 67.5%: MS (ES) M + H esperado 538.0, encontrado 538.1.

Procedimiento General K ejemplificado para 4-ter-butil-N-[4-cloro-2-[(S)-4-(1-isopropil-pirrolidin-3-il)-4H-[1,2,4]triazol-3-il]fenil)bencenosulfonamida



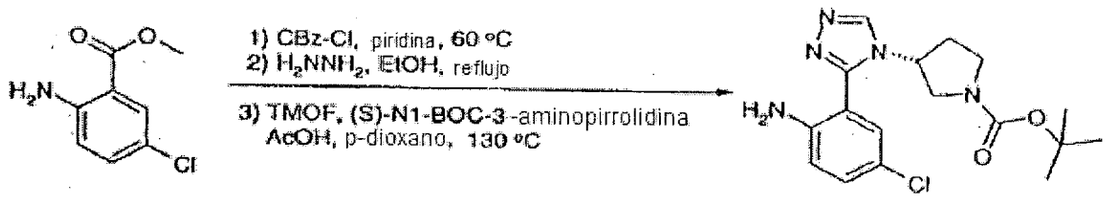
A una solución enfriada de 4-ter-butil-N-[4-cloro-2-[(S)-4-pirrolidin-3-il-4H-[1,2,4]triazol-3-il)fenil]bencenosulfonamida (200 mg, 0.43 mol) en MeOH (5 ml) se agregó acetona (0.048 ml, 0.65 mol) y después $NaCNBH_3$ (0.054 g, 0.86 mol). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas, se evaporó hasta secarse, se absorbió sobre gel de sílice, y se purificó mediante cromatografía automatizada en fase normal (50% MeOH en EtOAc) y después HPLC de preparación (20 - 95% CH_3CN en H_2O con 0.1% de TFA). Las fracciones puras se combinaron y se liofilizaron para obtener el compuesto del título como un polvo: MS (ES) M + H esperado 502.0, encontrado 502.1.

Procedimiento General L ejemplificado para N-[4-cloro-2-(4,5-dimetil-4H-[1,2,4]triazol-3-il)-fenil]3-fluoro-4-morfolin-4-il-bencenosulfonamida



Un vial de escintilación de 25 ml se cargó con 4-bromo-N-(4-cloro-2-(4,5-dimetil-4H-[1,2,4]triazol-3-il)-fenil)-3-fluoro-bencenosulfonamida (sintetizado de acuerdo con el procedimiento general C, 92 mg, 0.2 mol) monohidrato de fosfato de potasio (276 mg, 1.2 mol), BINAP (30 mg, 0.048 mol), morfolina (87 mg, 1.0 mol), $Pd_2(dba)_3$ (10 mg, 0.011 mol) y DMF (2 ml). El vial se selló, y se agitó a 90°C durante 20 horas. El producto crudo se purificó mediante cromatografía de columna instantánea (10-100% etil acetato y hexano) seguido por HPLC de preparación (10-90% gradiente de MeCN-agua) para producir el compuesto del título como un sólido blanco: ^{1}H NMR (400 MHz, $CDCl_3$/HCl) delta 2.4 (s, 3H), 2.7-3.7 (m, 8H), 3.8 (s, 3H), 6.7 (d, 1H), 7.1-7.3 (m, 3H), 7.4 (d, 1H), 7.5 (d, 1H), MS (ES) M + H esperado 466.0, encontrado 466.0.

Procedimiento General M ejemplificado para ter-butil éster de ácido 3-[(S)-3-(2-amino-5-cloro-fenil)-[1,2,4]triazol-4-il]-pirrolidina-1-carboxílico



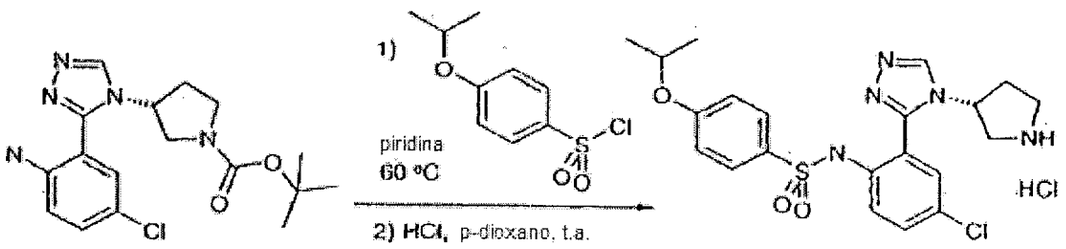
Etapa 1: se disolvió metil éster de ácido 2-amino-5-clorobenzoico (5 g, 27 mol) en 36 ml de piridina. Después se agregó CBz-Cl (4.2 ml, 29.6 mol) y la solución resultante se agitó a 60°C durante la noche. Al día siguiente, el análisis LCMS indicó que la reacción fue completa. La mezcla de reacción se vació subsecuentemente en una corriente lenta en 200 ml de 2M de HCl/H_2O en agitación rápida. La mezcla se transfirió a un embudo de separación y se extrajo con 2 x 50 ml de EtOAc. La fase acuosa se descartó y los orgánicos combinados se secaron sobre sulfato de sodio y se concentraron in vacuo para proporcionar 6 g de metil éster de ácido 2-benciloxicarbonilamino-5-cloro-benzoico (aceite amarillo pálido, rendimiento 70%): Tiempo de retención de HPLC = 3.15 minutos; MS (ES) M + H esperado 320.0, encontrado 320.0.

Etapa 2: se disolvió metil éster de ácido 2-benciloxicarbonilamino-5-cloro-benzoico (3 g, 9.4 mol) en 30 ml de etanol. Se agregó hidrato de hidrazina (1.5 ml, 30.0 mol) y la solución resultante se calentó a reflujo bajo una atmósfera de nitrógeno durante dos horas, a las cuales el análisis LCMS mostró una conversión completa al éster así

como el retiro del grupo de protección CBz. La mezcla de reacción se concentró subsecuentemente in vacuo para proporcionar 1.6 g de hidrazida de ácido 2-amino-5-cloro-benzoico (sólido café claro, rendimiento 92%): Tiempo de retención de HPLC = 2.21; MS (ES) M + H esperado 186.0, encontrado 186.0.

Etapa 3: se disolvió hidrazida de ácido 2-amino-5-cloro-benzoico (0.8 g, 4.3 mol) en 8 ml de p-dioxano en un recipiente a presión de 15 ml. Se agregó ortoformato de trimetilo (0.71 ml, 6.5 mol), (S)-N_1-Boc-3-aminopirrolidina (4.0 g, 21.6 mol) y ácido acético (5 gotas) y la solución resultante se calentó durante la noche en un baño de aceite a 130°C. La mezcla de reacción se concentró subsecuentemente in vacuo para producir un aceite espeso que se diluyó con una pequeña cantidad de diclorometano y se purificó mediante cromatografía de columna (MeOH/DCM, 0% a 15% gradiente) para proporcionar 1.4 g de ter-butil éster de ácido 3-[(S)-3-(2-amino-5-cloro-fenil)-[1,2,4]triazol-4-il]-pirrolidina-1-carboxílico (semisólido blanco, rendimiento 77%): Tiempo de retención de HPLC = 1.98; MS (ES) M + H esperado 364.0, encontrado 364.1.

Procedimiento General N ejemplificado para N-[4-cloro-2-((S)-4-pirrolidin-3-il-4H-[1,2,4]triazol-3-il)-fenil]-4-isopropoxi-bencenosulfonamida

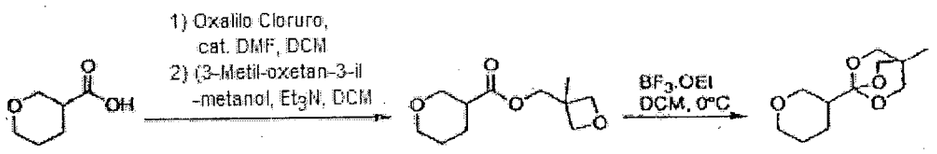


Etapa 1: Se disolvió ter-butil éster de ácido 3-[(S)-3-(2-amino-5-cloro-fenil)-[1,2,4]triazol-4-il]-pirrolidina-1-carboxílico (50 mg, 0.137 mol) en 0.5 ml de piridina en un vial de 4 ml. Se agregó cloruro de 4-isopropoxibencenosulfonilo42 mg, 0.179 mol) y la mezcla se calentó a 60°C durante la noche. Se agregó agua (-3 ml) a la mezcla de reacción lo cual indujo la precipitación de un aceite viscoso. El licor madre se descartó y el aceite se disolvió en -3 ml de acetonitrilo. La solución resultante se purificó mediante HPLC de fase inversa y las fracciones puras se liofilizaron para producir la sulfonamida deseada: Tiempo de retención de HPLC = 2.71 minutos; MS (ES) M + H esperado 562.0, encontrado 562.1.

Etapa 2: la sulfonamida anterior se disolvió en 1 ml de p-dioxano y se agregó 4 M de HCl/p-dioxano (4 ml, 16 mol). La mezcla resultante se agitó a temperatura ambiente durante una hora, durante la cual el LCMS indicó el retiro completo del grupo de protección BOC. La mezcla de reacción se concentró subsecuentemente in vacuo para generar un aceite espeso, que se diluyó con 10 ml de acetonitrilo/H_2O y se

liofilizó para producir hidrocloruro de N-[4-cloro-2-((S)-4-pirrolidin-3-il-4H-[1,2,4]triazol-3-il)-fenil]-4-isopropoxi-bencenosulfonamida: Tiempo de retención de HPLC = 1.67 minutos; MS (ES) M + H esperado 462.0, encontrado 462.4.

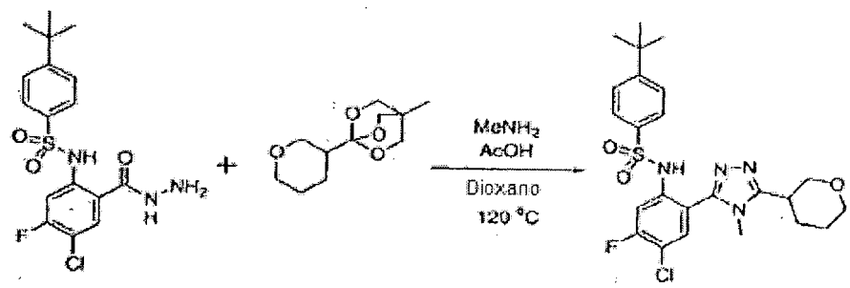
Procedimiento General O ejemplificado para 4-metil-1-(tetrahidro-piran-3-il)-2,6,7-trioxa-biciclo[2,2,2]octano



Etapa 1: A una solución en agitación de ácido tetrahidro-2H-piran-3-carboxílico (231 mg, 1.77 mol), bajo una atmósfera inerte, en 8 ml de DCM anhidroso y 358 ul de DMF, se agregó cloruro de oxalilo (155 ul, 1.77 mol). La mezcla se agitó a temperatura ambiente durante 4 horas. Esta solución se agregó entonces mediante jeringa a una solución de 4 ml de DCM conteniendo (3-metil-oxetan-3-il)-metanol (182 ul, 1.77 mol) y Et_3N (0.62 ml, 4.44 mol). La mezcla resultante se agitó a temperatura ambiente durante 4 horas. El solvente se evaporó subsecuentemente in vacuo y el residuo resultante se re-disolvió en etil acetato y se lavó con $NaHCO_3$ saturado, solución de NH_4Cl y salmuera. Los orgánicos combinados se secaron entonces sobre Na_2SO_4 anhidroso y se concentraron para proporcionar un producto crudo que se utilizó directamente en la siguiente etapa sin purificación adicional.

Etapa 2: El 3-metil-oxetan-3-ilmetil éster de ácido tetrahidro-piran-3-carboxílico crudo anterior (346 mg, 1.62 mol) se disolvió en 6 ml de DCM anhidroso. A esta solución a 0°C, bajo una atmósfera de nitrógeno, se agregó BF_3-Oet_2 (41 ul, 0.324 mol). La mezcla se agitó a 0°C durante dos horas, después se calentó a temperatura ambiente y se agitó durante la noche. Al día siguiente, se agregó Et_3N (0.23 ml, 91.6 mol) a 0°C para templar la reacción. Después de agitar durante 5 minutos, el solvente se retiró in vacuo. El residuo resultante se disolvió en etil acetato y se lavó con 3% de NH_4Cl, $NaHCO_3$ saturado y salmuera. Los orgánicos combinados se secaron subsecuentemente sobre Na_2SO_4 anhidroso y se concentraron para proporcionar el ortoéster deseado.

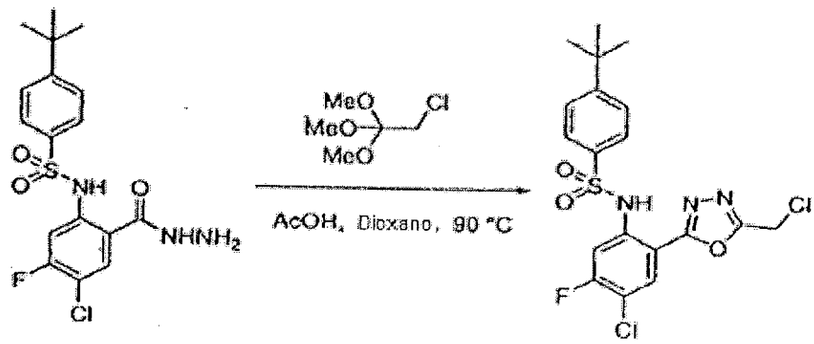
Procedimiento General P ejemplificado para 4-ter-butil-N-[4-cloro-5-fluoro-2-[4-metil-5(tetrahidro-piran-3-il)-4H-[1,2,4]triazol-3-il]-fenil)-bencenosulfonamida



Un vial de escintilación de 25 ml se cargó con 4-ter-butil-N-(4-cloro-3-fluoro-2-hidrazinocarbonil-fenil)bencenosulfonamida (253 mg, 0.633 mol), 4-metil-1-(tetrahidro-piran-3-il)-2,6,7-trioxa-biciclo[2.2.2]octano

(136 mg, 0.633 mol), metilamina (31 ul, 0.886 mol), AcOH (51 ul, 0.886 mol) y dioxano (1.0 ml). El vial se selló, se calentó a 120°C y se agitó durante la noche. Al día siguiente, los volátiles se evacuaron in vacuo y el residuo se purificó mediante cromatografía automatizada de gel de sílice para producir 4-ter-butil-N-[4-cloro-5-fluoro-2-[4-metil-5-(tetrahidro-piran-3-il)-4H-[1,2,4]triazol-3-il)-fenil]-bencenosulfonamida como un polvo blanco: MS (ES) M + H esperado 507.1, encontrado 507.1.

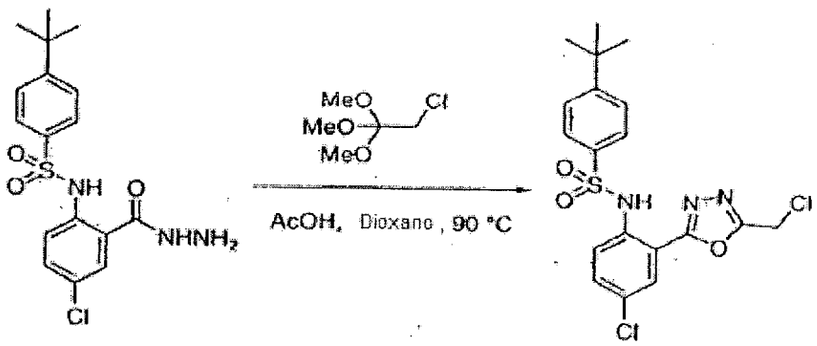
Procedimiento General Q ejemplificado para 4-ter-butil-N-[4-cloro-2-[5-clorometil-[1,3,4]oxodiazol-2-il)-5-fluoro-fenil]-bencenosulfonamida



Se agregó 2-cloro-1,1,1-trimetoxi-etano (0.507 ml, 3.76 mol) y AcOH (1.5 ml) a 4-ter-butil-N-(4-cloro-3-fluoro-2-hidrazinocarbonil-fenil)bencenosulfonamida (1.0 g, 2.51 mol) en dioxano (65 ml) y se agitó durante la noche a 90°C. La mezcla de reacción se enfrió subsecuentemente a temperatura ambiente y se almacenó durante 1 día para promover la precipitación del producto. El sólido blanco

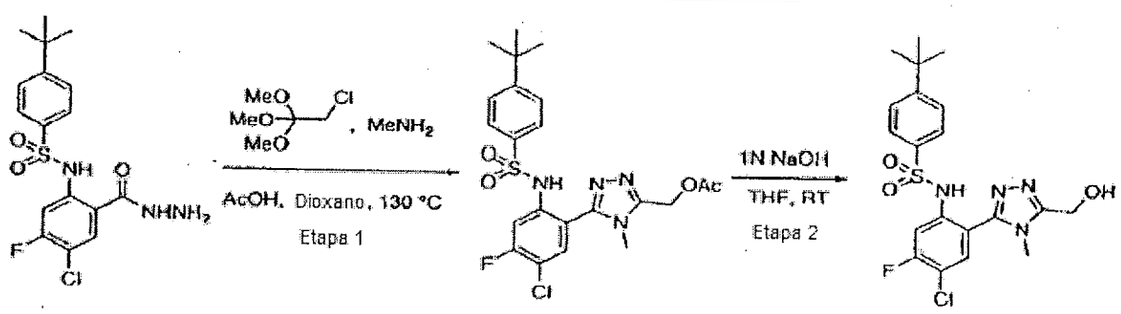
resultante se filtró, se lavó con Et_2O (2 x 10 ml) y se secó bajo vacío para generar el compuesto del título (0.74 g) en un rendimiento de 65% como un sólido blanco: MS (ES) M + H esperado 458.0, encontrado 458.3.

4-ter-butil-N-[4-cloro-2-(5-clorometil-[1,3,4]oxadiazol-2-il)-fenil]bencenosulfonamida



Se preparó 4-ter-butil-N-[4-cloro-2-(5-clorometil-[1,3,4]oxadiazol-2-il)-fenil]bencenosulfonamida de acuerdo con el procedimiento general Q: MS (ES) M + H esperado 440.0, encontrado 440.3.

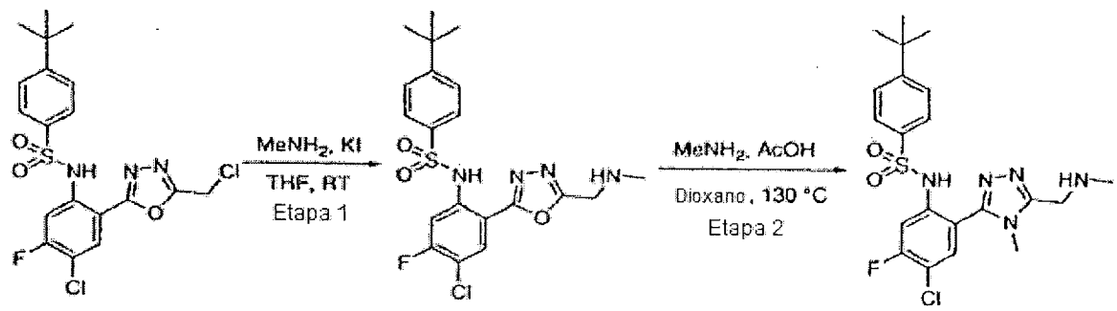
Procedimiento General R ejemplificado para 4-ter-butil-N-[4-cloro-5-fluoro-2-(5-hidroximetil-4-metil-4H-[1,2,4]triazol-3-il)-fenil]bencenosulfonamida



Etapa 1: Se agregó 2-cloro-1,1,1-trimetoxi-etano (0.220 ml, 3.76 mol), $MeNH_2$ (0.625 ml, 2.0 M en THF) y AcOH (0.4 ml) a 4-ter-butil-N-(4-cloro-3-fluoro-2-hidrazinocarbonil-fenil)bencenosulfonamida (0.50 g, 1.25 mol) en dioxano (5 ml) y se agitó 4 horas a 130°C. La mezcla de reacción resultante se evaporó hasta secar, se absorbió sobre gel de sílice y se purificó mediante cromatografía automatizada en fase normal (30% EtOAc en hexanos) para producir el "triazol-acetato" como un producto menor.

Etapa 2: A una solución de "triazol-acetato" (20 mg) en THF (2 ml) se agregó 1 N de NaOH acuoso (2 ml) y la solución se agitó a temperatura ambiente durante 30 minutos. Se agregó subsecuentemente 2 N de HCl (acuoso) y la capa acuosa se extrajo con EtOAc (2 x 15 ml). Los orgánicos combinados se secaron (Na_2SO_4), se concentraron in vacuo, y se purificaron mediante cromatografía automatizada en fase normal (50% EtOAc en hexanos) para generar el compuesto del título como un polvo blanco después de la liofilización: MS (ES) M + H esperado 453.0, encontrado 453.1.

Procedimiento General S ejemplificado para 4-ter-butil-N-[4-cloro-5-fluoro-2-(4-metil-5-metilaminometil-H-[1,2,4]triazol-3-il)-fenil]bencenosulfonamida

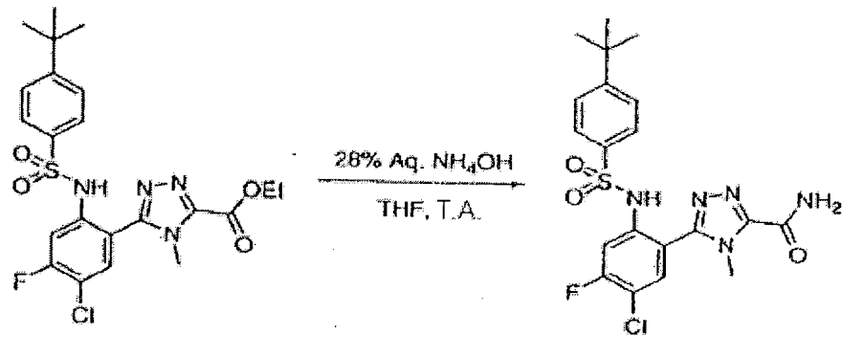


Etapa 1: A una solución de 4-ter-butil-N-[4-cloro-2-(5-clorometil-[1,3,4]oxadiazol-2-il)-5-fluoro-fenil]bencenosulfonamida (400 mg, 0.875 mol) en THF (5 ml) se agregó KI (0.145 g, 0.875 mol) y $MeNH_2$ (1.31 ml, 2.62 mol, 2.0 M en THF). La solución resultante se agitó a temperatura ambiente durante la noche. Al día siguiente, la mezcla de reacción se diluyó con EtOAc (30 ml) y la capa orgánica se lavó con agua (30 ml) y salmuera (30 ml), se secó (Na_2SO_4) y se concentró in vacuo para producir el "metilaminometil-oxadiazol" deseado (400 mg) como un sólido blanco en rendimiento cuantitativo: mMS (ES) M +`H esperado 453.0, encontrado 453.0.

Etapa 2: Al intermediario de oxadiazol anterior (100 mg, 0.22 mol) en 1,4-dioxano (3 ml) se agregó $MeNH_2$ (1.1 ml, 2.0 M en THF), seguido por AcOH (0.125 ml). La solución homogénea se calentó a 130°C y se agitó durante 4 horas. Al enfriarse a temperatura ambiente, la mezcla de reacción se diluyó con EtOAc (25 ml) y la capa orgánica se lavó con solución de $NaHCO_3$ saturado (25 ml), se secó (Na_2SO_4), se

concentró in vacuo y se purificó mediante cromatografía automatizada en fase normal (5% MeOH en EtOAc). Las fracciones puras se combinaron y se liofilizaron para producir el compuesto del título como un polvo: ^{1}H NMR (400 MHz, CD_3OD) delta 7.65 (d, 1H), 7.60-7.52 (m, 4H), 7.0 (d, 1H), 4.58 (s, 2H), 3.58 (s, 3H), 2.95 (s, 3H), 1.35 (s, 9H), MS (ES) M + H esperado 466.0, encontrado 466.1.

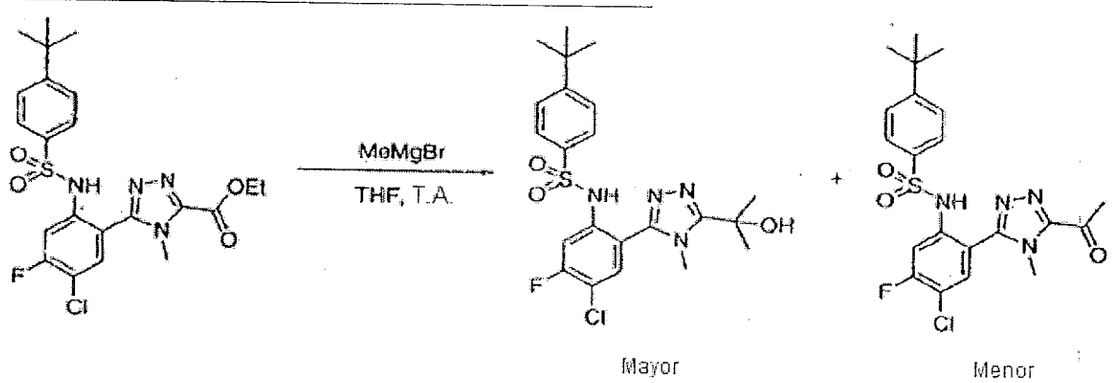
Procedimiento General T ejemplificado para amida de ácido 5-[2-(4-ter-butil-bencenosulfonilamino)-5-cloro-4-fluoro-fenil]-4-metil-4H-[1,2,4]triazol-3-carboxílico



A un vial conteniendo etil éster de ácido 5-[2-(4-ter-butil-bencenosulfonilamino)-5-cloro-4-fluoro-fenil]-4-metil-4H-[1,2,4]triazol-3-carboxílico (sintetizado de acuerdo con el procedimiento general C, 100 mg, 0.202 mol) se agregó THF (2 ml) y 28% de NH_4OH en agua (2 ml), y la solución resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se diluyó subsecuentemente con EtOAc (30 ml) y los orgánicos se lavaron con agua (2 x 10 ml), se secaron sobre Na_2SO_4, se concentraron in vacuo, y se

purificaron mediante cromatografía instantánea (50 - 100% gradiente de EtOAc en hexanos). Las fracciones puras se recolectaron y el solvente se retiró. El producto aislado se disolvió en MeCN/H_2O y el solvente se retiró mediante liofilización para producir el compuesto del título como un polvo blanco: MS (ES) M + H esperado 466.0, encontrado 466.0.

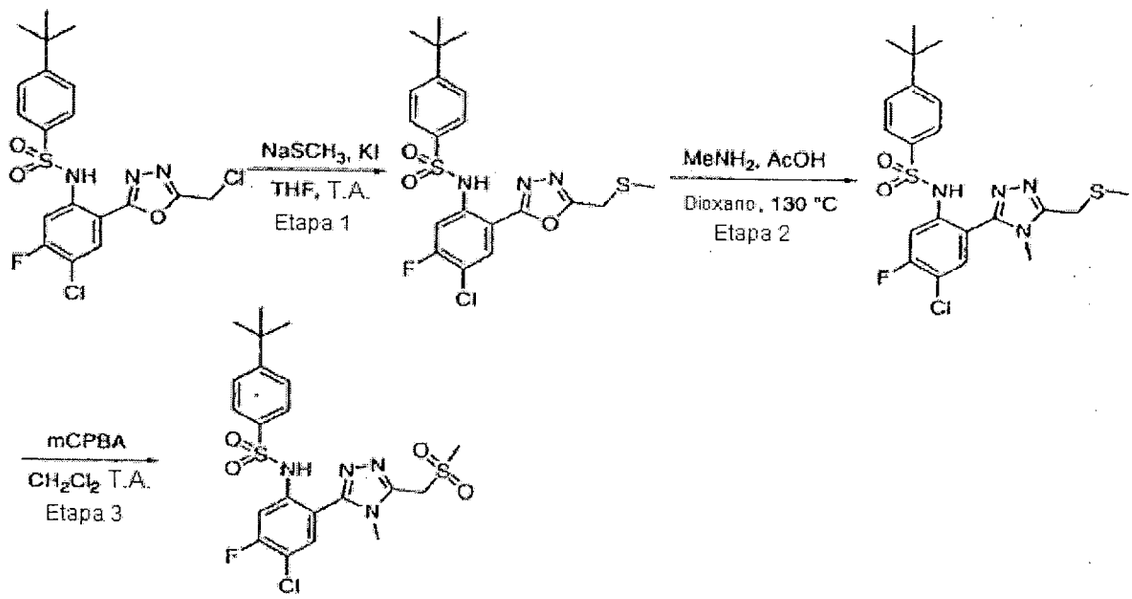
Procedimiento General U ejemplificado para 4-ter-butil-N-[4-cloro-5-fluoro-2-[5-(1-hidroxi-1-metil-etil)-4-metil-4H[1,2,4]triazol-3-il]-fenil]bencenosulfonamida y N-[2-(5-acetil-4-metil-4H-[1,2,4]triazol-3-il)-4-cloro-5-fluoro-fenil]-4-ter-butil-bencenosulfonamida



A una solución de etil éster de ácido 5-[2-(4-ter-butil-bencenosulfonilamino)-5-cloro-4-fluoro-fenil]-4-metil-4H-[1,2,4]triazol-3-carboxílico (sintetizado de acuerdo con el procedimiento general C, 100 mg, 0.254 mol) en THF (3 ml) a temperatura ambiente, se agregó MeMgBr (3 ml, 3.0 M en Et_2O). La solución resultante se agitó 30 minutos, seguido por la adición lenta de solución de NH_4Cl saturado acuoso para templar el exceso de MeMgBr. La capa acuosa se extrajo

subsecuentemente con EtOAc (2 x 25 ml) y los orgánicos combinados se secaron (Na_2SO_4), se concentraron in vacuo, y se purificaron mediante cromatografía automatizada en fase normal (EtOAc/hexanos) para producir el alcohol terciario (0.026 g, rendimiento 21%) como el producto principal y la metil cetona como el producto menor (0.020 g, rendimiento 17%): MS (ES) M + H (producto principal) esperado 481.0, encontrado 481.0. MS (ES) M + H (producto menor) esperado 465.0, encontrado 465.0.

Procedimiento General V ejemplificado para 4-ter-butil-N-[4-cloro-5-fluoro-2-(5-metanosulfonilmetil-4-metil-4H-[1,2,4]triazol-3-il)-fenil]bencenosulfonamida



Etapa 1: Se agregó KI (0.036 g, 0.218 mol) seguido por tiometóxido de sodio (0.046 g, 0.654 mol) a 4-ter-butil-N-[4-cloro-2-(5-clorometil-[1,3,4]oxadiazol-2-il)-5-fluoro-

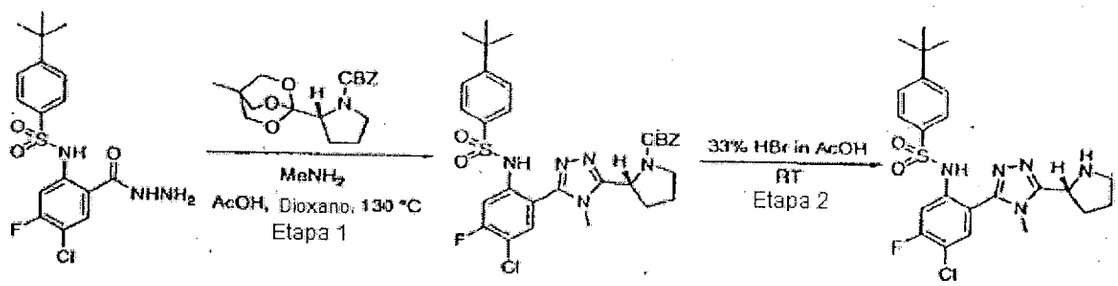
fenil]bencenosulfonamida (100 mg, 0.218 mol) en THF (3 ml) y se agitó a temperatura ambiente durante la noche. La mezcla de reacción resultante se diluyó con EtOAc (30 ml) y la capa orgánica se lavó con agua (30 ml) y salmuera (30 ml), se secó (Na_2SO_4) y se concentró in vacuo para generar el "oxadiazol metiltioéter" deseado (100 mg) como un jarabe espeso amarillo en rendimiento cuantitativo: MS (ES) M + H esperado 470.0, encontrado 470.0.

Etapa 2: Al "oxadiazol metiltioéter" anterior (100 mg, 0.21 mol) en 1,4-dioxano (3 ml) se agregó $MeNH_2$ (1.1 ml, 2.0 M en THF) y AcOH (0.128 ml) y la mezcla resultante se agitó a 130°C durante 4 horas. Al enfriarse a temperatura ambiente, la mezcla de reacción se diluyó con EtOAc (25 ml) y la capa orgánica se lavó con solución de $NaHCO_3$ saturado (25 ml), se secó (Na_2SO_4) se concentró in vacuo y se purificó mediante cromatografía automatizada en fase normal (EtOAc) para producir el "triazol metiltioéter" correspondiente: MS (ES) M + H esperado 483.0, encontrado 483.4.

Etapa 3: A una solución del "triazol metiltioéter" anterior (0.025 g, 0.05 mol) en CH_2Cl_2 (3 ml) se agregó mCPBA (0.027 g, 0.155 mol) y la mezcla resultante se agitó a temperatura ambiente durante la noche. Los volátiles se retiraron subsecuentemente y el producto se purificó utilizando HPLC de preparación (20 - 95% CH_3CN en H_2O con 0.1% de TFA). Las fracciones puras se combinaron y se

liofilizaron para generar el compuesto del título como un polvo amarillo: MS (ES) M + H esperado 515.0, encontrado 515.4.

Procedimiento General W ejemplificado para 4-ter-butil-N-[4-cloro-5-fluoro-2-((R)-4-metil-5-pirrolidin-2-il-4H-[1,2,4]triazol-3-il)fenil]bencenosulfonamida

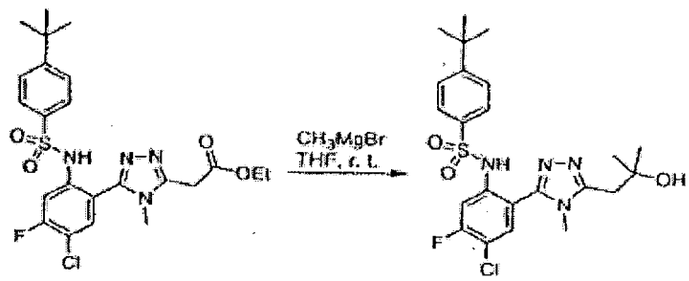


Etapa 1: se agregó bencil éster de ácido (R)-2-(4-metil-2,6,7-trioxa-biciclo[2.2.2]oct-1-il)-pirrolidina-1-carboxílico (sintetizado de acuerdo con el procedimiento general O, 0.296 g, 0.888 mol), $MeNH_2$ (0.888 ml, 2.0 M en THF) y AcOH (0.125 ml) a 4-ter-butil-N-(4-cloro-3-fluoro-2-hidrazinocarbonil-fenil)bencenosulfonamida (0.236 g, 0.59 mol) en dioxano (5 ml) y la solución se agitó durante la noche a 130°C. Al día siguiente, la mezcla de reacción se evaporó hasta secar y el triazol crudo resultante se utilizó directamente en la siguiente etapa.

Etapa 2: Al triazol crudo anterior se agregó 33& de HBr en AcOH (3 ml) y la mezcla de reacción resultante se agitó durante la noche a temperatura ambiente. Al día siguiente, los volátiles se retiraron in vacuo y el residuo

resultante se disolvió en una pequeña cantidad de MeOH y se purificó mediante HPLC de preparación (20 - 95% CH_3CN en H_2O con 0.1% de TFA). Las fracciones puras se recolectaron y se liofilizaron para producir el compuesto del título como un polvo amarillo: MS (ES) M + H esperado 492.0, encontrado 492.4.

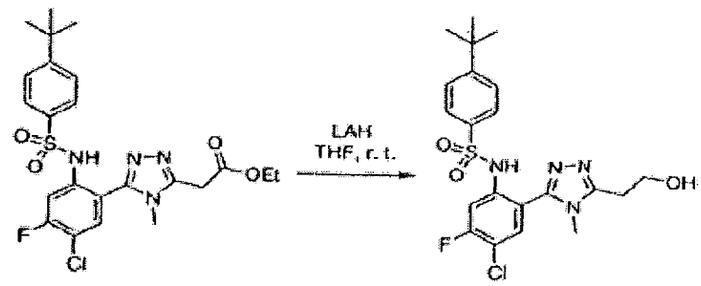
Procedimiento General X ejemplificado para 4-ter-butil-N-[4-cloro-5-fluoro-2-[5-(2-hidroxi-2-metil-propil]-4-metil-4H-[1,2,4]triazol-3-il]-fenil]bencenosulfonamida



Un vial de escintilación de 25 ml se cargó con etil éster de ácido [5-[2-(4-ter-butil-bencenosulfonilamino)-5-cloro-4-fluoro-fenil]-4-metil-4H-[1,2,4]triazol-3-il]acético (preparado de acuerdo con el procedimiento general P, 178 mg, 0.349 mol) en 7 ml de THF anhidroso. A esta solución, bajo una atmósfera de nitrógeno, se agregó metil magnesio bromuro (0.47 ml, 3.0 M en THF) a temperatura ambiente. Al consumirse completamente el material de inicio (mediante LCMS), la reacción se templó mediante la adición de una solución de NH_4Cl. El solvente se removió subsecuentemente in vacuo y el residuo se purificó mediante cromatografía

automatizada de gel de sílice para producir 4-ter-butil-N-(4-cloro-5-fluoro-2-[5-(2-hidroxi-2-metil-propil)-4-metil-4H-[1,2,4]triazol-3-il]fenil]bencenosulfonamida como un polvo blanco: ^{1}H NMR (400 MHz, $CDCl_3$) delta 9.85 (s, 1H), 7.64 (d, 1H), 7.60 (d, 2H), 7.41 (d, 2H), 7.30 (d, 1H), 4.0 (s, 1H), 3.81 (s, 2H), 3.41 (s, 3H), 1.57 (s, 9H), 1.31 (s, 6H), MS (ES) M + H esperado 495.2, encontrado 495.4.

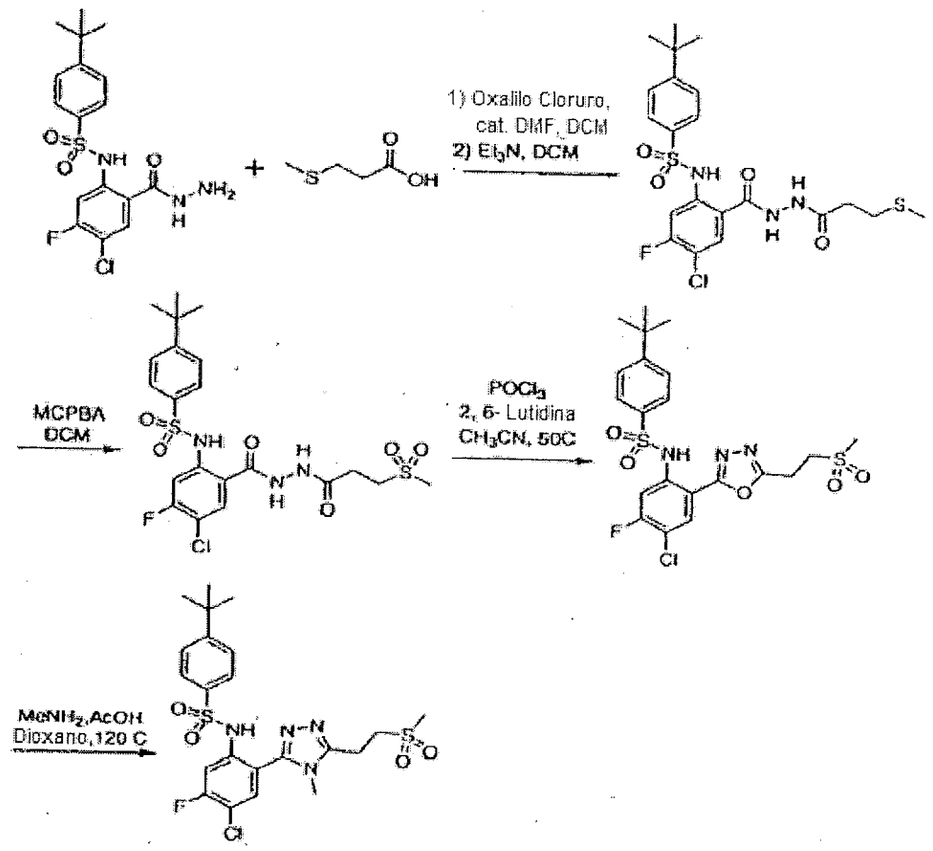
Procedimiento General Y ejemplificado para 4-ter-butil-N-(4-cloro-5-fluoro-2-[5-(2-hidroxi-etil)-4-metil-4H-[1,2,4]triazol-3-il]fenil]bencenosulfonilamida



Un vial de escintilación de 25 ml se cargó con etil éster de ácido [5-[2-(4-ter-butil-bencenosulfonilamino)-5-cloro-4-fluoro-fenil]-4-metil-4H-[1,2,4]triazol-3-il]acético (sintetizado de acuerdo con el procedimiento general P, 95 mg, 0.186 mol) en 2 ml de MeOH anhidroso. A esta solución, bajo una atmósfera de nitrógeno, se agregó hidruro de aluminio litio (14 mg, 0.372 mol) a temperatura ambiente. La LCMS indicó completa la reacción después de 30 minutos y se agregó 1 ml de 20% de H_2SO_4. El solvente se retiró subsecuentemente in vacuo y el residuo se extrajo con DCM.

La capa orgánica se lavó entonces con $NaHCO_3$ saturado y salmuera, se secó sobre Na_2SO_4 anhidroso, y se concentró in vacuo. El residuo resultante se purificó mediante cromatografía automatizada de gel de sílice para proporcionar 4-ter-butil-N-[4-cloro-5-fluoro-2-[5-(2-hidroxi-etil)-4-metil-4H-[1,2,4]triazol-3-il]fenil]bencenosulfonamida como un polvo blanco: MS (ES) M + H esperado 467.1, encontrado 467.4.

Procedimiento General Z ejemplificado para 4-ter-butil-N-(4-cloro-5-fluoro-2-[5-(2-metanosulfonil-etil)-4-metil-4H-[1,2,4]triazol-3-il]fenil]bencenosulfonilamida



Etapa 1: A una solución agitada de ácido 3-metilsulfanil-propiónico (120 mg, 1.0 mol) bajo una atmósfera inerte en 6 ml de DCM anhidroso y DMF (200 ul), se agregó cloruro de oxalilo (89 ul, 1.0 mol). La solución resultante se agitó a temperatura ambiente durante la noche y después se agregó a una solución de 4-ter-butil-N-(4-cloro-5-fluoro-2-hidrazinocarbonil-fenil)bencenosulfonamida (400 mg, 1.0 mol) y Et_3N (0.35 ml, 2.5 mol) a 0°C. La solución resultante se agitó a temperatura ambiente durante 4 horas y el solvente se retiró in vacuo. El residuo se purificó mediante cromatografía automatizada de gel de sílice para producir 4-ter-butil-N-[4-cloro-5-fluoro-2-[N'-(3-metilsulfanil-propionil)-hidrazinocarbonil]fenil]bencenosulfonamida como un aceite: MS (ES) M + H esperado 502.1, encontrado 502.0.

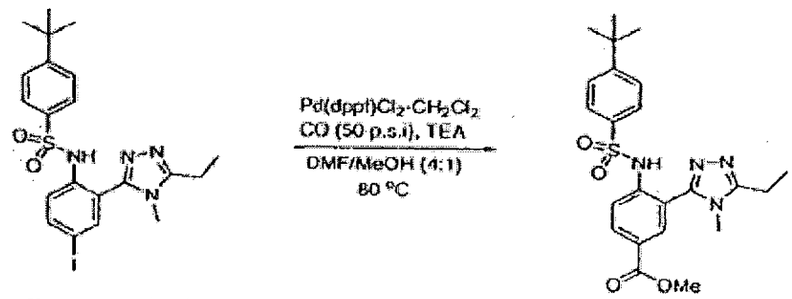
Etapa 2: A una solución de la diamida anterior (422 mg, 0.841 mol) en 10 ml de DCM, se agregó ácido 3-cloroperoxibenzoico (386 mg, 172 mol a 0°C. La mezcla de reacción se agitó subsecuentemente a temperatura ambiente durante la noche. Al día siguiente, el producto se había precipitado de la solución y se recolectó mediante filtración al vacío y se utilizó directamente en la siguiente etapa: MS (ES) M + H esperado 534.1, encontrado 534.0.

Etapa 3: Un vial de escintilación de 25 ml se cargó con la sulfona cruda anterior (307 mg, 0.574 mol), 2,6-lutidina (148 mg, 1.378 mol), $POCl_3$ (106 mg, 0.689 mol) y

CH_3CN (1.0 ml). El vial se selló, se calentó a 50°C y se agitó durante la noche. Al día siguiente, los volátiles se evacuaron in vacuo y el residuo se purificó mediante cromatografía automatizada de gel de sílice para producir 4-ter-butil-N-[4-cloro-5-fluoro-2-[5-(2-metanosulfonil-etil)-[1,3,4]oxadiazol-2-il]fenil]bencenosulfonamida como el producto deseado: MS (ES) M + H esperado 516.1, encontrado 516.0.

Etapa 4: Un vial de escintilación de 25 ml se cargó con 4-ter-butil-N-[4-cloro-5-fluoro-2-[5-(2-metanosulfonil-etil)-[1,3,4]oxadiazol-2-il]fenil]bencenosulfonamida (48 mg, 0.093 mol), metilamina (13 ul, 0.372 mol), AcOH (21 ul, 0.372 mol), y dioxano (1.0 ml). El vial se selló, se calentó a 120°C y se agitó durante la noche. Al día siguiente, los volátiles se evacuaron in vacuo y el residuo se purificó mediante cromatografía automatizada de gel de sílice para producir 4-ter-butil-N-[4-cloro-5-fluoro-2-[5-(2-metanosulfonil-etil)-4-metil-4H-[1,2,4]triazol-2-il]fenil]bencenosulfonamida como un polvo blanco: MS (ES) M + H esperado 529.1, encontrado 529.0.

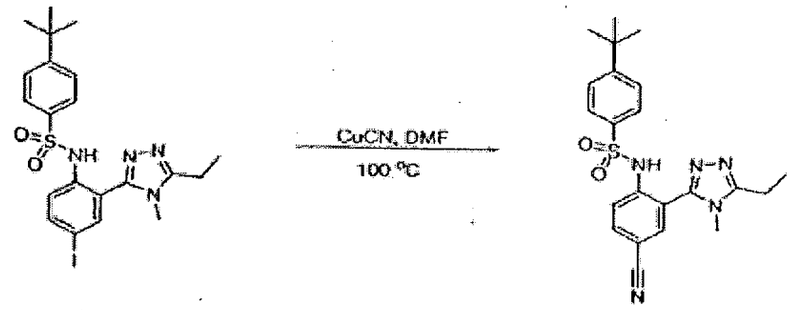
Procedimiento General AA ejemplificado para metil éster de ácido 4-(4-ter-butil-bencenosulfonilamino)-3-(5-etil-4-metil-4H-[1,2,4]triazol-3-il)benzoico



Un recipiente a presión de 15 ml se cargó con 4-ter-butil-N-[4-yodo-2-(5-etil-4-metil-4H-[1,2,4]triazol-3-il)fenil]bencenosulfonamida (preparada de acuerdo con el procedimiento general C, 551 mg, 1.05 mol), complejo de [1,1'-bis(difenilfosfino)ferroceno)dicloropaladio (II) con CH_2Cl_2 (1:1) (86 mg, 0.105 mol), trietilamina (290 ul, 2.1 mol) y DMF/MeOH (4:1) (5 ml). El recipiente se colocó bajo una atmósfera de CO (50 p.s.i.), se calentó a 80°C y se agitó durante la noche. Al día siguiente, los volátiles se retiraron in vacuo, el residuo se disolvió en EtOAc y los orgánicos se lavaron dos veces con 1 M de HCl. La solución acuosa se extrajo entonces tres veces con EtOAc. Las extracciones de EtOAc se depositaron entonces juntas y se lavaron con salmuera. El solvente orgánico se retiró entonces y el residuo resultante se purificó mediante cromatografía de gel de sílice para producir metil éster de ácido 4-(4-ter-butil-bencenosulfonilamino)-3-(5-etil-4-metil-4H-[1,2,4]triazol-3-il)benzoico como una espuma amarilla: MS (ES) M + H esperado 457.2, encontrado 457.1.

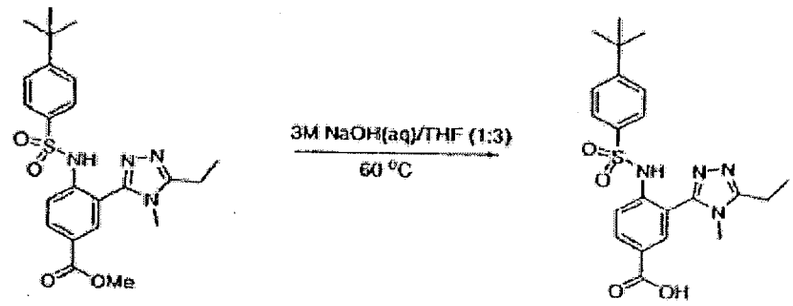
Procedimiento General BB ejemplificado para 4-ter-

butil-N-[4-ciano-2-[5-etil-4-metil-4H-[1,2,4]triazol-3-il)fenil]bencenosulfonamida



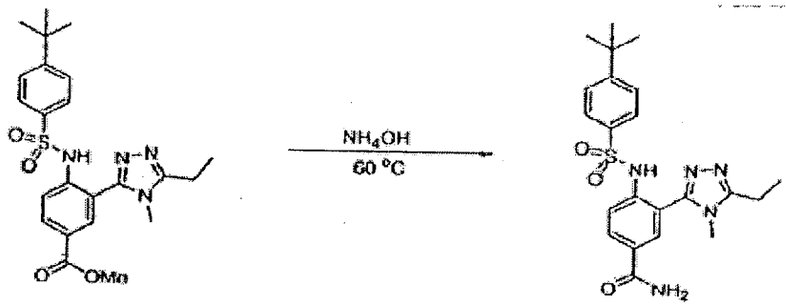
Un vial de escintilación de 4 ml se cargó con 4-ter-butil-N-[4-yodo-2-[5-etil-4-metil-4H-[1,2,4]triazol-3-il)fenil]bencenosulfonamida (preparada de acuerdo con el procedimiento general C, 18 mg, 0.034 mol), CuCN (15 mg, 0.17 mol) y DMF (500 ul). La reacción se calentó entonces a 100°C y se agitó durante 48 horas. La solución se diluyó entonces con EtOAc y se lavó con una solución acuosa de EDTA (5% peso/peso). La capa orgánica se concentró entonces y el residuo se purificó mediante TLC de preparación para producir 4-ter-butil-N-[4-ciano-2-[5-etil-4-metil-4H-[1,2,4]triazol-3-il)fenil]bencenosulfonamida como un sólido blanco: MS (ES) M + H esperado 424.2, encontrado 424.4.

Procedimiento General CC ejemplificado para ácido 4-(4-ter-butil-bencenosulfonilamino)-3-(5-etil-4-metil-4H-[1,2,4]triazol-3-il)benzoico



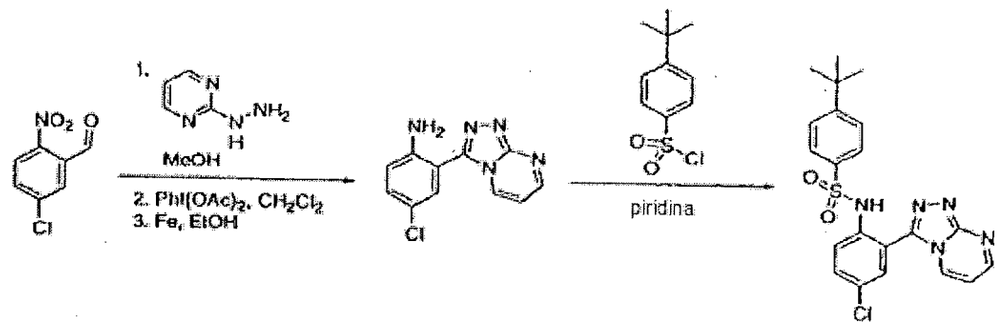
Un vial de escintilación de 10 ml se cargó con metil éster de ácido 4-(4-ter-butil-bencenosulfonilamino)-3-(5-etil-4-metil-4H-[1,2,4]triazol-3-il)benzoico (20 mg, 0.044 mol) y 3 M de NaOH (acuoso)/THF (1:3) (1.5 ml). La reacción se calentó a 60°C y se agitó durante la noche. Al siguiente día, los volátiles se retiraron un vacuo a aproximadamente 200 ul, en cuyo punto se purificó la solución mediante TLC de preparación para producir ácido 4-(4-ter-butil-bencenosulfonilamino)-3-(5-etil-4-metil-4H-[1,2,4]triazol-3-il)benzoico como un sólido amarillo claro: MS (ES) M + H esperado 443.2, encontrado 443.4.

Procedimiento General DD ejemplificado para 4-(4-ter-butil-bencenosulfonilamino)-3-(5-etil-4-metil-4H-[1,2,4]triazol-3-il)benzamida



Un vial de escintilación de 10 ml se cargó con metil éster de ácido 4-(4-ter-butil-bencenosulfonilamino)-3-(5-etil-4-metil-4H-[1,2,4]triazol-3-il)benzoico (20 mg, 0.044 mol) y 30% de NH_3 en H_2O (1.5 ml). La reacción se calentó a 60°C y se agitó durante la noche. Al siguiente día, los volátiles se retiraron un vacuo a aproximadamente 200 ul, en cuyo punto se purificó la solución mediante TLC de preparación para producir 4-(4-ter-butil-bencenosulfonilamino)-3-(5-etil-4-metil-4H-[1,2,4]triazol-3-il)benzamida como un aceite incoloro: MS (ES) M + H esperado 442.2, encontrado 442.4.

Procedimiento General EE ejemplificado para 4-ter-butil-N-(4-cloro-2-[1,2,4]triazolo(4,3-a)pirimidin-3-il-fenil)bencenosulfonamida



Etapa 1: Un vial de escintilación de 5 ml se cargó con 2-hidrazinopirimidina (61 mg, 0.55 mol), 2-nitro-5-clorobenzaldehído (112 mg, 0.60 mol) y MeOH (500 ul) y se calentó a 60°C durante 30 minutos. El MeOH se retiró entonces in vacuo y el sólido resultante se lavó con Et_2O.

El sólido crudo (30 mg) se suspendió entonces en CH_2Cl_2 (1 ml) y se agregó diacetato de yodobenceno (39 mg, 0.12 mol). La reacción se agitó a temperatura ambiente durante 30 minutos después de lo cual se retiró el solvente in vacuo. El residuo resultante se disolvió entonces en una solución al 10% de NH_4Cl saturado (acuoso) en EtOH y se agregó entonces hierro (19 mg, 0.33 mol) y la reacción se agitó a 80°C durante 4 horas. El solvente se retiró entonces in vacuo y el producto se purificó mediante cromatografía de gel de sílice para producir 4-cloro-2-[1,2,4]triazolo[4,3-a]pirimidin-3-il-fenilamina como un aceite amarillo claro.

Etapa 2: un vial de escintilación de 4 ml se cargó con la anilina anterior (10 mg, 0.04 mol), cloruro de ter-butilfenilsulfonilo (11 mg, 0.05 mol) y piridina (300 ul). La mezcla se calentó subsecuentemente a 60°C y se agitó durante la noche. Al siguiente día, la mezcla de reacción se diluyó en EtOAc y se lavó con 1 N de HCl (acuoso). La capa orgánica se concentró entonces y el residuo obtenido se purificó mediante TLC de preparación para producir la sulfonamida deseada: MS (ES) M + H esperado 442.1, encontrado 442.3.

Los compuestos en la Tabla 2 se prepararon mediante el procedimiento general indicado descrito anteriormente. Los datos de MS (ES) $[M+H]^+$ se recolectaron y se compararon con el valor esperado para confirmar la identidad del

compuesto.

Tabla 2 - Compuestos preparados por medio de los Procedimientos Generales y Datos de MS

Combinación	Procedimiento General	$[M+H]^+$ Previsto	$[M+H]^+$ Proceso
1	C	432.14	433.0
2	C	466.12	467.0
3	C	446.15	447.1
4	C	480.14	481.0
5	C	432.14	433.1
6	C	418.12	419.1
7	C	444.14	445.1
8	C	446.15	447.0
9	D	488.16	489.1
10	D	448.13	449.1
11	C	474.19	475.1
12	C	488.16	489.1
13	C	460.17	461.1
14	C	472.17	473.1
15	C	448.13	449.1
16	C	470.13	471.1
17	C	434.12	435.0
18	C	432.14	433.1
19	C	460.17	461.1
20	I	487.18	488.1
21	D	518.18	519.1
22	C	420.14	421.1

23	C	402.15	403.1
24	C	430.18	431.1
25	C	436.11	437.0
26	C	462.15	463.0
27	C	489.16	490.1
28	C	436.11	437.0
29	C	450.13	451.1
30	C	404.11	405.0
31	C	418.12	419.0
32	I	459.15	460.1
33	D	474.15	475.0
34	D	474.15	475.0
35	C	460.13	461.0
36	C	436.11	437.1
37	I	461.17	462.0
38	C	446.15	447.1
39	G	479.16	480.1
40	D	471.11	472.0
41	P	462.15	463.1
42	C	462.15	463.1
43	C	460.17	461.1
44	I	491.16	492.1
45	S	465.14	466.1
46	D	516.20	517.1
47	C	506.16	507.0
48	S	479.16	480.0
49	S	493.17	494.1
50	S	491.16	492.0

51	P	494.16	495.1
52	P	522.15	523.1
53	C	478.12	479.0
54	C	478.12	479.0
55	T	465.10	466.0
56	T	478.12	480.0
57	U	480.14	481.0
58	U	464.11	465.0
59	P	466.12	467.0
60	P	466.12	467.4
61	P	466.12	467.0
62	P	480.14	481.0
63	P	506.16	507.1
64	P	508.13	509.0
65	X	494.16	495.4
66	S	421.17	522.4
67	V	514.09	515.4
68	C	420.10	421.0
69	C	434.12	435.1
70	W	487.18	488.1
71	C	434.16	435.1
72	C	402.15	403.1
73	I	473.17	474.1
74	C	416.17	417.1
75	I	459.15	460.1
76	C	422.10	423.0
77	I	475.19	476.0

78	C	450.13	451.1
79	F	503.12	504.0
80	C	492.14	493.0
81	C	520.17	521.1
82	P	520.17	521.2
83	C	447.15	448.1
84	C	458.15	459.1
85	I	463.12	464.1
86	C	500.13	501.0
87	C	478.16	479.1
88	I	505.17	506.1
89	Z	528.11	529.0
90	C	491.12	429.0
91	C	529.19	530.1
92	H	547.15	448.1
93	J	565.16	566.1
94	J	530.19	531.1
95	C	446.15	447.1
96	D	476.16	477.1
97	D	481.13	482.1
98	G	489.20	490.1
99	I	473.17	474.1
100	C	420.14	421.1
101	C	474.15	475.1
102	D	474.15	475.1
103	E	476.16	477.1
104	C	474.15	475.1
105	C	432.14	433.1

106	I	491.16	492.1
107	P	466.12	467.1
108	C	492.14	473.1
109	I	477.14	478.1
110	C	450.13	451.1.
111	D	489.10	490.0
112	I	491.16	492.1
113	I	473.17	474.1
114	I	487.18	488.2
115	P	492.14	493.1
116	P	506.16	507.1
117	F	485.13	486.0
118	I	501.20	502.1
119	I	487.18	488.1
120	C	478.12	479.1
121	S	505.17	506.1
122	S	491.16	492.1
123	R	452.11	453.0
124	C	515.18	516.1
125	C	475.18	476.1
126	C	461.17	462.1
127	I	473.17	474.1
128	BB	423.17	424.4
129	DD	441.18	442.4
130	CC	442.17	443.4
131	I	445.13	446.0
132	S	447.15	448.4
133	AA	456.18	457.1

134	N	461.13	462.1
135	L	465.10	466.0
136	C	466.12	467.4
137	Y	466.12	467.4
138	S	475.18	476.4
139	T	480.14	481.4
140	W	491.16	492.4
141	K	501.20	502.1
142	N	501.16	502.1
143	J	502.16	503.1
144	S	503.18	504.5
145	W	505.17	506.5
146	I	519.19	520.1
147	S	520.18	521.5
148	S	521.17	522.5
149	S	523.18	524.5
150	D	530.21	531.1
151	S	534.20	535.6
152	S	535.18	536.5
153	J	537.13	538.0
154	S	549.20	550.5
155	C	501.20	502.4
156	EE	441.1	442.1
157	C	502.00	502.9
158	C	516.01	516.9
159	C	512.01	512.9
160	C	519.99	520.9
161	T	563.00	563.9

Medición de la Eficacia de los Moduladores de Quimiocina

Análisis in vitro

Puede utilizarse una variedad de análisis para evaluar los compuestos proporcionados en la presente, incluyendo análisis de señalización, análisis de migración, análisis de enlace de ligando, y otros análisis de respuesta celular. Pueden utilizarse análisis de señalización del receptor de quimiocina para medir la capacidad de un compuesto, tal como un antagonista de CCR2 potencial, para bloquear la señalización inducida por el ligando CCR2 (e.g., MCP-1) o un antagonista de CCR9 potencial, para bloquear la señalización inducida por el ligando CCR9 (e.g., TECK). Un análisis de migración puede utilizarse para medir la capacidad de un compuesto de interés, tal como un antagonista de quimiocina posible, para bloquear la migración celular mediada por quimiocina in vitro. Se cree que esta última se asemeja a la migración celular inducida por quimiocina in vivo. Puede utilizarse un análisis de enlace de ligando para medir la capacidad de un compuesto, tal como un antagonista de CCR2 potencia, para bloquear la interacción de MCP-1 con su receptor o un antagonista de CCR9 potencial para bloquear la interacción de TECK con su receptor.

En un análisis adecuado, se utiliza una proteína de quimiocina (ya sea aislada o recombinante) que tiene al menos

una propiedad, actividad o característica funcional de una proteína de quimiocina de mamífero. La propiedad puede ser una propiedad de enlace (por ejemplo, a un ligando o inhibidor), una actividad de señalización (e.g., activación de una proteína G de mamífero, inducción del incremento rápido o transitorio en la concentración del ion de calcio libre citosólico), la función de respuesta celular (e.g., estimulación de la quimiotaxis o la liberación del mediador inflamatorio mediante leucocitos) y lo similar.

El análisis puede ser un análisis a base de células que utiliza célula estable o transitoriamente transfectadas con un vector o casete de expresión que tiene una secuencia de ácido nucleico que codifica para el receptor de quimiocina. También pueden utilizarse líneas celulares que expresan naturalmente la quimiocina. Las células se mantienen bajo condiciones apropiadas para la expresión del receptor y se ponen en contacto con un agente putativo bajo las condiciones apropiadas para que se presente el enlace. El enlace puede detectarse utilizando técnicas estándar. Por ejemplo, el grado de enlace puede determinarse en relación con un control adecuado (por ejemplo, en relación con el antecedente en ausencia de un agente putativo, o en relación a un ligando conocido). Opcionalmente, puede utilizarse una fracción celular tal como una fracción de membrana, que contiene el receptor, en lugar de células completas.

La detección del enlace o formación de complejo puede detectarse directa o indirectamente. Por ejemplo, el agente putativo puede marcarse con una marca adecuada (e.g., marca fluorescente, marca quimioluminiscente, marca de isótopo, marca de enzima y lo similar) y el enlace puede determinarse mediante la detección de la marca. El enlace específico y/o competitivo puede evaluarse mediante estudios de competencia o desplazamiento, utilizando un agente o un ligando no marcado (e.g., MCP-1 o TECK) como competidor.

Pueden utilizarse análisis de inhibición de enlace para evaluar los presentes compuestos. En estos análisis, los compuestos se evalúan como inhibidores del enlace de ligando utilizando, por ejemplo, MCP-1 o TECK. En una modalidad, el receptor de CCR2 se pone en contacto con un ligando tal como MCP-1 y se efectúa una medición del enlace del ligando. El receptor se pone en contacto entonces con un agente de prueba en presencia de un ligando (e.g., MCP-1) y se efectúa una segunda medición del enlace. En otra modalidad, el receptor de CCR9 se pone en contacto con un ligando tal como TECK y se efectúa una medición del enlace del ligando. El receptor se pone en contacto entonces con un agente de prueba en presencia de un ligando (e.g., TECK) y se efectúa una segunda medición de enlace. Una reducción en el grado del enlace del ligando es indicativa de la inhibición del enlace por medio del agente de prueba. Los análisis de

inhibición de enlace pueden llevarse a cabo utilizando células completas que expresan la quimiocina o una fracción de membrana a partir de células que expresan la quimiocina.

El enlace de un receptor de acoplamiento a la proteína G, por ejemplo, mediante un agonista, puede dar como resultando un evento de señalización por el receptor. Por consiguiente, los análisis de señalización también pueden utilizarse para evaluar los compuestos de la presente invención y la inducción de la función de señalización mediante un agente puede monitorearse utilizando cualquier método adecuado. Por ejemplo, la actividad de la proteína G, tal como la hidrólisis de GTP a GDP, o eventos de señalización posteriores desencadenados por el enlace al receptor, pueden analizarse mediante métodos conocidos (ver, por ejemplo, PCT/US97/15915; Neote et al., Cell 72:415425 (1993); Van Riper et al., J. Exp. Med., 177:851-856 (1993) y Dahinden et al., J. Exp. Med., 179:751-756 (1994)).

También pueden utilizarse análisis de quimiotaxis para evaluar la función del receptor y para evaluar los compuestos proporcionados en la presente. Estos análisis se basan en la migración funcional de las células in vitro o in vivo inducida por un agente y pueden utilizarse para evaluar el enlace y/o el efecto en la quimiotaxis de ligandos, inhibidores o agonistas. Se conoce una variedad de análisis de quimiotaxis en la técnica, y puede utilizarse cualquier

análisis adecuado para evaluar los compuestos de la presente invención. Ejemplos de análisis adecuados incluyen aquellos descritos en la PCT/US97/15915; Springer et al., WO 94/20142; Berman et al., Immunol. Invest., 17:625-677 (1988); y Kavanaugh et al., J. Immunol., 146:4149-4156 (1991)).

Los análisis de señalización de calcio miden la concentración del calcio al paso del tiempo, preferentemente antes y después del enlace del receptor. Estos análisis pueden utilizarse para cuantificar la generación de un mediador de señalización del receptor, Ca^{++}, seguido por el enlace del receptor (o la ausencia del mismo). Estos análisis son útiles para determinar la capacidad de un compuesto, tal como los de la presente invención, para generar el mediador de señalización del receptor mediante el enlace a un receptor de interés. También, estos análisis son útiles para determinar la capacidad de un compuesto, tal como los de la presente invención, para inhibir la generación del mediador de señalización del receptor interfiriendo con el enlace entre un receptor de interés y un ligando.

En análisis de señalización de calcio utilizados para determinar la capacidad de un compuesto para interferir con el enlace entre un receptor de quimiocina y un ligando de quimiocina conocido, las células que expresan el receptor de quimiocina (células que expresan CCR2 tales como las células THP-1 o células que expresan CCR9 tales como la línea de

células T células MOLT-4) se incuban primero con un compuesto de interés tal como un antagonista de quimiocina potencial en concentraciones incrementadas. El número de células puede ser de 10^5 a 5 x 10^5 células por pozo en una placa de microtitulación de 96 pozos. La concentración del compuesto que se prueba puede variar de 0 a 100 uM. Después de un período de incubación (que puede variar de 5 a 60 minutos), las células tratadas se colocan en una placa de visualización fluorométrica (FLIPR®) (disponible de Molecular Devices Corp., Sunnyvale, CA) de acuerdo con las instrucciones del fabricante. El sistema FLIPR® es muy conocido por los expertos en la técnica como un método estándar para llevar a cabo análisis. Las células se estimulan entonces con una cantidad apropiada del ligando de quimiocina (MCP-1 para CCR2 o TECK para CCR9) a una concentración final de 5-100 nM, y se registra la señal del incremento del calcio intracelular (también llamado flujo de calcio). La eficacia de un compuesto como un inhibidor de enlace entre la quimiocina y el ligando puede calcularse como un IC_{50} (la concentración necesaria para ocasionar el 50% de inhibición en la señalización) o IC_{90} (a 90% de inhibición).

Pueden llevarse a cabo análisis de migración celular in vitro (pero no se limitan a este formato) utilizando la microcámara de 96 pozos (llamada ChemoTX™). El sistema ChemoTX™ es muy conocido por los expertos en la

técnica como un tipo de instrumento de quimiotáctica/migración celular. En este análisis, las células que expresan CCR2 (tales como THP-1) o las células que expresan CCR9 (tales como MOLT-4) se incuban primero con un compuesto de interés, tal como un posible antagonista de CCR2 o CCR9, respectivamente, en concentraciones incrementadas. Típicamente, se utilizaron cincuenta mil células por pozo, pero la cantidad puede variar de 10^3-10^6 células por pozo. El ligando de quimiocina (por ejemplo, el ligando de CCR2 MCP-1, típicamente a 0.1 nM (pero puede variar de 5-100 nM); o el ligando de CCR9 TECK, típicamente a 50 nM (pero puede variar de 5-100 nM)), se coloca en la cámara inferior y se ensambla el aparato de migración. Veinte microlitros de las células tratadas con el compuesto de prueba se colocan entonces sobre la membrana. Se permite que tenga lugar la migración a 37°C por un período de tiempo, típicamente 1.5 horas para CCR2 o 2.5 horas para CCR9. Al final de la incubación, el número de células que migraron a través de la membrana hacia la cámara inferior se cuantifica. La eficacia de un compuesto como un inhibidor de la migración celular mediada por quimiocina se calcula como un IC_{50} (concentración necesaria para reducir la migración celular por 50%) o IC_{90} (para 90% de inhibición).

Eficacia in vivo de modelos para IBD humana

La infiltración de células T en el intestino

delgado y el colon se ha vinculado con la patogénesis de enfermedades inflamatorias intestinales que incluyen enfermedad Coeliac, enfermedad de Crohn y colitis ulcerativa. Se cree que el bloqueo del tráfico de poblaciones relevantes de células T al intestino es un procedimiento efectivo para tratar IBD humana. El CCR9 se expresa en células T que se albergan en el intestino en sangre periférica, elevado en pacientes con inflamación del intestino delgado tal como en la enfermedad de Crohn y la enfermedad Coeliac. El ligando CCR9 TECK se expresa en el intestino delgado. Por tanto, se cree que este par de ligando-receptor juega un papel en el desarrollo de IBD mediante la migración de las células T al intestino. Existen diversos modelos animales y pueden utilizarse para evaluar los compuestos de interés, tales como los antagonistas de CCR9 potenciales, por su capacidad para afectar tal migración de células Y y/o la condición o enfermedad, lo cual puede permitir predicciones de eficacia de los antagonistas en humanos.

Modelos animales con patología similar a la colitis ulcerativa humana

Un modelo murino descrito por Panwala y colaboradores (Panwala, et al., J. Immunol., 161(10):5733-44 (1998)) implica la supresión genética del gen murino resistente a fármacos múltiples (MDR). Los ratones knockout de MDR (MDR-1-) son susceptibles a desarrollar severa

inflamación intestinal espontánea cuando se mantienen bajo condiciones específicas de instalaciones libres de patógenos. La inflamación intestinal observada en ratones MDR-1- tiene una patología similar a la de la enfermedad inflamatoria intestinal humana (IBD) y se define por la infiltración de células T tipo Th1 en la lamina propria del intestino grueso.

Otro modelo murino se describió por Davidson et al., J. Exp. Med., 184(1):241-51 (1986). En este modelo, el gel IL-10 murino se suprimió y los ratones se volvieron deficientes en la producción de interleucina 10 (IL-10-1-). Estos ratones desarrollan una enfermedad inflamatoria intestinal (IBD) crónica que predomina en el colon y que comparte características histopatológicas con la IBD humana.

Otro modelo murino para IBD se ha descrito por Powrie et al., Int. Immunol., 5(11):1461-71 (1993), en el cual un subconjunto de células T CD4+ (llamado CD45RB (alto)) de ratones inmunocompetentes, se purifica y se transfiere adoptivamente en ratones inmunodeficientes (tal como los ratones C.B-17 scid). El animal restaurado con la población de células T CD45RbaltoCD4+ desarrolló una enfermedad de desgaste letal con severon infiltrados de célula mononuclear en el colon, patológicamente similar a la IBD humana.

Modelos murinos con patología similar a la enfermedad de Crohn humana

Modelo TNF ARE (-1-). El papel de TNF en la

enfermedad de Crohn en humanos se ha demostrado más recientemente por el éxito del tratamiento utilizando anticuerpo anti-THF alfa por Targan et al., N. Engl. J. Med., 337 (15):1029-35 (1997). Los ratones con producción aberrante de TNF-alfa debido a la alteración genética en el gen TNF (ARE-1-) desarrollan enfermedades inflamatorias intestinales tipo Crohn (ver Kontoyiannis et al., Immunity., 10(3):387-98 (1999)).

Modelo SAMP/yit. Este modelo se describe por Kosiewicz et al., J. Clin. Invest, 107(6):695-702 (2001). La cepa de ratón SAMP/Yit, desarrolla espontáneamente una inflamación crónica localizada en terminal ilíaca. La ileitis resultante se caracteriza por la infiltración masiva de linfocitos T activados en la lamina propria y contiene una marcada semejanza con la enfermedad de Crohn humana.

Ejemplos de análisis in vitro

Reactivos

Las células THP-1 y las células MOLT-4 se obtuvieron del American Type Culture Collection (Manassas, VA) y se cultivaron en medio de cultivo de tejido RPMI suplementado con suero fetal de ternera al 10% (FCS) en un incubador de CO_2 humidificado al 5% a 37°C. Las proteínas de quimiocina recombinante humana MCP-1 y TECK se obtuvieron de R&D Systems (Minneapolis, MN). La proteína MCP-1 marcada con ^{125}I se obtuvo de Amersham (Piscataway, NJ). Las microcámaras

de quimiotaxis ChemoTX® se adquirieron de Neuro Probe (Gaithersburg, MD). Los equipos de proliferación celular CyQUANT® se adquirieron de Molecular Probes (Eugene, Oregon). El colorante de indicador de calcio Fluo-4 AM se adquirió de Molecular Devices (Mountain View, CA).

Análisis convencional de migración

Se utilizó el análisis convencional de migración para determinar la eficacia de potenciales antagonistas del receptor para bloquear la migración mediada mediante quimiocinas (tales como CCR2 y CCR9). Este análisis se llevó a cabo rutinariamente utilizando el sistema de microcámara ChemoTX® con una membrana de policarbonato de tamaño de poro de 5 um. Para comenzar con tal análisis, las células que expresan quimiocina (tales como las células THP-1 para el análisis de CCR2 y las células MOLT-4 para el análisis de CCR9) se cosecharon mediante centrifugación de la suspensión celular a 1000 RPM en una centrífuga GS-6R Beckman. El gránulo celular se resuspendió en amortiguador de quimiotaxis (HBSS con 0.1% de BSA) a 10 x 10^6 células/ml para el análisis de CCR2 (5 x 10^6 células/ml para el análisis de CCR9). Los compuestos de prueba en las concentraciones deseadas se prepararon a partir de soluciones de reserva de 10 mM mediante diluciones seriales en amortiguador de quimiotaxis. Se mezcló un volumen igual de células y compuestos se mezclaron y se incubaron a temperatura ambiente durante 15

minutos. Enseguida, se transfirieron 20 ul de la mezcla a la membrana porosa de una microcámara de migración, con 29 ul de ligando de quimiocina (0.1 nM de proteína MCP-1 de quimiocina para el análisis de CCR2 o 50 nm de proteína TECK de quimiocina para el análisis CCR9) colocados en la cámara inferior. Después de la incubación a 37°C (90 minutos para CCR2; 150 minutos para CCR9), durante lo cual las células migraron contra el gradiente de quimiocina, el análisis se terminó retirando las gotas celulares de la parte superior del filtro. Para cuantificar las células migradas a través de la membrana se agregaron 5 ul de solución de 7X CyQUANT® a cada pozo en la cámara inferior, y la señal de fluorescencia se midió en un lector de placa de fluorescencia Spectrafluor Plus (TECAN, Durham, NC). El grado de inhibición se determinó comparando las señales de migración entre las células tratadas con el compuesto y las no tratadas. El cálculo de IC_{50} se llevó a cabo además mediante análisis de regresión no lineales cuadrados utilizando el Graphpad Prism (Graphpad Software, San Diego, CA).

Análisis BiRAM

La selección primaria para identificar antagonistas de quimiocina se llevó a cabo utilizando análisis BiRAM (WO 02101350, US2004023286), que detecta golpes potenciales por su capacidad para activar la migración celular bajo concentración inhibidora de quimiocina. Para comenzar con

tal análisis, las células que expresan quimiocina (tales como las células THP-1 para el análisis de CCR2 y las células MOLT-4 para el análisis de CCR9) se cosecharon mediante centrifugación de la suspensión celular a 1000 RPM en una centrífuga GS-6R Beckman. El gránulo celular se resuspendió en amortiguador de quimiotaxis (HBSS con 0.1% de BSA) a 10 x 10^6 células/ml para el análisis de CCR2 (5 x 10^6 células/ml para el análisis de CCR9). Veinticinco microlitros de células se mezclaron con un volumen igual de un compuesto de prueba diluido a 20 uM en el mismo amortiguador. Veinte microlitros de la mezcla se transfirieron en el filtro en la cámara superior de quimiotaxis, conteniendo los 29 ul de la solución de quimiocina, el ligando de quimiocina (100 nM de quimiocina MCP-1 y proteína MIP-1alfa para el análisis de CCR2 o 500 nm de proteína TECK de quimiocina para el análisis de CCR9) se colocó en la cámara inferior. Después de una incubación a 37°C (90 minutos para CCR2; 150 minutos para CCR9), el análisis terminó retirando las gotas celulares de la parte superior del filtro. Para cuantificar las células migradas a través de la membrana se agregaron 5 ul de solución de 7X CyQUANT® a cada pozo en la cámara inferior, y la señal de fluorescencia se midió en un lector de placa de fluorescencia Spectrafluor Plus (TECAN, Durham, NC).

Para la selección de los golpes potenciales, el nivel de activación de migración se calculó como índice RAM,

la proporción entre la señal de un pozo particular y la señal media de la placa completa. Los compuestos con un índice RAM mayor que 1.5 para el análisis de CCR2 (1.8 para el análisis de CCR9) se consideraron RAM positivos, y se seleccionaron para las determinaciones de IC_{50} en análisis funcionales convencionales.

Análisis de flujo de calcio

El análisis de flujo de calcio mide el incremento en el calcio intracelular después de la activación del receptor inducida por el ligando. En la selección de antagonistas de quimiocina, se utilizó un análisis secundario llevado a cabo en una máquina FLIPR® (Molecular Devices, Mountain View, CA). Para comenzar un análisis, las células que expresan quimiocina (tales como las células THP-1 para el análisis de CCR2 y las células MOLT-4 para el análisis de CCR9) se cosecharon mediante centrifugación de la suspensión celular y se resuspendieron a 1.5 x 10^6 células/ml en HBSS (con suero fetal de ternera al 1%). Las células se marcaron con un colorante indicador de calcio Fluo-4 AM durante 45 minutos a 37°C con agitación suave. Después de la incubación, las células se granularon, se lavaron una vez con HBSS y se resuspendieron en el mismo amortiguador a una densidad de 1.6 x 10^6 células/ml. Cien microlitros de células marcadas se mezclaron con 10 ul del compuesto de prueba a las concentraciones apropiadas en una placa de

análisis. La proteína de quimiocina (MCP-1 a una concentración final de 0.1 nM para el análisis de CCR2 o TECK a una concentración final de 25 nM para el análisis de CCR9) para activar el receptor. El grado de inhibición se determinó comparando las señales de calcio entre células tratadas con el compuesto y las no tratadas. Los cálculos de IC_{50} se llevaron a cabo además mediante análisis de regresión no lineales cuadrados utilizando el Graphpad Prism (Graphpad Software, San Diego, CA).

Análisis de enlace de ligando

Se utilizó el análisis de enlace de ligando para determinar la capacidad de antagonistas de CCR2 potenciales para bloquear la interacción entre CCR2 y su ligando MCP-1. Las células THP-1 que expresan CCR2 se centrifugaron y se resuspendieron en amortiguador de análisis (20 mM HEPES pH 7.1, 140 mM de NaCl, 1 mM de $CaCl_2$, 5 mM de $MgCl_2$ y con albúmina de suero bovino al 0.2%) a una concentración de 2.2 x 10^5 células/ml. Los análisis de enlace se adaptaron como sigue. Primero se agregaron 0.09 ml de células (1 x 10^5 células THP-1/pozo) a las placas de análisis conteniendo los compuestos, proporcionando una concentración final de -2-10 uM de cada compuesto para la selección (o parte de una respuesta a la dosis para las determinaciones de IC_{50} del compuesto). Después se agregaron 0.09 ml de MCP-1 marcado con ^{125}I (obtenido de Amersham; Piscataway, NJ) diluido en

amortiguador de análisis a una concentración final de ~50 pM, produciendo ~30,000 cpm por pozo, las placas se sellaron y se incubaron durante aproximadamente 3 horas a 4°C en una plataforma de agitación. Las reacciones se aspiraron sobre filtros de vidrio GF/B pre-embebidos en solución de polietilenoimina (PEI) al 0.3% en un cosechador de células al vacío (Packard Instruments: Meriden, CT). Se agregó fluido de escintilación (50 ul; Microscint 20, Packard Instruments) a cada pozo, las placas se sellaron y se midió la radiactividad en un contador de escintilación Top Count (Packard Instruments). Los pozos de control conteniendo ya sea solo diluyente (para cuentas totales) o exceso de MCP-1 (1 ug/ml, para enlace no específico) se utilizaron para calcular el porcentaje de inhibición total para el compuesto. El programa computarizado Prism de Graphpad Inc. (San Diego, CA) se utilizó para calcular los valores IC_{50}. Los valores IC_{50} son aquellas concentraciones requeridas para reducir el enlace del MCP-1 marcado al receptor por 50%.

Descubrimiento de antagonistas de quimiocina

El descubrimiento de antagonistas de quimiocina se llevó a cabo en dos etapas: Primero, se utilizó un análisis BiRAM para seleccionar una biblioteca de compuestos de una manera en alto rendimiento. El análisis detectó compuestos por su capacidad de ocasionar una señal de migración positiva bajo una condición BiRAM. Segundo, los compuestos BiRAM

positivos se probaron para determinar sus valores IC_{50} utilizando la migración convencional, análisis de flujo de calcio y análisis de enlace de ligando.

Por ejemplo, en una selección de aproximadamente 100,000 compuestos, 2000 pozos individuales que representan aproximadamente el 2% de los compuestos totales, mostraron un índice RAM deseado (mayor que 1.5 para CCR2; mayor que 1.8 para CCR9). Estos compuestos se separaron y se probaron de nuevo en pozos en duplicado mediante análisis RAM. Un total de 156 compuestos se confirmaron BiRAM positivos.

Dado que una señal BiRAM positiva indica solamente la presencia de un antagonista del receptor y no qué tan fuertemente bloquea las funciones del receptor, los compuestos BiRAM positivos se probaron adicionalmente por la potencia en análisis convencionales de migración, flujo de calcio, y de enlace de ligando. Las determinaciones de IC_{50} en este sub-conjunto descubrieron varios compuestos con un IC_{50} menor que 1 uM y que no inhibieron otros receptores de quimiocina examinados a niveles significativos.

Eficacia in vivo

Se conduce un estudio de 17 días de artritis inducida por colágeno tipo II para evaluar los efectos de un modulador en hinchazón clínica de tobillo inducida por artritis. La artritis inducida por colágeno en ratas es un modelo experimental de poliartritis que se ha utilizado

ampliamente para pruebas preclínicas de numerosos agentes anti-artríticos (ver Trentham et al., J. Exp. Med., 146(3):857-868 (1997). Bendele et al., Toxicologic Pathol., 27:134-142 (1999), Bendele et al., Artritis Rheum., 42:498-506 (1999)). Las características de este modelo son el inicio y el progreso confiable de una robusta inflamación poliarticular fácilmente medible, marcada destrucción de cartílagos en asociación con formación de panus y reabsorción ósea de suave a moderada y proliferación ósea periosteal.

Se anestesian ratas Lewis hembra (aproximadamente de 0.2 kilogramos) con isoflurano y se inyectan con adyuvante incompleto de Freund conteniendo 2 mg/ml de colágeno bovino tipo II en la base del rabo y en dos sitios del lomo en los días 0 a 6 de este estudio de 17 días. El modulador de prueba se dosifica diariamente mediante inyección subcutánea desde el día 9 hasta el día 17 en una dosis de 100 mg/kg y un volumen de 1 ml/kg en el siguiente vehículo (24.5% Cremaphore EL, 24.5% aceite común, 1% bencilalcohol y 50% agua destilada). Las mediciones de calibre del diámetro de la articulación del tobillo se toman diariamente y la reducción de la hinchazón de la articulación se toma como una medida de eficacia.

Los ratones knockout MDR1a que carecen del gen P-glicoproteína, desarrollan espontáneamente colitis bajo una condición específica libre de patógeno. La patología en

estos animales se ha caracterizado como inflamación mediada por células T tipo Th1, similar a la colitis ulcerativa en humanos. La enfermedad normalmente comienza a desarrollarse alrededor de las 8-10 semanas después del nacimiento. Sin embargo, las edades a las cuales emerge la enfermedad y el nivel final de penetración varían frecuentemente de manera considerable entre diferentes instalaciones de animales.

En un estudio utilizando los ratones knockout MDR1a, se evalúa un antagonista de CCR9 por administración profiláctica por su capacidad para retardar el inicio de la enfermedad. Se dosifica a ratones hembra (n = 34) con 50 mg/kg dos veces al día mediante inyecciones subcutáneas durante 14 semanas consecutivas comenzando a la edad de 10 semanas. El estudio se evalúa por retraso en el crecimiento asociado con IBD.

Evaluación de un modulador de prueba en un modelo de rata de inflamación peritoneal inducida por tioglicolato

Se conduce un estudio de 2 días de inflamación inducida por tioglicolato para evaluar los efectos del modulador de prueba. Las características de este modelo son el inicio y progreso confiable de robusto infiltrado celular inflamatorio fácilmente medible. Para la inducción de peritonitis inflamatoria en ratas Lewis, se inyecta Brewer-tioglicolato (1.0 ml, solución al 4% en agua destilada) intraperitoneal (i.p.). Antes de esta inyección, el grupo de

tratamiento recibió el modulador o el vehículo de prueba y el grupo de control recibió el mismo volumen de PBS como inyección intraperitoneal. Después de 2 días, se llevó a cabo un lavado peritoneal con PBS helado conteniendo 1 mM de EDTA. Las células recuperadas se cuentan con un contador celular (Coulter Counter; Coulter Pharmaceutical, Palo Alto CA) y se identificaron los monocitos/macrófagos mediante citometría de flujo utilizando propiedades de dispersión de luz.

Evaluación de un modulador de prueba en un modelo de ratón de infección bacteriana

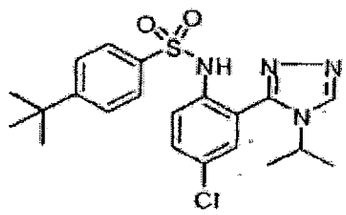
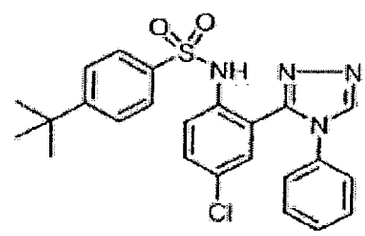
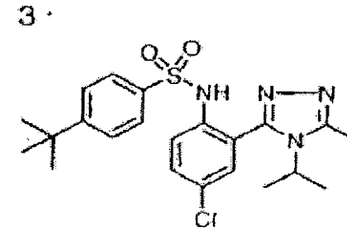
Se conduce un estudio de 1 día de infección por streptococcus pneumoniae para evaluar los efectos del modulador de prueba. El modelo mide la infección bacteriana y se esparce en un animal después de la infección pulmonar con cultivos bacterianos vivos, medidos mediante el infiltrado celular inflamatorio y la evaluación de la carga bacteriana. Los ratones C57/B6 se inoculan intranasalmente con LD50 400 CFU en el día 0. Los grupos se tratan ya sea con modulador de prueba o con control de vehículo 1 día antes de la inoculación bacteriana y dos veces diariamente a lo largo del estudio. La carga bacteriana se mide a las 24 horas colocando en placas diluciones seriales de tejido pulmonar homogeneizado en placas de agar y contando las colonias.

Pharmacologías que se utilizan en conjunción con compuestos de CCR2

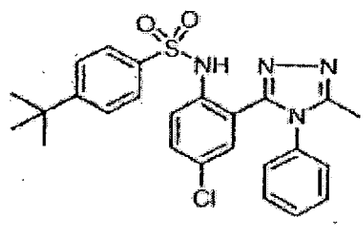
Los agentes farmacológicos que pueden utilizarse en conjunción con los antagonistas de CCR2 de la presente invención, incluyen aquellos utilizados para los tratamientos de aterosclerosis, restenosis, esclerosis múltiple, fibrosis pulmonar, enfermedad inflamatoria intestinal, artritis reumatoide, enfermedad de injerto contra huésped, fibrosis renal, psoriasis, rechazo al transplante, obesidad, diabetes, hipercolesterolemia y cáncer.

En las siguientes tablas, se proporcionan las estructuras y la actividad para los compuestos representativos descritos en la presente. La actividad se proporciona como sigue para cualquiera o ambos análisis de quimiotaxis y/o análisis de movilización de calcio descritos anteriormente.

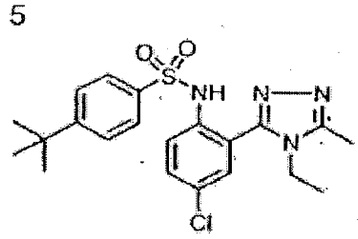
Tabla 3: Compuestos con actividad CCR9 en uno de los análisis de quimiotaxis, enlace o movilización de calció, con IC50 < 1000 nM.

1	2	3
		

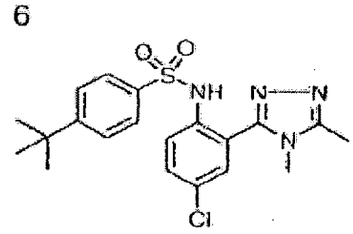
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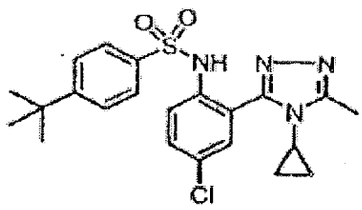
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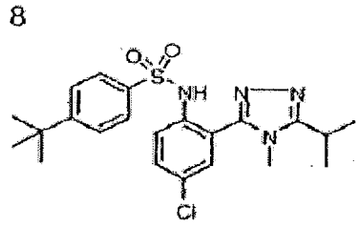
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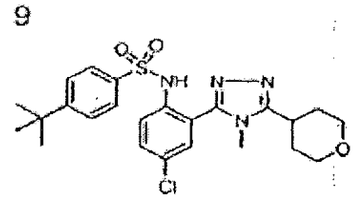
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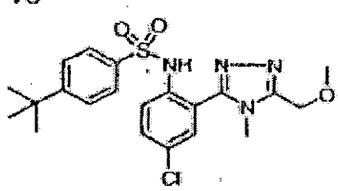
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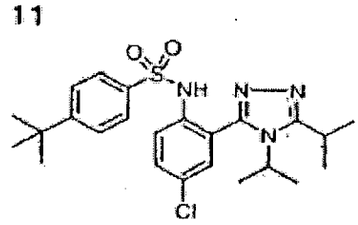
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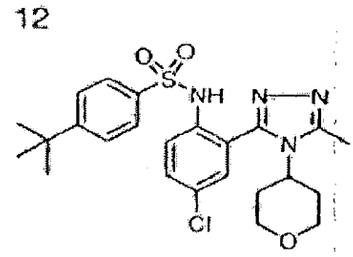
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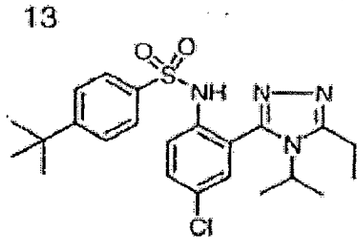
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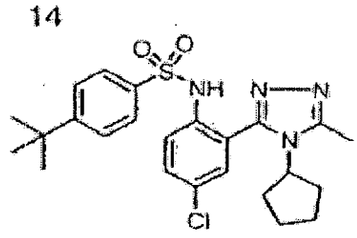
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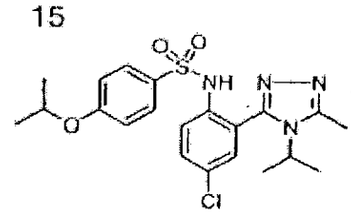
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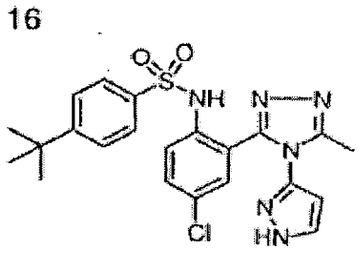
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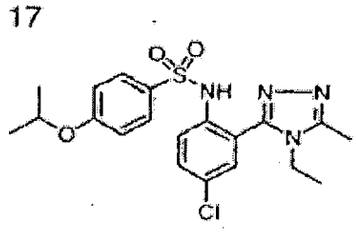
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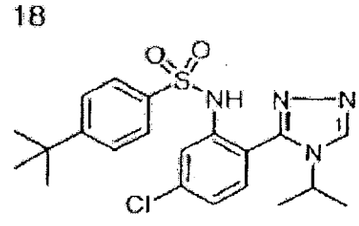
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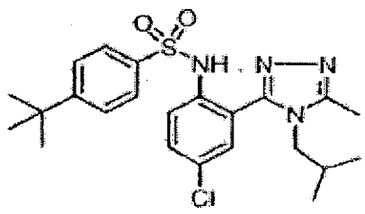
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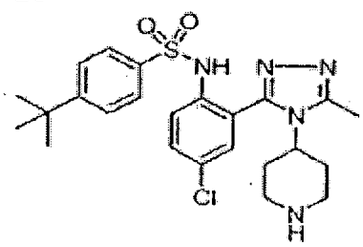
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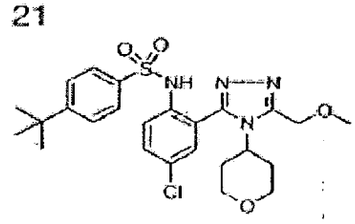
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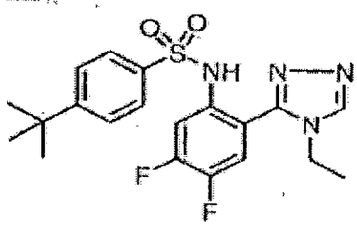
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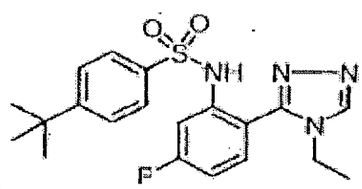
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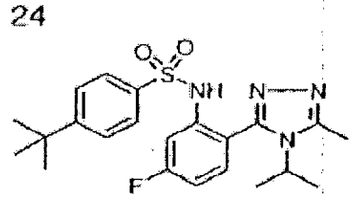
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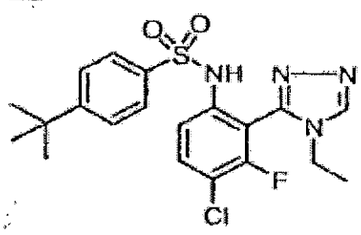
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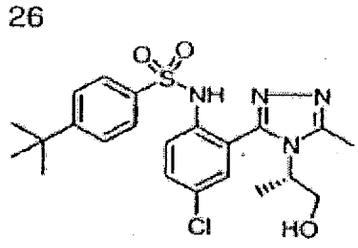
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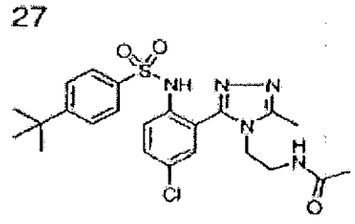
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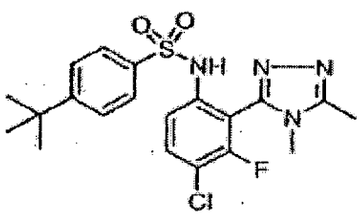
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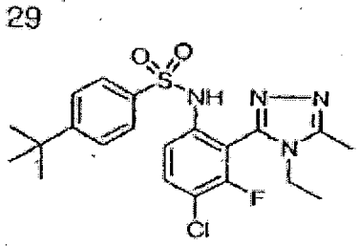
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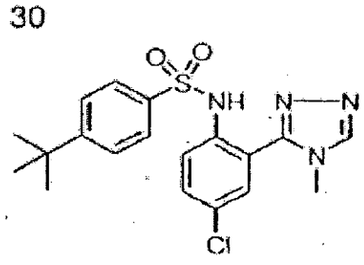
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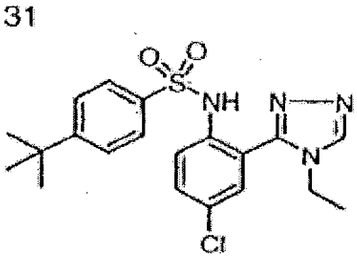
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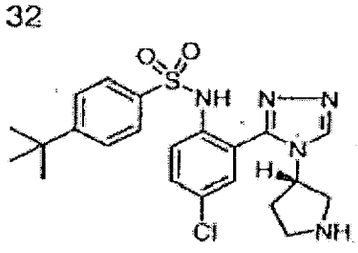
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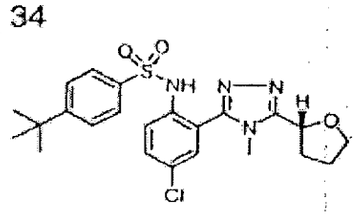
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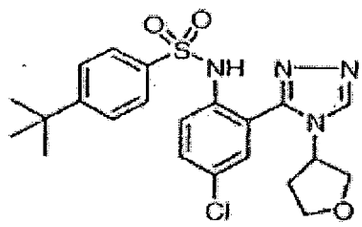
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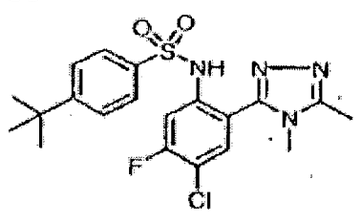
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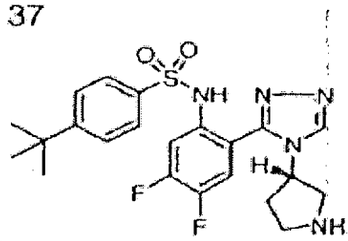
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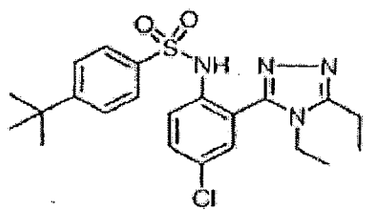
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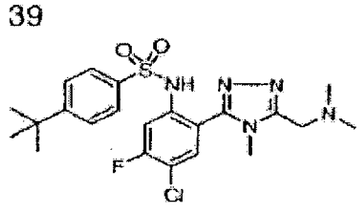
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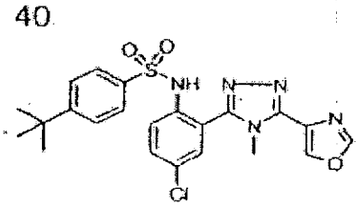
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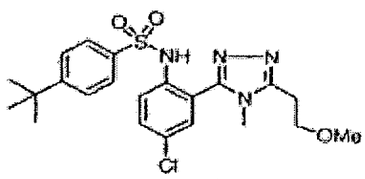
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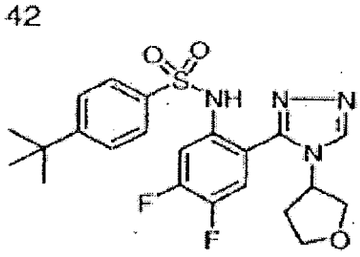
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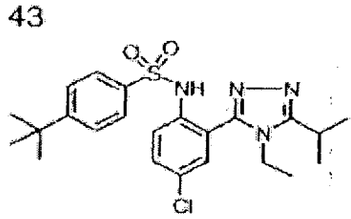
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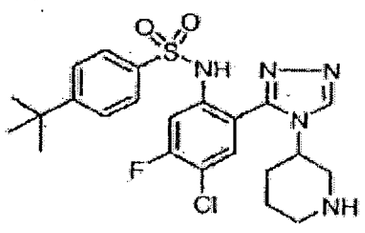
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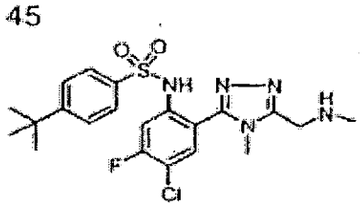
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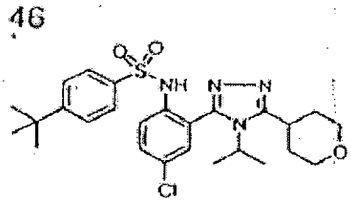
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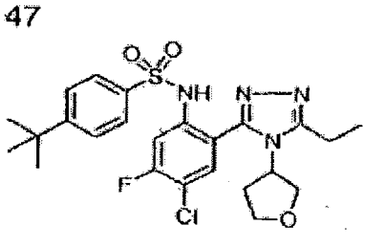
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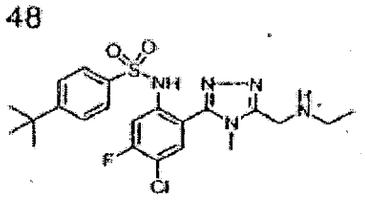
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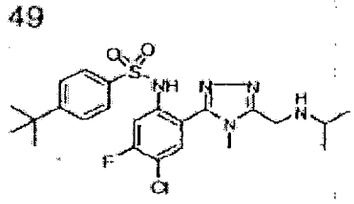
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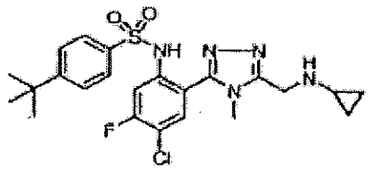
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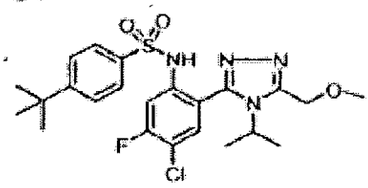
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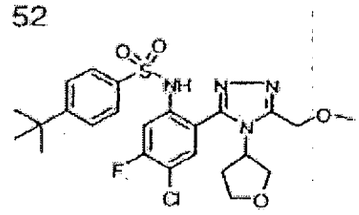
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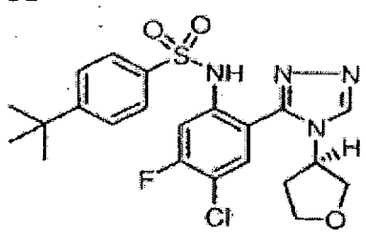
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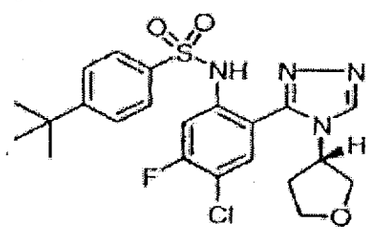
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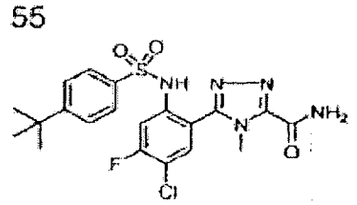
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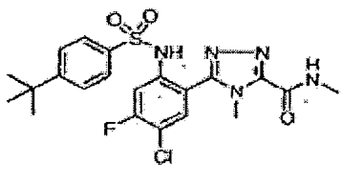
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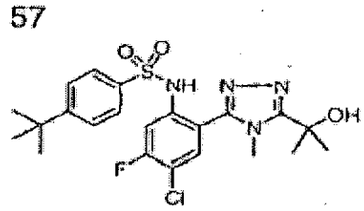
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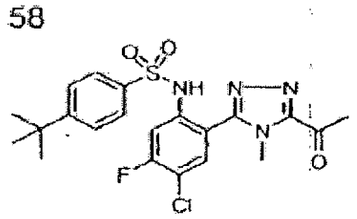
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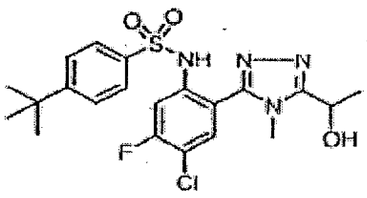
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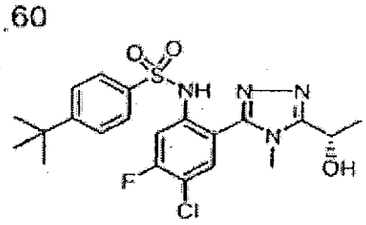
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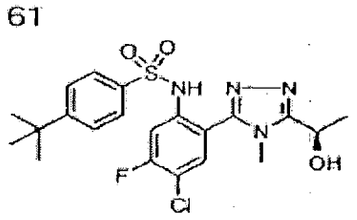
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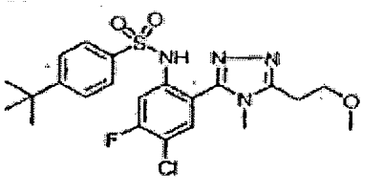
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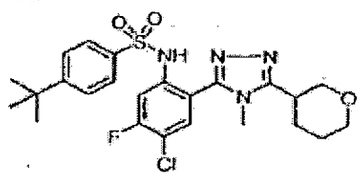
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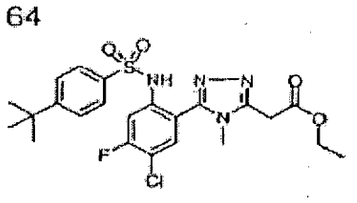
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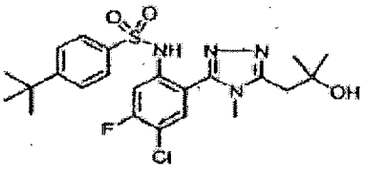
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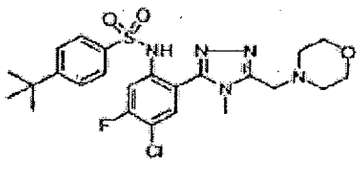
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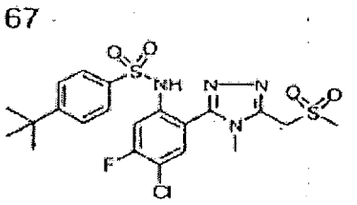
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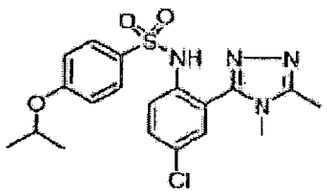
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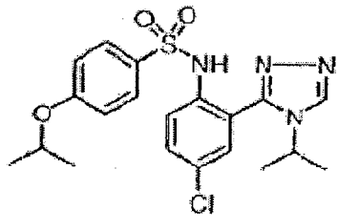
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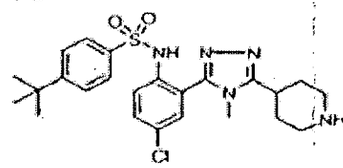
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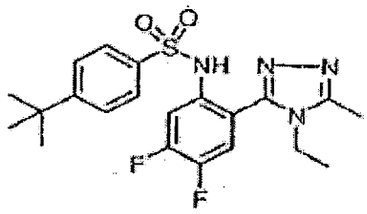
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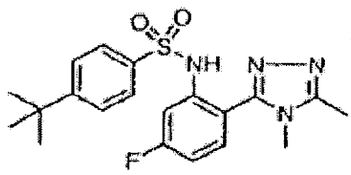
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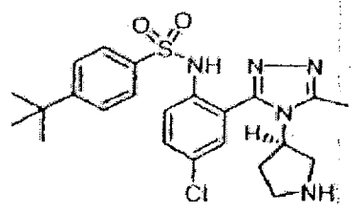
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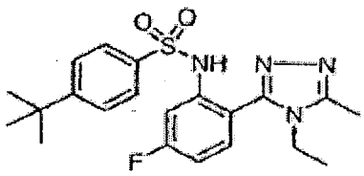
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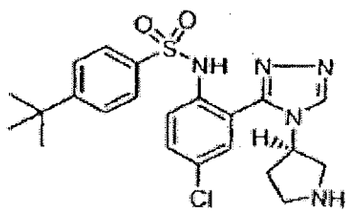
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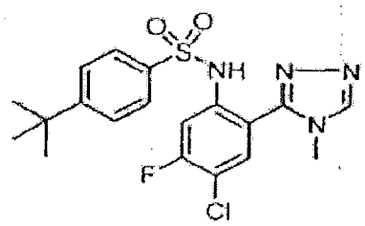
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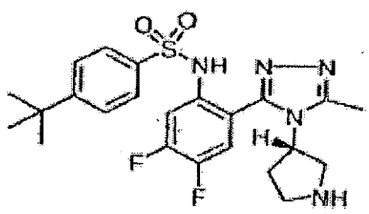
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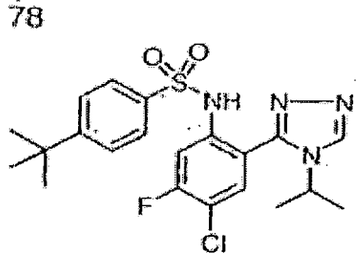
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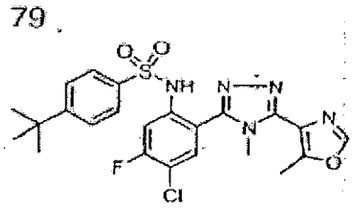
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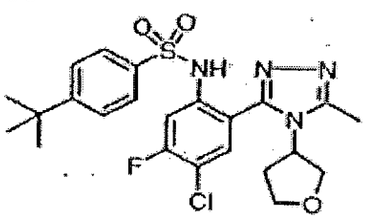
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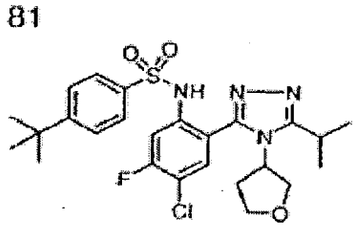
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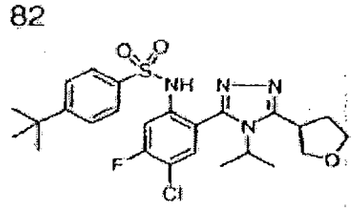
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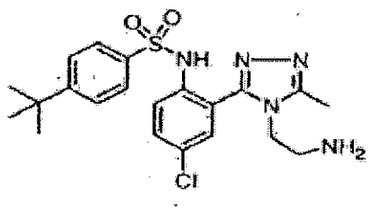
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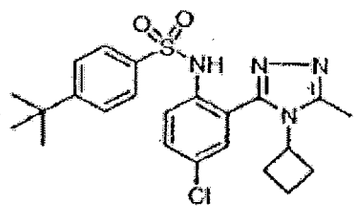
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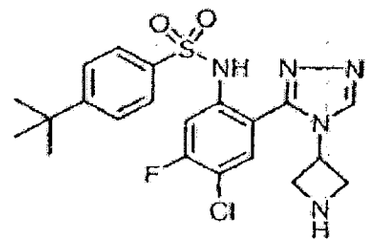
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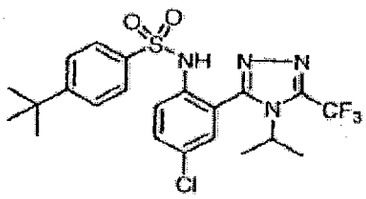
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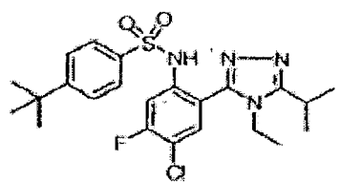
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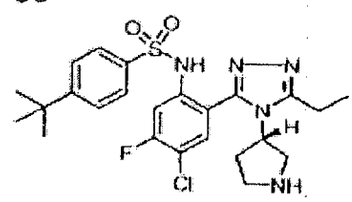
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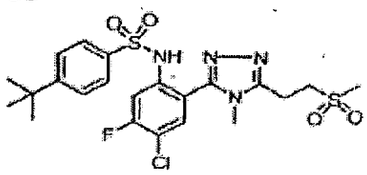
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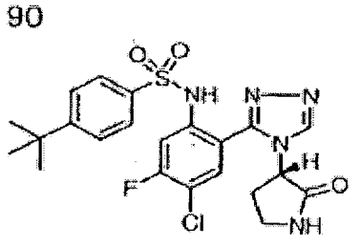
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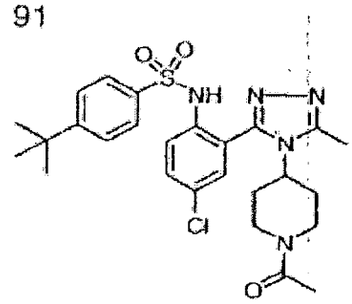
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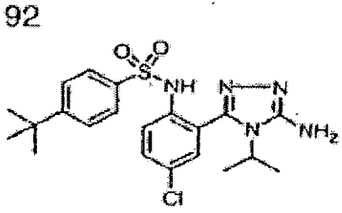
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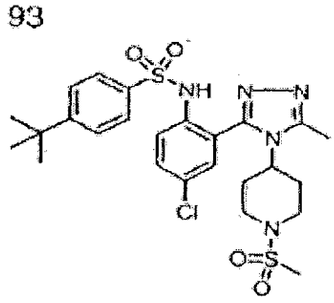
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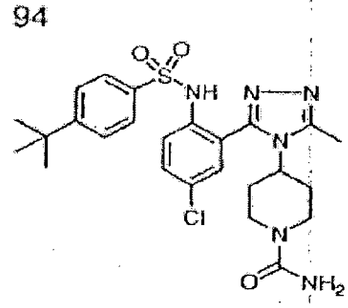
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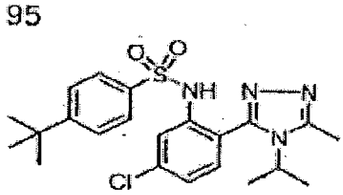
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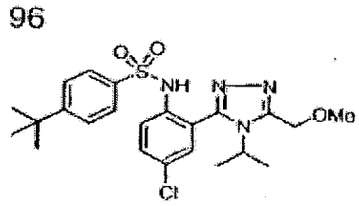
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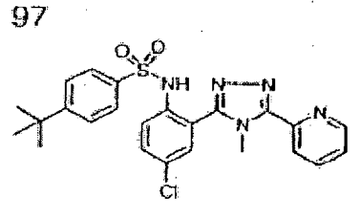
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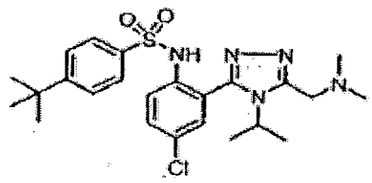
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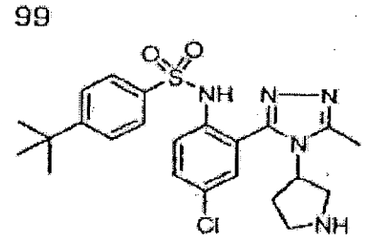
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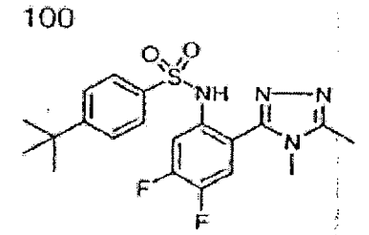
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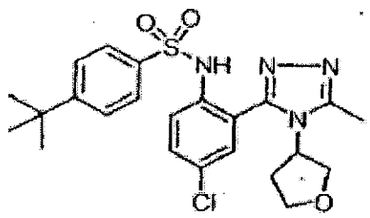
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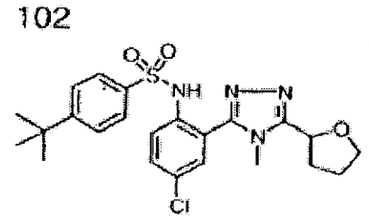
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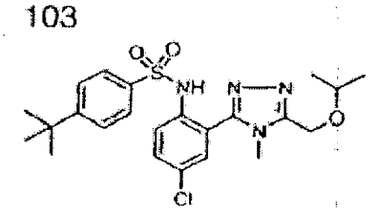
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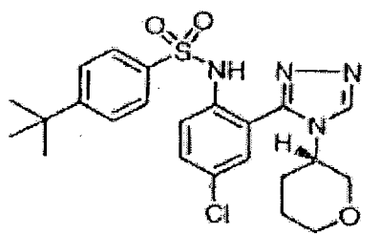
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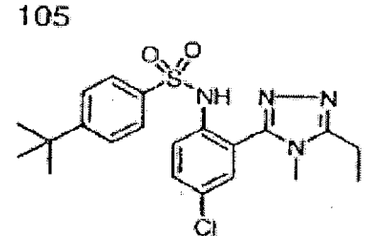
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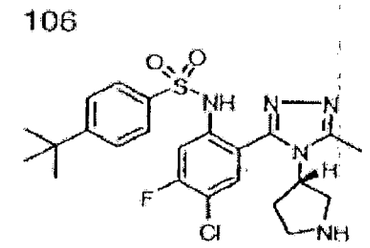
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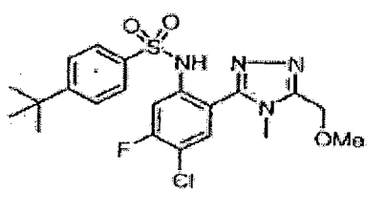
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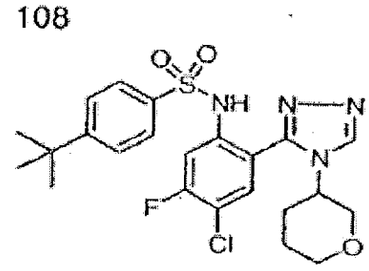
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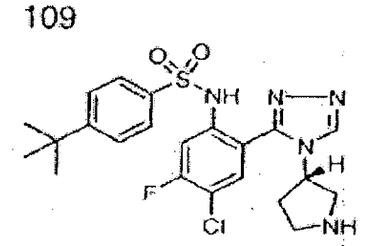
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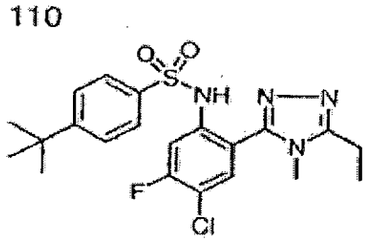
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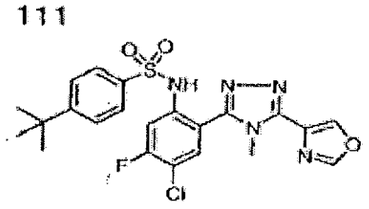
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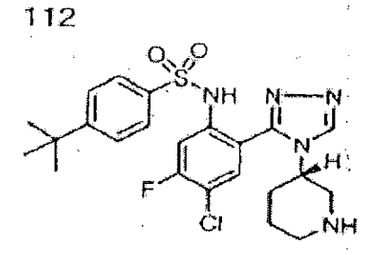
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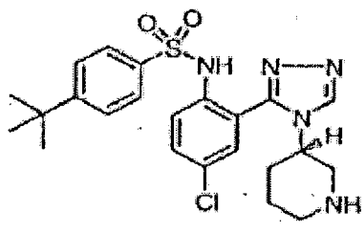
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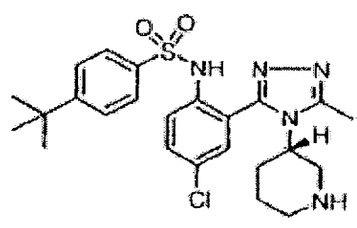
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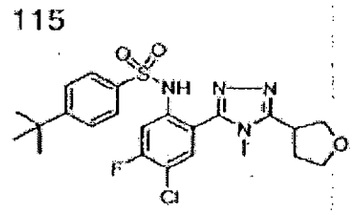
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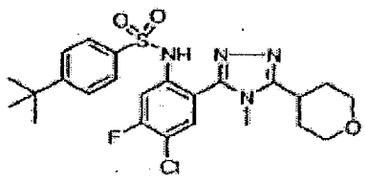
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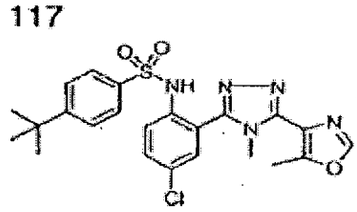
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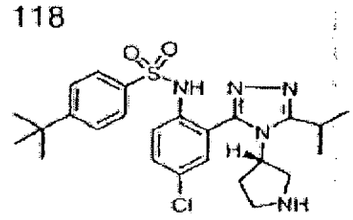
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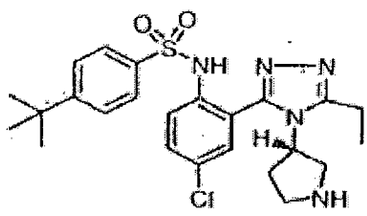
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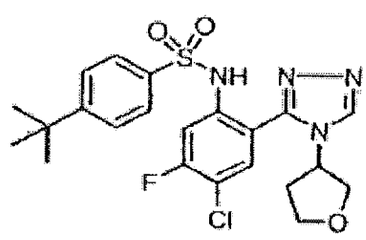
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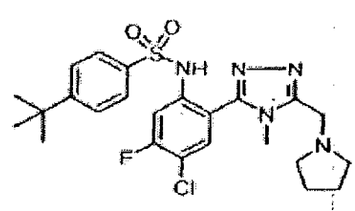
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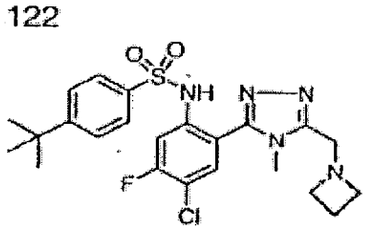
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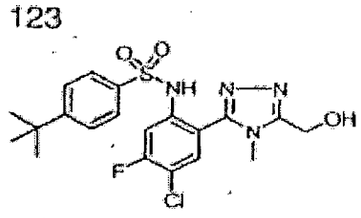
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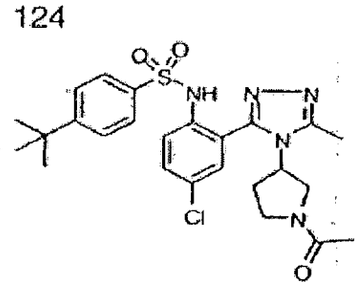
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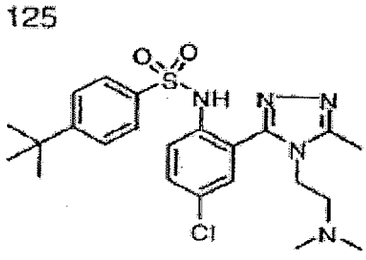
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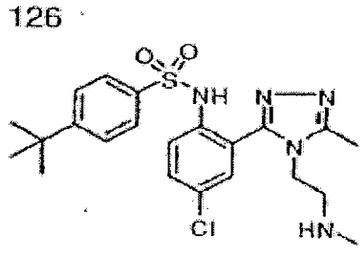
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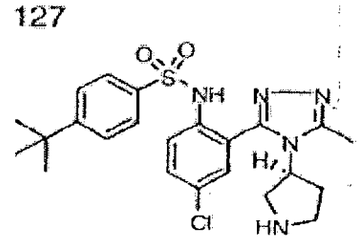
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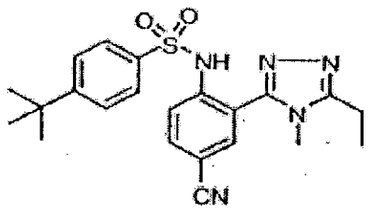
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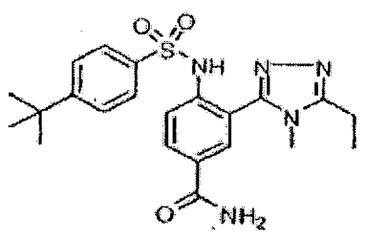
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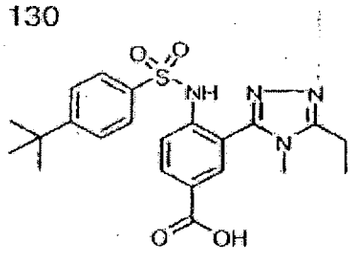
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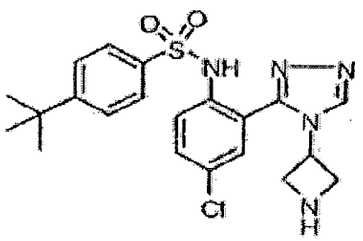
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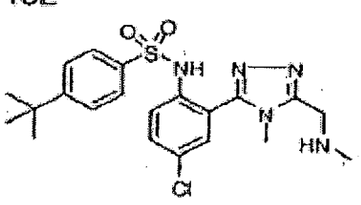
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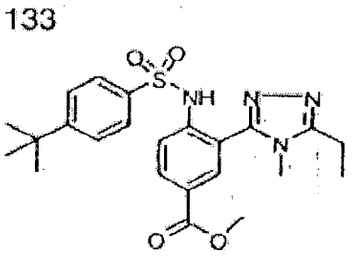
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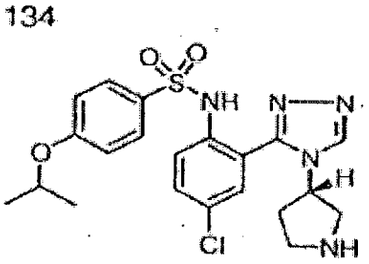
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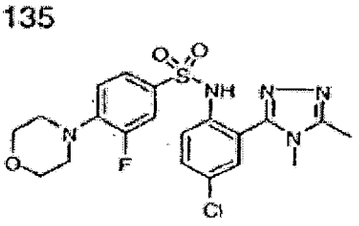
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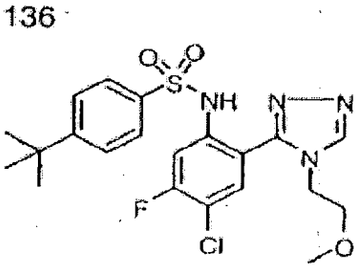
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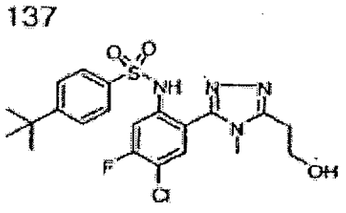
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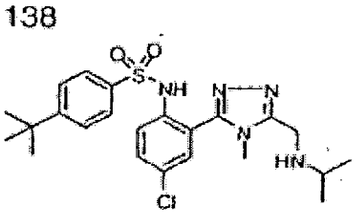
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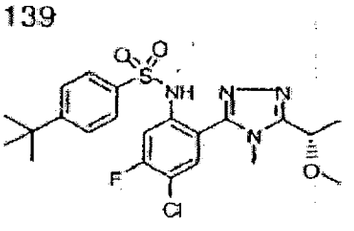
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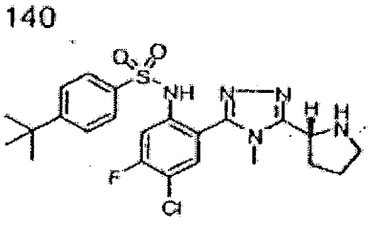
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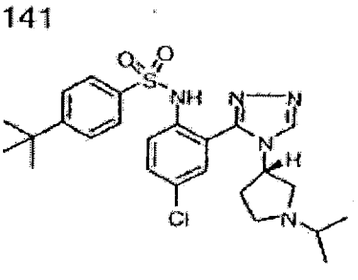
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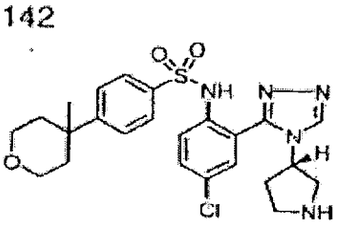
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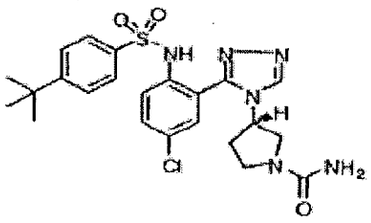
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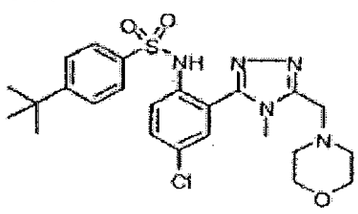
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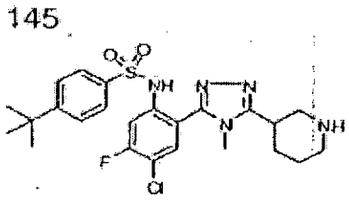
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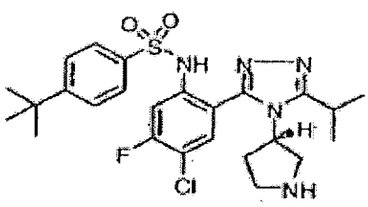
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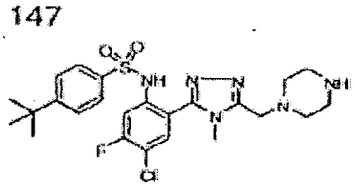
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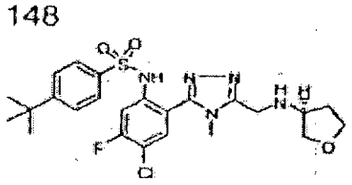
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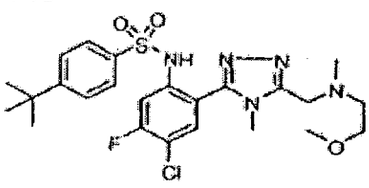
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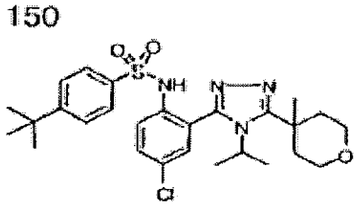
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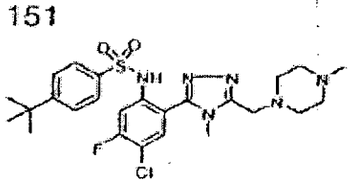
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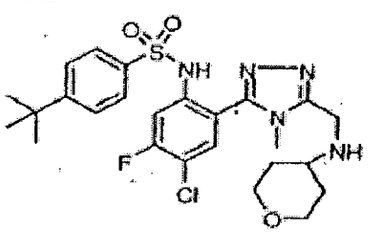
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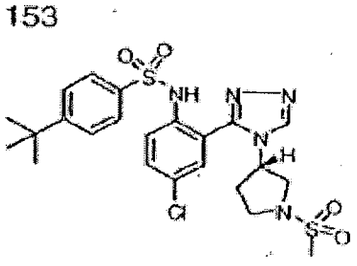
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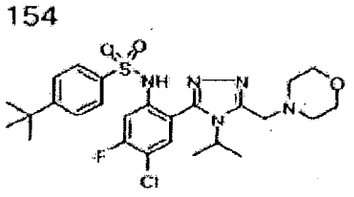
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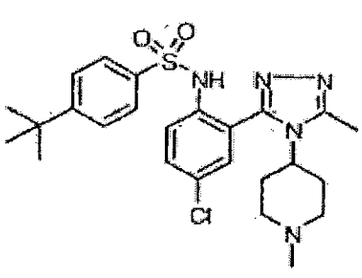
153



154



155



156

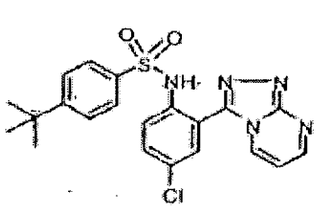
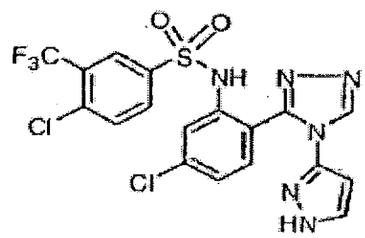
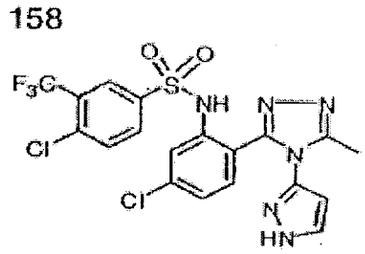


Tabla 4: Compuestos con actividad CCR2 en uno de los análisis de quimiotaxis, enlace o movilización de calcio, con IC50 < 1000 nM.

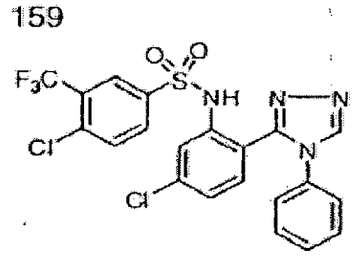
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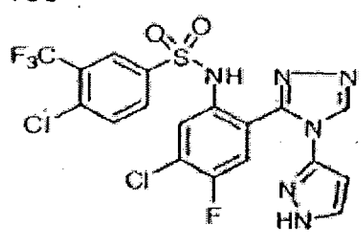
158



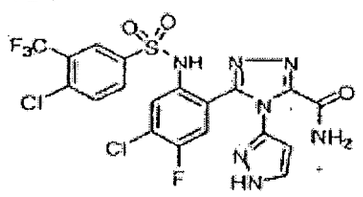
159



160



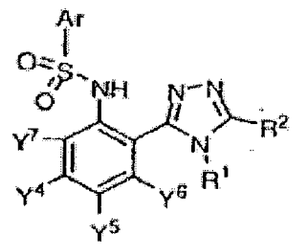
161



En consecuencia, se pretende que la descripción detallada anterior se considere ilustrativa más que limitante, y que se entienda que son las reivindicaciones siguientes, incluyendo todos los equivalentes, las que pretenden definir el espíritu y alcance de esta invención.

REIVINDICACIONES

1. Un compuesto de la fórmula (I) o una sal del mismo:



(I)

en donde

Ar se selecciona del grupo que consiste de arilo C_{6-10} sustituido o no sustituido y un heteroarilo de 5 a 10 miembros sustituido o no sustituido;

Y^4, Y^5, Y^6 y Y^7 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, halógeno, -CN, $-C(O)R^{15}$, $-CO_2R^{15}$, $-C(O)NR^{15}R^{16}$, $-OR^{15}$, $-OC(O)R^{15}$, $-OC(O)NR^{15}R^{16}$, $-SR^{15}$, $-S(O)R^{15}$, $-S(O)_2R^{15}$, $-S(O)_2NR^{15}R^{16}$, $-NO_2$, $-NR^{15}R^{16}$, $-NR^{15}C(O)R^{16}$, $-NR^{15}C(O)OR^{16}$, $-NR^{15}S(O)_2R^{16}$, $-NR^{15}C(O)NR^{16}R^{17}$, alquilo C_{1-8} sustituido o no sustituido, alquenilo C_{2-8} sustituido o no sustituido, alquinilo C_{2-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido, y heteroarilo de 5 a 10 miembros sustituido o no sustituido;

R^{15}, R^{16} y R^{17} se seleccionan cada uno independientemente del grupo que consiste de hidrógeno,

alquilo C_{1-8} sustituido o no sustituido, alquenilo C_{2-8} sustituido o no sustituido, alquinilo C_{2-8} sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido, heteroarilo de 5 a 10 miembros sustituido o no sustituido y heterociclilo de 3 a 10 miembros sustituido o no sustituido; y

R^{15} y R^{16}, R^{16} y R^{17} o R^{15} y R^{17} conjuntamente con los átomos a los cuales se encuentran unidos, pueden formar un anillo de 5, 6 o 7 miembros sustituido o no sustituido;

R^1 se selecciona del grupo que consiste de hidrógeno, $-C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2NR^7R^8$, alquilo C_{1-8} sustituido o no sustituido, alquenilo C_{2-8} sustituido o no sustituido, alquinilo C_{2-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido, o heteroarilo de 5 a 10 miembros sustituido o no sustituido;

R^2 se selecciona del grupo que consiste de hidrógeno, halógeno, $-CN$, $-C(O)R^7$, $-CO_2R^7$, $-C(O)NR^7R^8$, $-OR^7$, $-OC(O)R^7$, $-OC(O)NR^7R^8$, $-SR^7$, $-S(O)R^7$, $-S(O)_2R^7$, $-S(O)_2NR^7R^8$, $-NO_2$, $-NR^7R^8$, $-NR^7C(O)R^8$, $-NR^7C(O)OR^8$, $-NR^7S(O)_2R^8$, $-NR^7C(O)NR^8R^9$, alquilo C_{1-8} sustituido o no sustituido, alquenilo C_{2-8} sustituido o no sustituido, alquinilo C_{2-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido, y heteroarilo de 5 a 10 miembros sustituido o no sustituido;

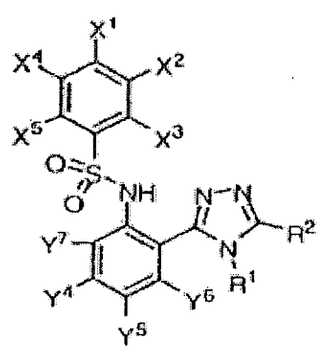
401

R^7, R^8 y R^9 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, alquilo C_{1-8} sustituido o no sustituido, alquenilo C_{2-8} sustituido o no sustituido, alquinilo C_{2-8} sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido, heteroarilo de 5 a 10 miembros sustituido o no sustituido y heterociclilo de 3 a 10 miembros sustituido o no sustituido;

R^7 y R^8, R^8 y R^9 o R^7 y R^9 conjuntamente con los átomos a los cuales se encuentran unidos, pueden formar un anillo de 5, 6 o 7 miembros sustituido o no sustituido; y

en donde R^1 y R^2 conjuntamente con los átomos a los cuales se encuentran unidos, pueden formar un anillo de 5, 6 o 7 miembros sustituido o no sustituido.

2. El compuesto de la reivindicación 1 o una sal del mismo, de la fórmula (II):



(II)

en donde

X^1, X^2, X^3, X^4 y X^5 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, halógeno, alquilo C_{1-8} sustituido o no sustituido, alquenilo

C_{2-8} sustituido o no sustituido, alquinilo C_{2-8} sustituido o no sustituido, -CN, $-NO_2$, $-C(O)R^{18}$, $-CO_2R^{18}$, $-C(O)NR^{18}R^{19}$, $-OR^{18}$, $-OC(O)R^{19}$, $-OC(O)NR^{18}R^{19}$, $-NO_2$, $-NR^{18}C(O)R^{19}$, $NR^{18}C(O)NR^{19}R^{20}$, $-NR^{18}R^{19}$, $-NR^{18}CO_2R^{19}$, $NR^{18}S(O)_2R^{19}$, $-SR^{18}$, $-S(O)R^{18}$, $-S(O)_2R^{18}$, $-S(O)_2NR^{18}R^{19}$, arilo C_{6-10} sustituido o no sustituido, heteroarilo de 5 a 10 miembros sustituido o no sustituido y heterociclilo de 3 a 10 miembros sustituido o no sustituido;

R^{18}, R^{19} y R^{20} se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, alquilo C_{1-8} sustituido o no sustituido, alquenilo C_{2-8} sustituido o no sustituido, alquinilo C_{2-8} sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido, heteroarilo de 5 a 10 miembros sustituido o no sustituido y heterociclilo de 3 a 10 miembros sustituido o no sustituido; y

R^{18} y R^{19}, R^{19} y R^{20} o R^{18} y R^{20} conjuntamente con los átomos a los cuales se encuentran unidos, pueden formar un anillo de 5, 6 o 7 miembros sustituido o no sustituido.

3. El compuesto de la reivindicación 2, o una sal del mismo, en donde

X^1 se selecciona del grupo que consiste de halógeno, alquilo C_{1-8}, sustituido o no sustituido, $-OR^{18}$, $-NR^{18}R^{19}$, y heterociclilo de 3 a 10 miembros sustituido o no sustituido;

Y^7 es hidrógeno;

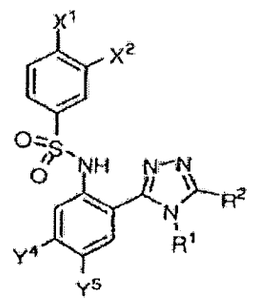
403

Y^4, Y^5 y Y^6 se seleccionan cada uno independientemente del grupo que consiste de hidrógeno, halógeno, -CN, $-CO_2R^{15}$, $-C(O)NR^{15}R^{16}$;

R^1 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido y heteroarilo de 5 a 10 miembros sustituido o no sustituido; y

R^2 se selecciona del grupo que consiste de hidrógeno, alquilo C_{1-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido y heteroarilo de 5 a 10 miembros sustituido o no sustituido.

4. El compuesto de la reivindicación 2, o una sal del mismo, de la Fórmula (III):



(III)

en donde al menos uno de X^1 y X^2 son diferentes a hidrógeno y al menos uno de Y^4 y Y^5 son diferentes a hidrógeno.

5. El compuesto de la reivindicación 4, o una sal

del mismo, de la fórmula (III):

en donde X^2 es hidrógeno o halógeno; Y^4 es hidrógeno, halógeno o -CN; y X^1 y X^5 son diferentes a hidrógeno.

6. El compuesto de la reivindicación 5, o una sal del mismo, en donde

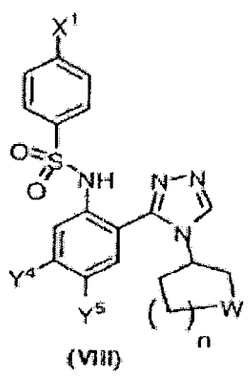
X^1 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o no sustituido, $-OR^{18}$, $-NR^{18}R^{19}$ y heterociclilo de 3 a 10 miembros sustituido o no sustituido;

Y^5 se selecciona del grupo que consiste de halógeno, -CN, $-CO_2R^{15}$, y $-C(O)NR^{15}R^{16}$;

R^1 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido y heteroarilo de 5 a 10 miembros sustituido o no sustituido; y

R^2 es hidrógeno.

7. El compuesto de la reivindicación 6, o una sal del mismo, de la fórmula (VIII)



(VIII)

en donde W es NH u O; y n es 0, 1 o 2.

8. El compuesto de la reivindicación 4 o una sal del mismo, en donde

X^1 es halógeno;

X^2 es halógeno o $-CF_3$;

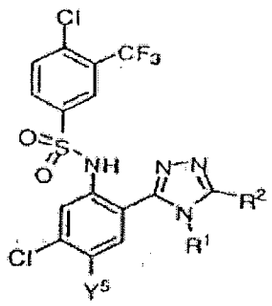
Y^4 es halógeno;

Y^5 es hidrógeno o halógeno;

R^1 es arilo o heteroarilo; y

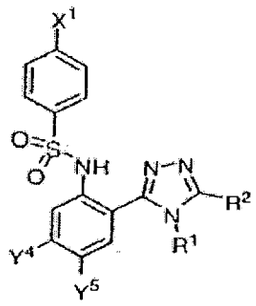
R^2 es hidrógeno o alquilo C_{1-8} sustituido o no sustituido.

9. El compuesto de la reivindicación 8 o una sal del mismo de la fórmula (V):



(V)

10. El compuesto de la reivindicación 2, o una sal del mismo de la fórmula (IV):



(IV)

406

en donde Y^4 es hidrógeno o fluoro; y X^1 y Y^5 son diferentes a hidrógeno.

11. El compuesto de la reivindicación 10, o una sal del mismo, en donde

X^1 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o no sustituido, $-OR^{18}$, $-NR^{18}R^{19}$ y heterociclilo de 3 a 10 miembros sustituido o no sustituido;

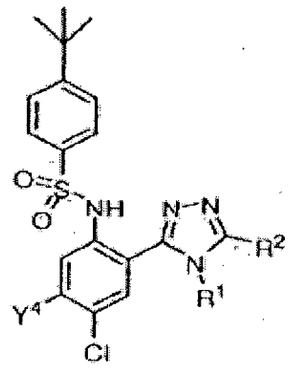
Y^5 se selecciona del grupo que consiste de halógeno, -CN, $-CO_2R^{15}$, $-C(O)NR^{15}R^{16}$;

R^1 se selecciona del grupo que consiste de alquilo C_{1-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido y heteroarilo de 5 a 10 miembros sustituido o no sustituido; y

R^2 se selecciona del grupo que consiste de hidrógeno, alquilo C_{1-8} sustituido o no sustituido, heterociclilo de 3 a 10 miembros sustituido o no sustituido, arilo C_{6-10} sustituido o no sustituido y heteroarilo de 5 a 10 miembros sustituido o no sustituido.

12. El compuesto de la reivindicación 11, o una sal del mismo, de la fórmula (VI):

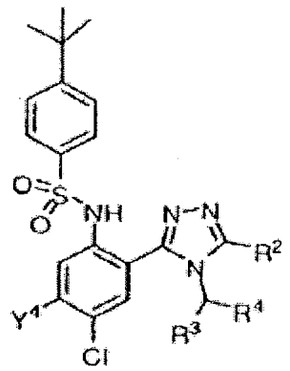
407



(VII)

en donde Y^4 es hidrógeno o halógeno.

13. El compuesto de la reivindicación 12, o una sal del mismo, de la fórmula (VII):



(VII)

en donde

Y^4 es hidrógeno o halógeno; y

R^3 y R^4 son cada uno independientemente hidrógeno, alquilo C_{1-8} no sustituido o sustituido, o R^3 y R^4 conjuntamente con el carbono al cual sustituyen forman un anillo carbocíclico de 3-10 miembros, heterocíclico de 4-10 miembros, heteroarilo de 5-10 miembros o un anillo de arilo de 6-10 miembros.

408

14. El compuesto de la reivindicación 13 o una sal del mismo, en donde R^2 es hidrógeno.

15. El compuesto de la reivindicación 1, seleccionado del grupo que consiste de

4-ter-butil-N-(4-cloro-2-(4,5-diisopropil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4,5-dimetil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-ciclopentil-5-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-ciclopropil-5-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-etil-5-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-isopropil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-isopropil-5-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-metil-5-(tetrahidro-2H-piran-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-fenil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-(metoximetil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-etil-4-isopropil-4H-

1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-isopropil-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-(1H-pirazol-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-(piridin-2-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-(piridin-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-(tetrahidro-2H-piran-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-fenil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

N-(4-cloro-2-(4-isopropil-5-metil-4H-1,2,4-triazol-3-il)fenil)-4-isopropoxibencenosulfonamida;

N-(2-(3-(2-(4-ter-butilfenilsulfonamido)-5-clorofenil)-5-metil-4H-1,2,4-triazol-4-il)etil)acetamida;

(R)-4-ter-butil-N-(4-cloro-2-(4-metil-5-(tetrahidrofuran-2-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4,5-difluoro-2-(4-pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(4-(1-hidroxipropan-2-

il)-5-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(4-metil-5-(tetrahidrofuran-2-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(2-(4-etil-4H-1,2,4-triazol-3-il)-4,5-difluorofenil)bencenosulfonamida;

4-ter-butil-N-(2-(4-etil-4H-1,2,4-triazol-3-il)-5-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4,5-difluoro-2-(4-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4,5-dietil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4,5-dimetil-4H-1,2,4-triazol-3-il)-3-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4,5-dimetil-4H-1,2,4-triazol-3-il)-5-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-etil-4H-1,2,4-triazol-3-il)-3-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-etil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-etil-5-isopropil-4H-

1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-etil-5-metil-4H-1,2,4-triazol-3-il)-3-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-isobutil-5-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-metil-5-(oxazol-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-(dimetilamino)metil)-4-metil-4H-1,2,4-triazol-3-il)-5-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-(2-metoxietil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-(metoximetil)-4-(tetrahidro-2H-piran-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-(piperidin-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-(piperidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(5-cloro-2-(4-isopropil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(5-cloro-2-(4-isopropil-5-(4-metiltetrahidro-2H-piran-4-il)-4H-1,2,4-triazol-3-

412

il)fenil)bencenosulfonamida;

4-ter-butil-N-(5-fluoro-2-(4-isopropil-5-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

N-(4-cloro-2-(4-etil-5-metil-4H-1,2,4-triazol-3-il)fenil)-4-isopropoxibencenosulfonamida;

etil 2-(5-(2-(4-ter-butilfenilsulfonamido)-5-cloro-4-fluorofenil)-4-metil-4H-1,2,4-triazol-3-il)acetato;

5-(2-(4-ter-butilfenilsulfonamido)-5-cloro-4-fluorofenil)-4-metil-4H-1,2,4-triazol-3-carboxamida;

5-(2-(4-ter-butilfenilsulfonamido)-5-cloro-4-fluorofenil)-N,4-dimetil-4H-1,2,4-triazol-3-carboxamida;

(R)-4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(1-hidroxietil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(4-(piperidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(4-(tetrahidro-2H-piran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(5-metil-4-(piperidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-5-fluoro-2-(4-(piperidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-5-fluoro-2-(4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-

413

il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-5-fluoro-2-(4-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(1-hidroxietil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-5-fluoro-2-(5-metil-4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-N-(4-cloro-2-(4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)-4-isopropoxibencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-isopropil-5-(tetrahidro-2H-piran-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-metil-5-(5-metiloxazol-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-((ciclopropilamino)metil)-4-metil-4H-1,2,4-triazol-3-il)-5-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-((etilamino)metil)-4-metil-4H-1,2,4-triazol-3-il)-5-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-etil-4-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)-5-

fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-etil-4-metil-4H-1,2,4-triazol-3-il)-5-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-etil-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-(tetrahidro-2H-piran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-isopropil-5-(metoximetil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-((metilamino)metil))-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-(metilsulfonilmetil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-(morfolinometil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-(oxazol-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-

(pirrolidin-1-ilmetil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-(tetrahidro-2H-piran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-(tetrahidro-2H-piran-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-((isopropilamino)metil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(1-hidroxietil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(2-hidroxi-2-metilpropil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(2-hidroxipropan-2-il)—4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(2-metoxietil)-4-metil-4H-1,2,4-triazol-3-

il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(hidroximetil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(metoximetil)-4-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(metoximetil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

N-(2-(5-(azetidin-1-ilmetil)-4-metil-4H-1,2,4-triazol-3-il)-4-cloro-5-fluorofenil)-4-ter-butilbencenosulfonamida;

N-(2-(5-acetil-4-metil-4H-1,2,4-triazol-3-il)-4-cloro-5-fluorofenil)-4-ter-butilbencenosulfonamida;

(S)-4-ter-butil-N-(4,5-difluoro-2-(5-(metil-4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(5-etil-4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(5-isopropil-4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(5-metil-4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(2-(4,5-dimetil-4H-1,2,4-triazol-3-il)-5-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(2-(4-etil-5-metil-4H-1,2,4-triazol-3-il)-4,5-difluorofenil)bencenosulfonamida;

4-ter-butil-N-(2-(4-etil-5-metil-4H-1,2,4-triazol-3-il)-5-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-metil-5-(piperidin-4-il)-4H-1,2,4-triazol-3-il)-5-fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-isopropil-4H-1,2,4-triazol-3-il)-5-fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-isopropil—5-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil—5-(metiloxazol-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-isopropil—4-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-metil—4-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

N-(4-cloro-2-(4,5-dimetil-4H-1,2,4-triazol-3-

il)fenil)-4-isopropoxibencenosulfonamida;

N-(4-cloro-2-(4-isopropil-4H-1,2,4-triazol-3-il)fenil)-4-isopropoxibencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(5-etil-4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)-5-fluorofenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-5-fluoro-2-(oxopirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-5-fluoro-2-(5-isopropil-4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-N-(4-cloro-2-(4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)-4-(4-metilterahidro-2H-piran-4-il)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-ciclobutil-5-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-etil-5-isopropil-4H-1,2,4-triazol-3-il)-5-fluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-isopropil-5-(trifluorometil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-(1-metilpiperidin-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-(2-metilsulfonil)etil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

N-(2-(4-(1-acetilpiperidin-4-il)-5-metil-4H-1,2,4-triazol-3-il)-4-clorofenil)-4-ter-butilbencenosulfonamida;

N-(2-(4-(2-aminoetil)-5-metil-4H-1,2,4-triazol-3-il)-4-clorofenil)-4-ter-butilbencenosulfonamida;

N-(2-(4-(1-acetidin-3-il)-4H-1,2,4-triazol-3-il)-4-cloro-5-fluorofenil)-4-ter-butilbencenosulfonamida;

(R)-4-ter-butil-N-(4-cloro-2-(5-metil-4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(2-(4,5-dimetil-4H-1,2,4-triazol-3-il)-4,5-difluorofenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-isopropil-5-(metoximetil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-metil-5-(piridin-2-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-metil-5-(tetrahidrofuran-2-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-((dimetilamino)metil)-4-isopropil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-(isopropoximetil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-(3-(2-(4-ter-butilfenilsulfonamido)-5-clorofenil)-5-metil-4H-1,2,4-triazol-3-il)piperidina-1-carboxamida;

4-ter-butil-N-(4-cloro-2-(4-(2-(dimetilamino)etil)-5-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-(1-(metilsulfonil)piperidin-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-metil-4-(2-(metilamino)etil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(5-cloro-2-(4-isopropil-5-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

N-(2-(4-(1-acetilpirrolidin-3-il)-5-metil-4H-1,2,4-triazol-3-il)-4-clorofenil)-4-ter-butilbencenosulfonamida;

N-(2-(5-amino-4-isopropil-4H-1,2,4-triazol-3-il)-4-clorofenil)-4-ter-butilbencenosulfonamida;

(R)-4-ter-butil-N-(4-cloro-5-fluoro-2-(4-(tetrahidrofuran-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

42)

(R)-4-ter-butil-N-(4-cloro-2-(4-(pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-ciano-2-(5-etil-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-(4-ter-butilfenilsulfonamido)-3-(5-etil-4-metil-4H-1,2,4-triazol-3-il)benzamida;

ácido 4-(4-ter-butilfenilsulfonamido)-3-(5-etil-4-metil-4H-1,2,4-triazol-3-il)benzoico;

N-(2-(4-(azetidin-3-il)-4H-1,2,4-triazol-3-il)-4-clorofenil)-4-ter-butilbencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-metil-5-((metilamino)metil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

metil 4-(4-ter-butilfenilsulfonamido)-3-(5-etil-4-metil-4H-1,2,4-triazol-3-il)benzoato;

N-(4-cloro-2-(4,5-dimetil-4H-1,2,4-triazol-3-il)fenil)-3-fluoro-4-morfolinobencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-(2-metoxietil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(2-hidroxietil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(5-(isopropilamino)metil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(1-

422

metoxietil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(R)-4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-(pirrolidin-2-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(4-(1-isopropilpirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-3-(3-(2-(4-ter-butilfenilsulfonamido)-5-clorofenil)-4H-1,2,4-triazol-4-il)pirrolidina-1-carboxamida;

4-ter-butil-N-(4-cloro-2-(4-metil-5-(morfolinometil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-(piperidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-(piperazin-1-ilmetil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-((tetrahidrofuran-3-ilamino)metil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(5-(((2-metoxietil)metil)amino)metil)-4-metil-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-2-(4-isopropil-5-(4-metiltetrahidro-2H-piran-4-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-((4-metilpiperazin-1-il)metil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-metil-5-((tetrahidro-2H-piran-4-ilamino)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

(S)-4-ter-butil-N-(4-cloro-2-(4-(1-(metilsulfonil)pirrolidin-3-il)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

4-ter-butil-N-(4-cloro-5-fluoro-2-(4-isopropil-5-(morfolinometil)-4H-1,2,4-triazol-3-il)fenil)bencenosulfonamida;

N-(2-(1H-pirazol-3-il)-4H-1,2,4-triazol-3-il)-5-clorofenil)-4-cloro-3-(trifluorometil)bencenosulfonamida;

4-cloro-N-(5-cloro-2-(5-metil-4-(1H-pirazol-3-il)-4H-1,2,4-triazol-3-il)fenil)-3-(trifluorometil)bencenosulfonamida;

4-cloro-N-(5-cloro-2-(5-fenil-4H-1,2,4-triazol-3-il)fenil)-3-(trifluorometil)bencenosulfonamida;

N-(2-(4-(1H-pirazol-3-il)-4H-1,2,4-triazol-3-il)-5-cloro-4-fluorofenil)-4-cloro-3-(trifluorometil)bencenosulfonamida;

5-(4-cloro-2-(4-cloro-3-(trifluorometil)fenilsulfonamido)-5-fluorofenil)-4-(1H-pirazol-3-il)-4H-1,2,4-triazol-3-carboxamida; y

N-(2-([1,2,4]triazol[4,3-a]pirimidin-3-il)-4-clorofenil)-4-ter-butilbencenosulfonamida.

16. Una composición que comprende un vehículo farmacéuticamente aceptable y un compuesto de la reivindicación 1.

17. Un método para tratar una condición o enfermedad mediada por CCR2 o una condición o enfermedad mediada por CCR9 que comprende administrar a un sujeto una cantidad efectiva de un compuesto de cualquiera de las reivindicaciones 1-15, o una sal del mismo.

18. El método de la reivindicación 17, en donde la enfermedad o condición se selecciona del grupo que consiste de aterosclerosis, restenosis, esclerosis múltiple, enfermedad inflamatoria intestinal, fibrosis renal, artritis reumatoide, obesidad, diabetes, enfermedad pulmonar obstructiva crónica, fibrosis pulmonar idiopática, síndrome de neumonía idiopática, fibrosis pulmonar, rechazo al transplante, enfermedad de injerto contra huésped, cáncer y dolor neuropático.

19. El método de la reivindicación 17, en donde la administración es oral, parenteral, rectal, transdérmica, sublingual, nasal o tópica.

20. El método de la reivindicación 17, que comprende además administrar un agente anti-inflamatorio o analgésico.

21. Un método para modular la función de CCR2 en una célula, que comprende poner en contacto la célula con una cantidad moduladora de CCR2 del compuesto de cualquiera de las reivindicaciones 1-15.

22. Un método para modular la función de CCR9 en una célula, que comprende poner en contacto la célula con una cantidad moduladora de CCR9 del compuesto de cualquiera de las reivindicaciones 1-15.

23. Un método para tratar una condición o enfermedad mediada por CCR9 que comprende administrar a un sujeto una cantidad efectiva del compuesto de cualquiera de las reivindicaciones 1-15.

24. Un método para tratar una condición o enfermedad mediada por CCR2 que comprende administrar a un sujeto una cantidad efectiva del compuesto de cualquiera de las reivindicaciones 1-15.

RESUMEN

Se proporcionan compuestos que actúan como potentes antagonistas del receptor CCR2 o CCR9. Las pruebas en animales demuestran que estos compuestos son útiles para tratar inflamación, una enfermedad característica para CCR2 y CCR9. Los compuestos son generalmente derivados de aril sulfonamida y son útiles en composiciones farmacéuticas, métodos para el tratamiento de enfermedades mediadas por CCR2, enfermedades mediadas por CCR9, como controles en análisis para la identificación de antagonistas de CCR2 y como controles en análisis para la identificación de antagonistas de CCR9.

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PATENT COOPERATION TREA.

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:
BRINKS HOFER GILSON & LIONE
Attn. Seaney, Lisa M.
P.O. Box 10087
Chicago, IL 60611
ETATS-UNIS D'AMERIQUE

BRINKS HOFER GILSON & LIONE
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INT'L PATENT

Applicant's or agent's file reference 10709-240	Date of mailing *(day/month/year)* 30/01/2008
International application No. PCT/US2007/015808	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant CHEMOCENTRYX, INC.	International filing date *(day/month/year)* 10/07/2007

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Federico Bonomelli

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREA..

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
10709-240		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2007/015808	10/07/2007	14/07/2006
Applicant		
CHEMOCENTRYX, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

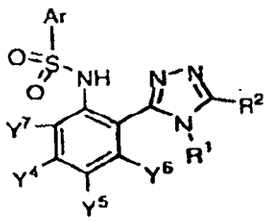
6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/015808

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

Compounds (I) are provided that act as potent antagonists of the CCR2 or CCR9 receptor. Animal testing demonstrates that these compounds are useful for treating inflammation, a hallmark disease for CCR2 and CCR9. The compounds are generally aryl sulfonamide derivatives and are useful in pharmaceutical compositions, methods for the treatment of CCR2-mediated diseases, CCR9-mediated diseases, as controls in assays for the identification of CCR2 antagonists and as controls in assays for the identification of CCR9 antagonists.



(I)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/015808

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D249/08 C07D401/04 C07D403/04 C07D405/04 C07D405/12
C07D413/04 A61K31/41 A61P29/00

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/004818 A (IMCLONE SYSTEMS INC [US]; OUYANG XIAOHU [US]; KISELYOV ALEXANDER [US];) 20 January 2005 (2005-01-20) page 130; claim 8; compounds 127,128	1,2
A	WO 2004/058741 A (MERCK & CO INC [US]; WADDELL SHERMAN T [US]; SANTORELLI GINA M [US]; M) 15 July 2004 (2004-07-15) example 54	1-16
A	WO 2005/113513 A (CHEMOCENTRYX [US]; UNGASHE SOLOMON [US]; WRIGHT JOHN JESSEN [US]; PENN) 1 December 2005 (2005-12-01) paragraph [0001]; claim 1	1-24

-/--

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 January 2008	30/01/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Gettins, Marc

2

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/015808

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2004/171654 A1 (UGASHE SOLOMON [US] ET AL UNGASHE SOLOMON [US] ET AL) 2 September 2004 (2004-09-02) cited in the application paragraph [0002]; claim 1	1-24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/015808

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17-24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

ormation on patent family members

ternational application No
PCT/US2007/015808

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005004818 A	20-01-2005	NONE	
WO 2004058741 A	15-07-2004	AT 375336 T	15-10-2007
		AU 2003297231 A1	22-07-2004
		AU 2003302255 A1	22-07-2004
		BR 0317451 A	16-11-2005
		CA 2510540 A1	15-07-2004
		EP 1581515 A1	05-10-2005
		HR 20050575 A2	28-02-2006
		IS 7876 A	31-05-2005
		JP 2006513266 T	20-04-2006
		KR 20050085790 A	29-08-2005
		MA 27579 A1	03-10-2005
		MX PA05006726 A	08-09-2005
		NZ 540465 A	22-12-2006
		WO 2004058730 A2	15-07-2004
		US 2005154038 A1	14-07-2005
		US 2004133011 A1	08-07-2004
WO 2005113513 A	01-12-2005	AU 2005245401 A1	01-12-2005
		CA 2566387 A1	01-12-2005
		EP 1748989 A2	07-02-2007
US 2004171654 A1	02-09-2004	US 2005165067 A1	28-07-2005
		US 2005137193 A1	23-06-2005

109374 435

PATENT COOPERATION T[illegible]ATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2007/015808	10.07.2007	14.07.2006

International Patent Classification (IPC) or both national classification and IPC
INV. C07D249/08 C07D401/04 C07D403/04 C07D405/04 C07D405/12 C07D413/04 A61K31/41 A61P29/00

Applicant
CHEMOCENTRYX, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Gettins, Marc Telephone No. +49 89 2399-8273

Form (PCT/ISA/237) (Cover Sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2007/015808

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2007/015808

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 17-24

because:

☒ the said international application, or the said claims Nos. 17-24 relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2007/015808

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-24
	No:	Claims	1,2
Inventive step (IS)	Yes:	Claims	
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-24
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 17-24 relate to a subject-matter considered by this Authority to be covered by the provision of Rule 39.1 iv /67.1 (iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for in a first or further medical treatment.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Relevant prior art is provided by:

   D1: WO 2005/004818
   D2: WO 2004/058741
   D3: WO 2005/113513
   D4: US 2004/171654

2. Claims 17-24 relate to a subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv)/67.1(iv) PCT.

3. The current application is novel vis-à-vis D2 on account of R2 and is novel vis-à-vis D3 and D4 on account of the 1,2,4 triazole ring. The current application appears to be anticipated by compounds 127 and 128 of D1.

4. The current application addresses the problem of producing further inhibitors of chemokine receptors. Compounds with this activity are known from D3 and D4. Given the structural differences between the current application and D3/D4 the skilled man would not have predicted the qualitative retention of the desired activity. Accordingly an inventive step can be acknowledged for the claimed compounds which actually solve the given problem.

Re Item VII

Certain defects in the international application

1. It should be noted that the claims 17 and 21-24 are defined in functional terms that are not considered to be clear. The therapeutic application is functionally defined by a mechanism of action which does not allow any practical application in the form of a defined real treatment of a pathological condition (disease). The objection could be overcome by either introducing in the claims a list of pathological conditions (diseases) cited in the application or by showing that means are available which would allow the skilled person to recognise which additional conditions would fall within the functional definition.

2. There is an unacceptable discrepancy between the claims and the description since the description (see pages 9-10) makes it clear that various hydrocarbon substituents such as alkyl, alkenyl and aryl can be substituted even when this is not specifically mentioned. Furthermore alkyl is apparently also meant to include possibilities such as cycloalkyl. The skilled person would not have been aware of this from a reading of the claims since the skilled person would assume that standard IUPAC nomenclature was being used. In the current case, however, the Applicant has obviously seen fit to use non-standard interpretations of standard nomenclature. The intended scope of the claims cannot be understood without referring to the description which contravenes (Rule 6 PCT). The claims and description should be fully harmonised so that their scope is the same and so that the claims are fully clear in their own right.

3. It must be made credible that essentially all of the claimed matter solves the given problem. With the present scope of the claims this is not the case. The expressions in the claims "unsubstituted" (with no further limitation)" and derivatives thereof are non-limitative and are therefore not regarded as obvious modifications or equivalents of the examples which have been given in the description. Accordingly, the said expressions should be restricted in this respect to the particular meanings specified in the description e.g. pp13-14 (**Article** 6 PCT). It should be borne in mind that only those compounds which are suitable for solving the problem underlying the present application can be claimed.

Re Item VIII
Certain observations on the international application

1. [0001], 2nd sentence should be deleted as should [00521] and the reference in [00531] to "not limited to".

2. Prodrugs and metabolites are neither claimed nor allowed. [0060] to [0062] should therefore be deleted.

3. The prior art documents D1 and D3 should be cited (Rule 5.1 (a) (ii) PCT).

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT). If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003

BNSDOCID: <XS_____200704010CK_I_>

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GILSON & LIONE

PATENT COOPERATION TREATY

PCT/US2007/015808

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From the INTERNATIONAL BUREAU

To:

SEANEY, Lisa, M.
Brinks Hofer Gilson & Lione
P.O. Box 10087
Chicago, IL 60610
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF THE RECORDING OF A CHANGE

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

Date of mailing *(day/month/year)*
05 December 2007 (05.12.2007)

Applicant's or agent's file reference
10709-240

IMPORTANT NOTIFICATION

International application No.
PCT/US2007/015808

International filing date *(day/month/year)*
10 July 2007 (10.07.2007)

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.

Teleprinter No.

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

PUNNA, Sreenivas
1240 Vicente Dr, Apt #E
Sunnyvale, CA 94086
United States of America

State of Nationality: IN | State of Residence: US

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:
The person identified in Box 2 should be added to the record as applicant for the United States of America only and inventor for all designated States.

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

☒ the receiving Office
☒ the International Searching Authority
☐ 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 87 20

Authorized officer
Craker Alexander
e-mail pt03.pct@wipo.int
Telephone No. +41 22 338 74 03

Form PCT/IB/306 (October 2005)

I/DG7U9ZI30

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PATENT COOPERATION TREATY

PCT/US2007/015808

PCT

From the INTERNATIONAL BUREAU

To:

SEANEY, Lisa, M.
Brinks Hofer Gilson & Lione
P.O. Box 10087
Chicago, IL 60610
ETATS-UNIS D'AMERIQUE

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

Date of mailing *(day/month/year)* 27 November 2007 (27.11.2007)	
Applicant's or agent's file reference 10709-240	**IMPORTANT NOTIFICATION**
International application No. PCT/US2007/015808	International filing date *(day/month/year)* 10 July 2007 (10.07.2007)
International publication date *(day/month/year)* **Not yet published**	Priority date *(day/month/year)* 14 July 2006 (14.07.2006)
Applicant CHEMOCENTRYX, INC. et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. *(If applicable)* **The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau** under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. *(If applicable)***An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)** (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
22 June 2007 (22.06.2007)	60/945,839	US	13 October 2007 (13.10.2007)

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

Facsimile No. +41 22 338 82 70

Authorized officer
Beate Giffo-Schmitt
e-mail PT03.PCT@WIPO.INT
Telephone No. +41 22 338 74 03

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PATENT COOPERATION TREA'.

PCT/US2007/015808

From the INTERNATIONAL BUREAU

To:

SEANEY, Lisa, M.
Brinks Hofer Gilson & Lione
P.O. Box 10087
Chicago, IL 60610
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF RECEIPT OF RECORD COPY

(PCT Rule 24.2(a))

Date of mailing *(day/month/year)*	IMPORTANT NOTIFICATION
09 November 2007 (09.11.2007)	
Applicant's or agent's file reference	International application No.
10709-240	PCT/US2007/015808

The applicant is hereby **notified** that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

CHEMOCENTRYX, INC. (for all designated States except US)
CHARVAT, Trevor, T. et al (for US)

COPY TO ATTY
W/OUT FILE

International filing date: 10 July 2007 (10.07.2007)

Priority date(s) claimed: 14 July 2006 (14.07.2006)

Date of receipt of the record copy by the International Bureau: 19 October 2007 (19.10.2007)

List of designated Offices:

AP: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW
EA: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
EP: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR
OA: BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
National: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

ATTENTION: The applicant should carefully check the data appearing in this notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau. **In addition, the applicant's attention is drawn to the information contained in the Annex**, relating to:

- time limits for entry into the national phase - **see updated important information (as of April 2002)**
- requirements regarding priority documents (if applicable)

A copy of this notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Marquis Catherine
Facsimile No. +41 22 338 87 20	e-mail pt03.pct@wipo.int Telephone No. +41 22 338 74 03

446

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

To:
LISA M. SEANEY
BRINKS HOFER GILSON & LIONE
P.O.BOX 10087
CHICAGO, ILLINOIS 60610

Confirmation No: 9995

PCT

NOTIFICATION OF THE INTERNATIONAL APPLICATION NUMBER AND OF THE INTERNATIONAL FILING DATE

(PCT Rule 20.2(c))

Date of mailing *(day/month/year)*	17 Oct 2007
Applicant's or agent's file reference: 10709-240	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2007/015808	10 Jul 2007	14 Jul 2006

Applicant: CHEMOCENTRYX, INC.

Title of the invention: TRIAZOLYL PHENYL BENZENESULFONAMIDES

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.

2. The applicant is further notified that the record copy of the international application:

☒ was transmitted to the International Bureau on 17 Oct 2007

☐ has not yet been transmitted to the International Bureau for the reason indicated below and a copy of this notification has been sent to the International Bureau*:

☐ because the necessary national security clearance has not yet been obtained.

☐ because *(reason to be specified)*:

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

3. FOREIGN TRANSMITTAL LICENSE INFORMATION Completed by: TS

☐ Additional license for foreign transmittal not required. This subject matter is covered by a license already granted or the equivalent U.S. national application. Refer to that license for information concerning its scope.

☐ License for foreign transmittal not required. 37 CFR 5.11(e)(1) or 37 CFR 5.11(e)(2). However, a license may be required for additional subject matter. See 37 CFR 5.15(b).

☒ Foreign transmittal license granted. 35 U.S.C. 184; 37 CFR 5.11 on 11 Oct 2007 (date):

☐ 37 CFR 5.15(a) ☒ 37 CFR 5.15(b)

Name and mailing address of the receiving Office	Authorized officer
Mail Stop PCT, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450	Theodosia Simpkins
Facsimile No. 571-273-3201	Telephone No. 703-308-9290 EX 109

Form PCT/RO/105 (April 2007)

109374
GRT

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 10709-240

Box No. I TITLE OF INVENTION

TRIAZOLYL PHENYL BENZENESULFONAMIDES

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ChemoCentryx, Inc.
850 Maude Avenue
Mountain View, California 94043
United States of America

Telephone No.

Facsimile No.

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SEANEY, Lisa M.
BRINKS HOFER GILSON & LIONE
P.O. Box 10087
Chicago, Illinois 60610
United States of America

Telephone No.
312-321-4200

Facsimile No.
312-321-4299

Agent's registration No. with the Office
56,246

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CHARVAT, Trevor T.
3320 Parkhaven Drive
San Jose, California 95132
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

HU, Cheng
250 Waverly Street, #6
Menlo Park, California 94025
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: CN

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

MELIKIAN, Anita
4150 17th Street, #25
San Francisco, California 94114
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: FR

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

NOVACK, Aaron
92 Mirabelli Circle
San Jose, California 95134
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

PENNELL, Andrew M.K.
442 Arlington Street
San Francisco, California 94131
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: IN

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SULLIVAN, Edward J.
900 Golden Wheel Park Drive, Spc. 94
San Jose, California 95112
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

TAN, Xuefei
32666 Foxglove Way
Union City, California 94587
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: CN

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

THOMAS, William D.
14803 Charmeran Avenue
San Jose, California 95124
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

UNGASHE, Solomon
36641 Reynolds Drive
Fremont, California 94536
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: ET

State *(that is, country)* of residence: US

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ZENG, Yibin
144 McLellan Avenue
San Mateo, California 94403
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: CN

State *(that is, country)* of residence: US

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATIONS

The filing of this request **constitutes under Rule 4.9(a), the designation** of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

☐ DE Germany **is not designated** for any kind of national protection
☐ JP Japan **is not designated** for any kind of national protection
☐ KR Republic of Korea **is not designated** for any kind of national protection
☐ RU Russian Federation **is not designated** for any kind of national protection

(The check-boxes above may only be used to exclude (irrevocably) the designations concerned if, at the time of filing or subsequently under Rule 26bis.1, the international application contains in Box No. VI a priority claim to an earlier national application filed in the particular State concerned, in order to avoid the ceasing of the effect, under the national law, of this earlier national application.)

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application: regional Office	international application: receiving Office
item (1) 14 July 2006 (14.07.2006)	60/831,042	US		
item (2)				
item (3)				

☐ Further priority claims are indicated in the Supplemental Box.

Transmit certified copy: the receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☒ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

Restore the right of priority: the receiving Office is requested to restore the right of priority for the earlier application(s) identified above or in the Supplemental Box as item(s) (_____). *(See also the Notes to Box No. VI; further information must be provided to support a request to restore the right of priority.)*

Incorporation by reference: where an element of the international application referred to in Article 11(1)(iii)(d) or (e) or a part of the description, claims or drawings referred to in Rule 20.5(a) is not otherwise contained in this international application but is completely contained in an earlier application whose priority is claimed on the date on which one or more elements referred to in Article 11(1)(iii) were first received by the receiving Office, that element or part is, subject to confirmation under Rule 20.6, incorporated by reference in this international application for the purposes of Rule 20.6.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA / EP

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following **declarations** are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*:		Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor :	
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent :	
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application :	
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America) :	
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty :	

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) **on paper**, the following number of sheets:

request (including declaration and supplemental sheets)	:	6
description (excluding sequence listing and/or tables related thereto)	:	137
claims	:	18
abstract	:	1
drawings	:	0
Sub-total number of sheets	:	162
sequence listing	:	
tables related thereto	:	
(for both, actual number of sheets if filed on paper, whether or not also filed in electronic form; see (c) below)		
Total number of sheets	:	162

(b) ☐ **only in electronic form** (Section 801(a)(i))
- (i) ☐ sequence listing
- (ii) ☐ tables related thereto

(c) ☐ **also in electronic form** (Section 801(a)(ii))
- (i) ☐ sequence listing
- (ii) ☐ tables related thereto

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the
- ☐ sequence listing: .....
- ☐ tables related thereto: .....

(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)

This international application is **accompanied by** the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*:

		Number of items
1. ☒ fee calculation sheet	:	1
2. ☐ original separate power of attorney	:	
3. ☐ original general power of attorney	:	
4. ☐ copy of general power of attorney; reference number, if any:	:	
5. ☐ statement explaining lack of signature	:	
6. ☐ priority document(s) identified in Box No. VI as item(s):	:	
7. ☐ translation of international application into *(language)*:	:	
8. ☐ separate indications concerning deposited microorganism or other biological material	:	
9. ☐ sequence listing in electronic form *(indicate type and number of carriers)*		
(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	:	
(ii) ☐ *(only where check-box (b)(i) or (c)(i) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:	
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column	:	
10. ☐ tables in electronic form related to sequence listing *(indicate type and number of carriers)*		
(i) ☐ copy submitted for the purposes of international search under Section 802(b-*quater*) only (and not as part of the international application)	:	
(ii) ☐ *(only where check-box (b)(ii) or (c)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-*quater*)	:	
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column	:	
11. ☒ other *(specify)*: Certificate of Service and postcard	:	2

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Lisa M. Seaney, Ph.D.
Agent for Applicant

For receiving Office use only

1. Date of actual receipt of the purported international application:		2. Drawings: ☐ received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		☐ not received:
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid	

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International Application No.

Date stamp of the receiving Office

Applicant's or agent's file reference 10709-240

Applicant

ChemoCentryx, Inc., et al.

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . 300 [T]

2. SEARCH FEE . . . . . 2059 [S]

International search to be carried out by EP

(If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FILING FEE

Where items (b) and/or (c) of Box No. IX apply, enter **Sub-total number of sheets** } 162
Where items (b) and (c) of Box No. IX do not apply, enter **Total number of sheets** }

[i1] first 30 sheets . . . . . 1086 [i1]

[i2] 132 (number of sheets in excess of 30) x 12 (fee per sheet) = 1584 [i2]

[i3] additional component (only if a sequence listing and/or tables related thereto are filed in electronic form under Section 801(a)(i), or both in that form and on paper, under Section 801(a)(ii)):

400 x _____ (fee per sheet) = _____ [i3]

Add amounts entered at i1, i2 and i3 and enter total at I . . . . 2670 [I]

(Applicants from certain States are entitled to a reduction of 75% of the international filing fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the international filing fee.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . 20 [P]

5. TOTAL FEES PAYABLE . . . . . 5049 TOTAL

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

MODE OF PAYMENT *(Not all modes of payment may be available at all receiving Offices)*

[X] authorization to charge deposit account (see below) [ ] postal money order [ ] cash [ ] coupons

[ ] cheque [ ] bank draft [ ] revenue stamps [ ] other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all receiving Offices)

[X] Authorization to charge the total fees indicated above.

[X] *(This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

[X] Authorization to charge the fee for priority document.

Receiving Office: RO/ US

Deposit Account No.: 23-1925

Date: July 10, 2007

Name: Lisa M. Seaney, Ph.D.

Signature: [signature]

See Notes to the fee calculation sheet

109374

454

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPL NO.	FILING OR 371 (c) DATE	ART UNIT	FIL FEE REC'D	ATTY.DOCKET NO	DRAWINGS	TOT CLMS	IND CLMS
60/831,042	07/13/2006		225	10709-161			

00757
BRINKS HOFER GILSON & LIONE
P.O. BOX 10395
CHICAGO, IL 60610

BRINKS HOFER GILSON & LIONE
RECEIVED
AUG 0 8 2006
RECEIVED
U. S. DOCKET

CONFIRMATION NO. 4821

FILING RECEIPT

OC000000019774351

Date Mailed: 07/27/2006

Receipt is acknowledged of this provisional Patent Application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please mail to the Commissioner for Patents P.O. Box 1450 Alexandria Va 22313-1450. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s)

Solomon Ungashe, Fremont, CA;
Yibin Zeng, San Mateo, CA;
Sreenivas Punna, Sunnyvale, CA;
Jeff Jin, Freemont, CA;
Arindrajit Basak, Mountain View, CA;
Trevor T. Charvat, San Jose, CA;
Jimmie Moore, Redwood City, CA;
Aaron Novak, Mountain View, CA;

Power of Attorney:
Lisa Seaney--56246

Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: Not applicable

Early-Publication Request: Not applicable

**** SMALL ENTITY ****

Title

Triazole sulfonamides

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

455

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of

Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

456

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

109374
457

UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

SEPTEMBER 01, 2006

PTAS

500146389A

500146389A

LISA SEANEY
P.O BOX 10395
CHICAGO, IL 60610-0395

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM 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 EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 571-272-3350. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT SERVICES BRANCH, P.O. BOX 1450, ALEXANDRIA, VA 22313.

RECORDATION DATE: 09/01/2006

REEL/FRAME: 018199/0714
NUMBER OF PAGES: 12

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).
DOCKET NUMBER: 10709-161

ASSIGNOR:
UNGASHE, SOLOMON — DOC DATE: 08/16/2006

ASSIGNOR:
ZENG, YIBIN — DOC DATE: 08/17/2006

ASSIGNOR:
PUNNA, SREENIVAS — DOC DATE: 08/17/2006

ASSIGNOR:
JIN, JEFF — DOC DATE: 08/16/2006

ASSIGNOR:
BASAK, ARINDRAJIT — DOC DATE: 08/16/2006

458

ASSIGNOR:
CHARVAT, TREVOR T. DOC DATE: 08/16/2006

ASSIGNOR:
MOORE, JIMMIE DOC DATE: 08/16/2006

ASSIGNOR:
NOVACK, AARON DOC DATE: 08/16/2006

ASSIGNEE:
CHEMOCENTRYX, INC.
850 MAUDE AVENUE
MOUNTAIN VIEW, CALIFORNIA 94043

SERIAL NUMBER: 60831042 FILING DATE: 07/14/2006
PATENT NUMBER: ISSUE DATE:
TITLE: TRIAZOLE SULFONAMIDES

ASSIGNMENT SERVICES BRANCH
PUBLIC RECORDS DIVISION

PATENT ASSIGNMENT

459

Electronic Version v1.1
Stylesheet Version v1.1

09/01/2006
500146389

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
Solomon Ungashe	08/16/2006
Yibin Zeng	08/17/2006
Sreenivas Punna	08/17/2006
Jeff Jin	08/16/2006
Arindrajit Basak	08/16/2006
Trevor T. Charvat	08/16/2006
[illegible]mmie Moore	08/16/2006
Aaron Novack	08/16/2006

RECEIVING PARTY DATA

Name:	ChemoCentryx, Inc.
Street Address:	850 Maude Avenue
City:	Mountain View
State/Country:	CALIFORNIA
Postal Code:	94043

PROPERTY NUMBERS Total: 1

Property Type	Number
Application Number:	60831042

CH $40.00 60831042

CORRESPONDENCE DATA

Fax Number: (312)321-4299
Correspondence will be sent via US Mail when the fax attempt is unsuccessful.
Phone: 312-321-4255
Email: lseaney@brinkshofer.com
Correspondent Name: Lisa Seaney
Address Line 1: P.O Box 10395
Address Line 4: Chicago, ILLINOIS 60610-0395

US DOCKET
COURTESY COPY ATTORNEY

ATTORNEY DOCKET NUMBER:	10709-161
NAME OF SUBMITTER:	Lisa Seaney

Total Attachments: 10
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Case No. 10709/161

ASSIGNMENT

WHEREAS, Solomon Ungashe, Yibin Zeng, Sreenivas Punna, Jeff Jin, Arindrajit Basak, Trevor T. Charvat, Jimmie Moore, and Aaron Novack, hereinafter called the "Assignors", have made the invention described in the United States patent application entitled TRIAZOLE SULFONAMIDES, for a full description of which reference is here made to an application for Letters Patent of the United States filed on July 14, 2006, and assigned Application Serial No. 60/831,042;

WHEREAS, ChemoCentryx, Inc., a corporation organized and existing under the laws of the State of Delaware, having a place of business at 850 Maude Avenue, Mountain View, CA 94043, hereinafter called the "Assignee", desires to acquire the entire right, title and interest in and to the invention and the patent application identified above, and all patents which may be obtained for said invention, as set forth below;

NOW, THEREFORE, in consideration of the sum of One Dollar ($1.00), and other valuable and legally sufficient consideration, the receipt of which by the Assignors from the Assignee is hereby acknowledged, the Assignors have sold, assigned and transferred, and by these presents do sell, assign and transfer to the Assignee, the entire right, title and interest for the United States in and to the invention and the patent application identified above, and any patents that may issue for said invention in the United States; together with the entire right, title and interest in and to said invention and all patent applications and patents therefor in all countries foreign to the United States, including the full right to claim for any such application all benefits and priority rights under any applicable convention; together with the entire right, title and interest in and to all continuations, divisions, renewals and extensions of any of the patent applications and patents defined above; to have and to hold for the sole and exclusive use and benefit of the Assignee, its successors and assigns, to the full end of the term or terms for all such patents.

The Assignors hereby covenant and agree, for both the Assignors and the Assignors' legal representatives, that the Assignors will assist the Assignee in the prosecution of the patent application identified above; in the making and prosecution of any other patent applications that the Assignee may elect to make covering the invention identified above; in

vesting in the Assignee like exclusive title in and to all such other patent applications and patents; and in the prosecution of any interference which may arise involving said invention, or any such patent application or patent; and that the Assignors will execute and deliver to the Assignee any and all additional papers which may be requested by the Assignee to carry out the terms of this Assignment.

The Commissioner of Patents and Trademarks is hereby authorized and requested to issue patents to the Assignee in accordance with the terms of this Assignment.

IN TESTIMONY WHEREOF, the Assignors have executed this agreement.

DATED: 8/16/06 — Solomon Ungashe

DATED: 8/17/06 — Yibin Zeng

DATED: 8/17/06 — Sreenivas Punna

DATED: 8/16/06 — Jeff Jin

DATED: 8/16/06 — Arindrajit Basak

DATED: 8/16/06 — Trevor T. Charvat

DATED: 8/16/06 — Jimmie Moore

DATED: 8/16/06 — Aaron ~~Novak~~ NOVACK

STATE OF California)
) ss.
COUNTY OF San Mateo)

I, Patrice Henderson, a Notary Public in and for the County and State aforesaid, do hereby certify that Solomon Ungashe, personally known to me to be the same person whose name is subscribed to the foregoing instrument, appeared before me this day in person and acknowledged that (s)he signed, sealed and delivered the said instrument as his/her free and voluntary act for the uses and purposes therein set forth.

IN WITNESS WHEREOF, I have hereunto set my hand and Notarial Seal, this 16 day of Aug, 2006.

Patrice Henderson
Notary Public

My Commission Expires:

OFFICIAL SEAL
PATRICE HENDERSON
COMMISSION #1517977
NOTARY PUBLIC-CALIFORNIA
COUNTY OF SAN MATEO
My Commission Expires Oct. 4, 2008

STATE OF California)
) ss.
COUNTY OF San Mateo)

I, Patrice Henderson, a Notary Public in and for the County and State aforesaid, do hereby certify that Yibin Zeng, personally known to me to be the same person whose name is subscribed to the foregoing instrument, appeared before me this day in person and acknowledged that (s)he signed, sealed and delivered the said instrument as his/her free and voluntary act for the uses and purposes therein set forth.

IN WITNESS WHEREOF, I have hereunto set my hand and Notarial Seal, this 17 day of Aug, 2006.

Patrice Henderson
Notary Public

My Commission Expires:

OFFICIAL SEAL
PATRICE HENDERSON
COMMISSION #1517977
NOTARY PUBLIC-CALIFORNIA
COUNTY OF SAN MATEO
My Commission Expires Oct. 4, 2008

STATE OF California)
) ss.
COUNTY OF San Mateo)

I, Patrice Henderson, a Notary Public in and for the County and State aforesaid, do hereby certify that Sreenivas Punna, personally known to me to be the same person whose name is subscribed to the foregoing instrument, appeared before me this day in person and acknowledged that (s)he signed, sealed and delivered the said instrument as his/her free and voluntary act for the uses and purposes therein set forth.

IN WITNESS WHEREOF, I have hereunto set my hand and Notarial Seal, this 17 day of Aug., 2006.

Patrice Henderson
Notary Public

My Commission Expires:

OFFICIAL SEAL
PATRICE HENDERSON
COMMISSION #1517977
NOTARY PUBLIC-CALIFORNIA
COUNTY OF SAN MATEO
My Commission Expires Oct. 4, 2008

STATE OF California)
) ss.
COUNTY OF San Mateo)

I, Patrice Henderson, a Notary Public in and for the County and State aforesaid, do hereby certify that Jeff Jin, personally known to me to be the same person whose name is subscribed to the foregoing instrument, appeared before me this day in person and acknowledged that (s)he signed, sealed and delivered the said instrument as his/her free and voluntary act for the uses and purposes therein set forth.

IN WITNESS WHEREOF, I have hereunto set my hand and Notarial Seal, this 16 day of Aug, 2006.

Patrice Henderson
Notary Public

My Commission Expires:

OFFICIAL SEAL
PATRICE HENDERSON
COMMISSION #1517977
NOTARY PUBLIC-CALIFORNIA
COUNTY OF SAN MATEO
My Commission Expires Oct. 4, 2008

STATE OF California)
) ss.
COUNTY OF San Mateo)

I, Patrice Henderson, a Notary Public in and for the County and State aforesaid, do hereby certify that Arindrajit Basak, personally known to me to be the same person whose name is subscribed to the foregoing instrument, appeared before me this day in person and acknowledged that (s)he signed, sealed and delivered the said instrument as his/her free and voluntary act for the uses and purposes therein set forth.

IN WITNESS WHEREOF, I have hereunto set my hand and Notarial Seal, this 16 day of Aug, 2006.

Patrice Henderson
Notary Public

My Commission Expires:

OFFICIAL SEAL
PATRICE HENDERSON
COMMISSION #1517977
NOTARY PUBLIC-CALIFORNIA
COUNTY OF SAN MATEO
My Commission Expires Oct. 4, 2008

STATE OF California)
) ss.
COUNTY OF San Mateo)

I, Patrice Henderson, a Notary Public in and for the County and State aforesaid, do hereby certify that Trevor T. Charvat, personally known to me to be the same person whose name is subscribed to the foregoing instrument, appeared before me this day in person and acknowledged that (s)he signed, sealed and delivered the said instrument as his/her free and voluntary act for the uses and purposes therein set forth.

IN WITNESS WHEREOF, I have hereunto set my hand and Notarial Seal, this 16 day of Aug, 2006.

Patrice Henderson
Notary Public

My Commission Expires:

OFFICIAL SEAL
PATRICE HENDERSON
COMMISSION #1517977
NOTARY PUBLIC-CALIFORNIA
COUNTY OF SAN MATEO
My Commission Expires Oct. 4, 2008

469

STATE OF California)
) ss.
COUNTY OF San Mateo)

I, Patrice Henderson, a Notary Public in and for the County and State aforesaid, do hereby certify that Jimmie Moore, personally known to me to be the same person whose name is subscribed to the foregoing instrument, appeared before me this day in person and acknowledged that (s)he signed, sealed and delivered the said instrument as his/her free and voluntary act for the uses and purposes therein set forth.

IN WITNESS WHEREOF, I have hereunto set my hand and Notarial Seal, this 16 day of Aug, 2006.

Patrice Henderson
Notary Public

My Commission Expires:

OFFICIAL SEAL
PATRICE HENDERSON
COMMISSION #1517977
NOTARY PUBLIC-CALIFORNIA
COUNTY OF SAN MATEO
My Commission Expires Oct. 4, 2008

470

STATE OF California)
) ss.
COUNTY OF San Mateo)

I, Patrice Henderson, a Notary Public in and for the County and State aforesaid, do hereby certify that Aaron Novak, personally known to me to be the same person whose name is subscribed to the foregoing instrument, appeared before me this day in person and acknowledged that (s)he signed, sealed and delivered the said instrument as his/her free and voluntary act for the uses and purposes therein set forth.

IN WITNESS WHEREOF, I have hereunto set my hand and Notarial Seal, this 16 day of Aug, 2006.

Patrice Henderson
Notary Public

My Commission Expires:

OFFICIAL SEAL
PATRICE HENDERSON
COMMISSION #1517977
NOTARY PUBLIC-CALIFORNIA
COUNTY OF SAN MATEO
My Commission Expires Oct. 4, 2008

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
POT

PATENTE DE INVENCION [✓] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de 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 [✓]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Fecha

No. 09-010534- -00000-0000

Fecha: 2009-02-04 16:31:39 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 470

Carrera 13 No. 27-00 Piso 6, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CADENA SARMIENTO JUAN PABLO

REFERENCIA	Radicación No.	9 10534
	Solicitud internacional	PCT/US2007/015808
	Fecha inicio fase nacional	14/02/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	2267

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

Continua en la página siguiente...

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Radicación No.:9 10534

DORIS ELENA POLO CORDOBA
Jefe de la división de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista de fecha 27 FEB. 2009
adpall