Industria y Comercio
SUPERINTENDENCIA
República de Colombia
Ministerio de Comercio, Industria y Turismo

CSA836328 Organización y Digitalización CSA Ltda

PCT

Delegatura de Propiedad Industrial
División de Nuevas

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-098383- -00000-0000
Fecha: 2010-08-11 13:38:17 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 488

SOLICITUD

PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No. 10-98383

54. TITULO: **DERIVADOS HETEROCÍCLICOS FUSIONADOS Y MÉTODOS DE USO COMO INHIBIDORES C-MET**

52. CLASIFICACION INTERNACIONAL: **C07D 471/04, A61K 31/4355, A61P 35/00**

71. SOLICITANTE: **AMGEN INC.**

DOMICILIO: **One Amgen Center Drive, Thousand Oaks, California 91320-1799, ESTADOS UNIDOS DE AMERICA**

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

22. BOGOTA, D.C., _____

Pdex ~ Tit.
15-08-2010

Industria y Comercio
SUPERINTENDENCIA

PETITO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-098383- -00000-0000
Fecha: 2010-08-11 13:38:17 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 488

ication

FORMULARIO UNICO DE SOLICITUD DE PATENTES
PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE:

(1)

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

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

(2) **SOLICITANTE (71)**

Nombre: **AMGEN INC.**

Dirección: **One Amgen Center Drive**
Thousand Oaks,
California 91320-1799
ESTADOS UNIDOS DE AMERICA

Domicilio: **Thousand Oaks, California,**
ESTADOS UNIDOS DE AMERICA

Lugar de Constitución: **ESTADOS UNIDOS DE AMERICA**

Teléfono: Fax:
E-mail:

IDENTIFICACIÓN

C.C. [ ] NIT [ ]

C.E. [ ] Otro [ ]

Número _____ Cual _____

(3) **REPRESENTANTE O APODERADO**

Nombre: **MARGARITA CASTELLANOS A.**

Dirección: **CALLE 94A No. 7A-09**

Teléfono: **7560770** Fax: **7550158**

E-mail: info@castellanosyco.com

IDENTIFICACIÓN

C.C. [X] NIT [ ]

C.E. [ ] Otro [ ] Cual _____

Número **39'779.654** TPA **70.819**

(4) **INVENTOR (ES) (72)**

VER ANEXO No. 1

(5) **PCT (86)**

Solicitud Internacional No. **PCT/US2008/011724** Fecha **14/10/2008**

Publicación Internacional No. **WO 2009/091374 A3** Fecha **23/07/2009**

(6) **Título (54)** **DERIVADOS HETEROCICLICOS FUSIONADOS Y METODOS DE USO COMO INHIBIDORES C-MET** (Folio 492)

(7) **Clasificación Internacional (51)** **C07D 471/04, A61K 31/4355, A61P 35/00**

(8) **Prioridad**

SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	15/01/2008	12/009,123

(9) **Comprobantes de pago Nos.** 10-65641 y 10-65642 **Fecha** 10-AGO-2010

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

(10) Anexos

000002

- [X] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [ ] Poderes, si fuere el caso, junto con la sustitución del mismo a mi favor
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [X] Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos).
- [X] Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: **Tarjeta Propietario, Extracto para la publicación, Formas PCT/IB/306**

(11) FIGURA CARACTERISTICA:

(12) Solicito la concesión de la patente,

NOMBRE: **MARGARITA CASTELLANOS ABONDANO**

FIRMA:

C.C. No. 39'779.654 Usaquén - TPA 70.819 C.S.J.

CASTELLANOS & CO LTDA
ABOGADOS
Calle 94 A No. 7 A-09
Bogotá, D.C. – COLOMBIA

ANEXO # 1
INVENTORES

1. **TAE-SEONG KIM**
1580 Dover Avenue,
Thousand Oaks, CALIFORNIA 91360
ESTADOS UNIDOS DE AMERICA

2. **DAVID BAUER**
627 Concord Road,
Sudbury, MASSACHUSETTS 01776
ESTADOS UNIDOS DE AMERICA

3. **STEVEN BELLON**
14 Greenlawn Avenue,
Wellesley, MASSACHUSETTS 02139
ESTADOS UNIDOS DE AMERICA

4. **ALESSANDRO BOEZIO**
54 Myrtle Street, Unit #1,
Somerville, MASSACHUSETTS 02145
ESTADOS UNIDOS DE AMERICA

5. **SHON BOOKER**
71 McAfee Court,
Thounsand Oaks, CALIFORNIA 91360
ESTADOS UNIDOS DE AMERICA

6. **DEBORAH CHOQUETTE**
17 Blakely Road,
Medford, MASSACHUSETTS 02155
ESTADOS UNIDOS DE AMERICA

7. **DERIN D'AMICO**
4571 Calle Norte,
Newbury Park, CALIFORNIA 91320
ESTADOS UNIDOS DE AMERICA

8. **JEAN-CHRISTOPHE HARMANGE**
57 William Street,
Andover, MASSACHUSETTS 01810
ESTADOS UNIDOS DE AMERICA

9. **SATOKO HIRAI**
101 Monmouth Street # 320,
Brookline, MASSACHUSETTS 02446
ESTADOS UNIDOS DE AMERICA

10. **LONGBIN LIU**
753 Rushing Creek Place,
Thounsand Oaks, CALIFORNIA 91360
ESTADOS UNIDOS DE AMERICA

11. **MARK H. NORMAN**
130 Venus Street,
Thousand Oaks, CALIFORNIA 91360
ESTADOS UNIDOS DE AMERICA

12. **MICHELLE POTASHMAN**
19 Clary Street,
Cambridge, MASSACHUSETTS 02139
ESTADOS UNIDOS DE AMERICA

13. **AARON C. SIEGMUND**
311 Mariposa Drive,
Ventura, CALIFORNIA 93001
ESTADOS UNIDOS DE AMERICA

14. **NING XI**
565 Timberwood Avenue,
Thounsand Oaks, CALIFORNIA 91360
ESTADOS UNIDOS DE AMERICA

15. **KEVIN YANG**
8871 Camino Real Avenue,
San Gabriel, CALIFORNIA 91775
ESTADOS UNIDOS DE AMERICA

16. **BRIAN K. ALBRECHT**
163 Allston Street, # 3,
Cambridge, MASSACHUSETTS 02139
ESTADOS UNIDOS DE AMERICA

17. **CHRISTIANE M. BODE**
156 3rd Street,
Cambridge, MASSACHUSETTS 02141
ESTADOS UNIDOS DE AMERICA

18. **RANDALL W. HUNGATE**
640 W. Highland Drive,
Camarillo, CALIFORNIA 93010
ESTADOS UNIDOS DE AMERICA

19. **RICHARD T. LEWIS**
722 Grove Street,
Framingham, MASSACHUSETTS 01701
ESTADOS UNIDOS DE AMERICA

20. **JULIA LOHMAN**
94A Sussex Street,
San Francisco, CALIFORNIA 94131
ESTADOS UNIDOS DE AMERICA

21. **STEPHANIE SPRINGER**
271 Walden Street, # 2,
Cambridge, MASSACHUSETTS 02138
ESTADOS UNIDOS DE AMERICA

22. **MARKIAN STEC**
11210 Shadyridge Drive,
Moorpark, CALIFORNIA 93021
ESTADOS UNIDOS DE AMERICA

23. **EMILY ANNE PETERSON**
60 Fairfield Street Apt. 3,
Cambridge, MASSACHUSETTS 024140
ESTADOS UNIDOS DE AMERICA

24. **KARINA ROMERO**
2 Lamont Avenue,
Cambridge, MASSACHUSETTS 02138
ESTADOS UNIDOS DE AMERICA

25. **KATRINA W. COPELAND**
17 Oakridge Road,
Sudbury, MASSACHUSETTS 01776
ESTADOS UNIDOS DE AMERICA

2022

000006

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 65,641
FECHA : AGOSTO 10 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-098383- -00000-0000
Fecha: 2010-08-11 13:38:17 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 488

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754387	383932942	10/08/2010	3,037,000.00

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

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

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

000007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800[illegible]

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-098383- -00000-0000

Fecha: 2010-08-11 13:38:17 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 488

RECIBO OFICIAL DE CAJA : 10 - 65,642
FECHA : AGOSTO 10 DE 2010

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754387	383932942	10/08/2010	3,037,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
6	50005-01-01 SOLICITUDES	*** REIVINDICACION UNITARIA ADICIONAL	156,000.00
		TOTAL : $	156,000.00

SON: CIENTO CINCUENTA Y SEIS MIL PESOS

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
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PCT

(10) International Publication Number
WO 2009/091374 A3

(51) International Patent Classification:
C07D 471/04 (2006.01) *A61K 31/4365* (2006.01)
C07D 487/04 (2006.01) *A61K 31/437* (2006.01)
C07D 493/04 (2006.01) *A61K 31/4375* (2006.01)
C07D 495/04 (2006.01) *A61K 31/5377* (2006.01)
C07D 498/04 (2006.01) *A61P 35/00* (2006.01)
A61K 31/4355 (2006.01)

(21) International Application Number:
PCT/US2008/011724

(22) International Filing Date:
14 October 2008 (14.10.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
12/009,123 15 January 2008 (15.01.2008) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 12/009,123 (CIP)
Filed on 15 January 2008 (15.01.2008)

(71) Applicant *(for all designated States except US)*: **AMGEN INC.** [US/US]; One Amgen Center Drive, Thousand Oaks, California 91320-1799 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ALBRECHT, Brian K.** [US/US]; 179 Chestnut Street, #2, Cambridge, Massachusetts 02139 (US). **BAUER, David** [FR/US]; 627 Concord Road, Sudbury, Massachusetts 01776 (US). **BELLON, Steven** [US/US]; 14 Greenlawn Avenue, Wellesley, Massachusetts 02139 (US). **BODE, Christiane M.** [US/US]; 156 3rd Street, Cambridge, Massachusetts 02141 (US). **BOOKER, Shon** [US/US]; 71 McAfee Court, Thousand Oaks, California 91360 (US). **BOEZIO, Alessandro** [CA/US]; 54 Myrtle Street, Somerville, Massachusetts 02145 (US). **CHOQUETTE, Deborah** [US/US]; 17 Blakely Road, Medford, Massachusetts 02155 (US). **D'AMICO, Erin** [US/US]; 4571 Calle Norte, Newbury Park, California 91320 (US). **HARMANGE, Jean-christophe** [FR/US]; 57 William Street, Andover, Massachusetts 01810 (US). **HIRAI, Satoko** [JP/US]; 101 Monmouth Street, #320, Brookline, Massachusetts 02446 (US). **HUNGATE, Randall W.** [US/US]; 650 W. Highland Drive, Camarillo, California 93010 (US). **KIM, Tae-seong** [US/US]; 1580 Dover Avenue, Thousand Oaks, California 91360 (US). **LEWIS, Richard T.** [GB/US]; 722 Grove Street, Framingham, Massachusetts 01701 (US). **LIU, Longbin** [US/US]; 753 Rushing Creek Place, Thousand Oaks, California 91360 (US). **LOHMAN, Julia** [US/US]; 9 Dana Street, Cambridge, Massachusetts 02138 (US). **NORMAN, Mark H.** [US/US]; 130 Venus Street, Thousand Oaks, California 91360 (US). **POTASHMAN, Michelle** [US/US]; 19 Clary Street, Cambridge, Massachusetts 02139 (US). **SIEGMUND, Aaron C.** [US/US]; 311 Mariposa Drive, Ventura, California 93001 (US). **SPRINGER, Stephanie** [US/US]; 271 Walden Street, #2, Cambridge, Massachusetts 02138 (US). **STEC, Markian** [US/US]; 11210 Shadyridge Drive, Moorpark, California 93021 (US). **XI, Ning** [US/US]; 565 Timberwood Avenue, Thousand Oaks, California 91360 (US). **YANG, Kevin** [US/US]; 8871 Camino Real Avenue, San Gabriel, California 91775 (US). **PETERSON, Emily, A.** [US/US]; 60, Fairfield Street, Apt. 3, Cambridge, Massachusetts 024140 (US). **ROMERO, Karina** [PE/US]; 2 Lamont Avenue, Cambridge, MA 02138 (US). **COPELAND, Katrina, W.** [US/US]; 17 Oakridge Road, Sudbury, MA 01776 (US).

(74) Agent: **HERMENAU, Ronald S.**; 1120 Veterans Boulevard, South San Francisco, California 94080 (US).

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

(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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
17 December 2009

(54) Title: FUSED HETEROCYCLIC DERIVATIVES AND METHODS OF USE AS C-MET INHIBITORS

(57) Abstract: Selected compounds are effective for prophylaxis and treatment of diseases, such as HGF mediated diseases. The invention encompasses novel compounds, analogs, prodrugs and pharmaceutically acceptable salts thereof, pharmaceutical compositions and methods for prophylaxis and treatment of diseases and other maladies or conditions involving, cancer and the like. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

WO 2009/091374 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/011724

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 C07D487/04 C07D493/04 C07D495/04 C07D498/04
A61K31/4355 A61K31/4365 A61K31/437 A61K31/4375 A61K31/5377
A61P35/00

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 A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, 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 2007/075567 A (JANSSEN PHARMACEUTICA NV [BE]; LU TIANBAO [US]; ALEXANDER RICHARD [US]) 5 July 2007 (2007-07-05) page 1, line 13 - line 15; claims 1-48; examples 1-104	1-10, 12-17
X	WO 2007/138472 A (PFIZER PROD INC [US]; CHENG HENGMIAO [US]; CUI JINGRONG JEAN [US]; HOF) 6 December 2007 (2007-12-06) page 5, line 4 - line 10; claims 1-13; compound 5	1,12-17
P,X	WO 2008/008539 A (AMGEN INC [US]; ALBRECHT BRIAN [US]; BAUER DAVID [US]; BELLON STEVEN [) 17 January 2008 (2008-01-17) the whole document	1,12-17

-/--

[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
20 October 2009	02/11/2009

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/011724

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2008/155378 A (JANSSEN PHARMACEUTICA NV [BE]; GOVAERTS TOM CORNELIS HORTENSE [BE]; WE) 24 December 2008 (2008-12-24) the whole document	1,12-17
P,X	WO 2008/051805 A (SGX PHARMACEUTICALS INC [US]; SMITH CHRISTOPHER RONALD [US]; BOUNAUD P) 2 May 2008 (2008-05-02) the whole document	1,12-17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/011724

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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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:

see additional sheet

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.:

1-10,12-17

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1(part), 12(part)-17(part)

   The 134 specific compounds of claim 1 that fall within formula I in which R1 is not oxo substituted, pharmaceutical compositions containing them and their use

   ---

2. claims: 1(part), 2-10, 12(part)-17(part)

   The 35 specific compounds of claim 1 that fall within formula I in which R1 bears a carbonyl group, the compounds of formula I of claim 2, and the compounds of formula IJ of claim 7, pharmaceutical compositions containing them and their use

   ---

3. claim: 11

   The compounds of formula VII of claim 11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/011724

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007075567 A	05-07-2007	AR 058703 A1	20-02-2008
		AU 2006331912 A1	05-07-2007
		CA 2634721 A1	05-07-2007
		CN 101374843 A	25-02-2009
		EA 200870085 A1	30-12-2008
		EC SP088573 A	30-07-2008
		EP 1966214 A1	10-09-2008
		JP 2009525263 T	09-07-2009
		KR 20080085154 A	23-09-2008
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		UY 30041 A1	31-05-2007
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		EP 2032578 A2	11-03-2009
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		AU 2007272783 A1	17-01-2008
		CA 2657327 A1	17-01-2008
		CN 101528743 A	09-09-2009
		CR 10614 A	23-03-2009
		EA 200900178 A1	30-06-2009
		EP 2081931 A2	29-07-2009
		KR 20090029843 A	23-03-2009
		US 2009124612 A1	14-05-2009
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WO 2008051805 A	02-05-2008	AU 2007309237 A1	02-05-2008
		CA 2667453 A1	02-05-2008
		EP 2081937 A2	29-07-2009
		KR 20090069303 A	30-06-2009

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 July 2009 (23.07.2009)

PCT

(10) International Publication Number
WO 2009/091374 A2

(51) International Patent Classification:
C07D 471/04 (2006.01) *C07D 495/04* (2006.01)
C07D 487/04 (2006.01) *C07D 498/04* (2006.01)
C07D 493/04 (2006.01) *A61K 31/4355* (2006.01)

(21) International Application Number:
PCT/US2008/011724

(22) International Filing Date: 14 October 2008 (14.10.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
12/009,123 15 January 2008 (15.01.2008) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 12/009,123 (CIP)
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(71) Applicant *(for all designated States except US)*: **AMGEN INC.** [US/US]; One Amgen Center Drive, Thousand Oaks, California 91320-1799 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ALBRECHT, Brian K.** [US/US]; 179 Chestnut Street, #2, Cambridge, Massachusetts 02139 (US). **BAUER, David** [FR/US]; 627 Concord Road, Sudbury, Massachusetts 01776 (US). **BELLON, Steven** [US/US]; 14 Greenlawn Avenue, Wellesley, Massachusetts 02139 (US). **BODE, Christiane M.** [US/US]; 156 3rd Street, Cambridge, Massachusetts 02141 (US). **BOOKER, Shon** [US/US]; 71 McAfee Court, Thousand Oaks, California 91360 (US). **BOEZIO, Alessandro** [CA/US]; 54 Myrtle Street, Somerville, Massachusetts 02145 (US). **CHOQUETTE, Deborah** [US/US]; 17 Blakely Road, Medford, Massachusetts 02155 (US). **D'AMICO, Erin** [US/US]; 4571 Calle Norte, Newbury Park, California 91320 (US). **HARMANGE, Jean-christophe** [FR/US]; 57 William Street, Andover, Massachusetts 01810 (US). **HIRAI, Satoko** [JP/US]; 101 Monmouth Street, #320, Brookline, Massachusetts 02446 (US). **HUNGATE, Randall W.** [US/US]; 650 W. Highland Drive, Camarillo, California 93010 (US). **KIM, Tae-seong** [US/US]; 1580 Dover Avenue, Thousand Oaks, California 91360 (US). **LEWIS, Richard T.** [GB/US]; 722 Grove Street, Framingham, Massachusetts 01701 (US). **LIU, Longbin** [US/US]; 753 Rushing Creek Place, Thousand Oaks, California 91360 (US). **LOHMAN, Julia** [US/US]; 9 Dana Street, Cambridge, Massachusetts 02138 (US). **NORMAN, Mark H.** [US/US]; 130 Venus Street, Thousand Oaks, California 91360 (US). **POTASHMAN, Michelle** [US/US]; 19 Clary Street, Cambridge, Massachusetts 02139 (US). **SIEGMUND, Aaron C.** [US/US]; 311 Mariposa Drive, Ventura, California 93001 (US). **SPRINGER, Stephanie** [US/US]; 271 Walden Street, #2, Cambridge, Massachusetts 02138 (US). **STEC, Markian** [US/US]; 11210 Shadyridge Drive, Moorpark, California 93021 (US). **XI, Ning** [US/US]; 565 Timberwood Avenue, Thousand Oaks, California 91360 (US). **YANG, Kevin** [US/US]; 8871 Camino Real Avenue, San Gabriel, California 91775 (US). **PETERSON, Emily, A.** [US/US]; 60, Fairfield Street, Apt. 3, Cambridge, Massachusetts 024140 (US). **ROMERO, Karina** [PE/US]; 2 Lamont Avenue, Cambridge, MA 02138 (US). **COPELAND, Katrina, W.** [US/US]; 17 Oakridge Road, Sudbury, MA 01776 (US).

(74) Agent: **HERMENAU, Ronald S.**; 1120 Veterans Boulevard, South San Francisco, California 94080 (US).

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

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(54) Title: FUSED HETEROCYCLIC DERIVATIVES AND METHODS OF USE

(57) Abstract: Selected compounds are effective for prophylaxis and treatment of diseases, such as HGF mediated diseases. The invention encompasses novel compounds, analogs, prodrugs and pharmaceutically acceptable salts thereof, pharmaceutical compositions and methods for prophylaxis and treatment of diseases and other maladies or conditions involving, cancer and the like. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

WO 2009/091374 A2

FUSED HETEROCYCLIC DERIVATIVES AND METHODS OF USE

FIELD OF THE INVENTION

This invention is in the field of pharmaceutical agents and specifically relates to compounds, compositions, uses and methods for treating cancer.

BACKGROUND OF THE INVENTION

Protein kinases represent a large family of proteins, which play a central role in the regulation of a wide variety of cellular processes, maintaining control over cellular function. A partial list of such kinases includes abl, Akt, bcr-abl, Blk, Brk, Btk, c-kit, c-Met, c-src, c-fms, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK10, cRaf1, CSF1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, Erk, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, flt-1, Fps, Frk, Fyn, Hck, IGF-1R, INS-R, Jak, KDR, Lck, Lyn, MEK, p38, PDGFR, PIK, PKC, PYK2, ros, tie, tie2, TRK, Yes, and Zap70. Inhibition of such kinases has become an important therapeutic target.

The hepatocyte growth factor receptor ("c-Met") is a unique receptor tyrosine kinase shown to be overexpressed in a variety of malignancies. c-Met typically comprises, in its native form, a 190-kDa heterodimeric (a disulfide-linked 50-kDa α-chain and a 145-kDa β-chain) membrane-spanning tyrosine kinase protein (Proc. Natl. Acad. Sci. USA, 84:6379-6383 (1987)). c-Met is mainly expressed in epithelial cells and stimulation of c-Met leads to scattering, angiogenesis, proliferation and metastasis. (See Cytokine and Growth Factor Reviews, 13:41-59 (2002)).

The ligand for c-Met is hepatocyte growth factor (also known as scatter factor, HGF and SF). HGF is a heterodimeric protein secreted by cells of mesodermal origin (Nature, 327:239-242 (1987); J. Cell Biol., 111:2097-2108 (1990)).

Various biological activities have been described for HGF through interaction with c-met (Hepatocyte Growth Factor- Scatter Factor (HGF-SF) and the c-Met Receptor, Goldberg and Rosen, eds., Birkhauser Verlag-Basel, 67-79 (1993). The biological effect of HGF/SF may depend in part on the target cell. HGF induces a spectrum of biological activities in epithelial cells, including mitogenesis, stimulation of cell motility and promotion of matrix invasion (Biochem. Biophys. Res. Comm., 122:1450-1459 (1984); Proc. Natl. Acad. Sci. U.S.A., 88:415-419 (1991)). It stimulates the motility and invasiveness of carcinoma cells, the former having been implicated in the migration of cells required for metastasis. HGF can also act as a "scatter factor", an activity that promotes the dissociation of epithelial and vascular endothelial

cells (Nature, 327:239-242 (1987); J. Cell Biol., 111:2097-2108 (1990); EMBO J., 10:2867-2878 (1991); Proc. Natl. Acad. Sci. USA, 90:649-653 (1993)). Therefore, HGF is thought to be important in tumor invasion (Hepatocyte Growth Factor-Scatter Factor (HGF-SF) and the C-Met Receptor, Goldberg and Rosen, eds., Birkhauser Verlag-Basel, 131-165 (1993)).

HGF and c-Met are expressed at abnormally high levels in a large variety of solid tumors. High levels of HGF and/or c-Met have been observed in liver, breast, pancreas, lung, kidney, bladder, ovary, brain, prostate, gallbladder and myeloma tumors in addition to many others. The role of HGF/c-Met in metastasis has been investigated in mice using cell lines transformed with HGF/c-Met (J. Mol. Med., 74:505-513 (1996)). Overexpression of the c-Met oncogene has also been suggested to play a role in the pathogenesis and progression of thyroid tumors derived from follicular epithelium (Oncogene, 7:2549-2553 (1992)). HGF is a morphogen (Development, 110:1271-1284 (1990); Cell, 66:697-711 (1991)) and a potent angiogenic factor (J. Cell Biol., 119:629-641 (1992)).

Recent work on the relationship between inhibition of angiogenesis and the suppression or reversion of tumor progression shows great promise in the treatment of cancer (Nature, 390:404-407 (1997)), especially the use of multiple angiogenesis inhibitors compared to the effect of a single inhibitor. Angiogenesis can be stimulated by HGF, as well as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF).

Angiogenesis, the process of sprouting new blood vessels from existing vasculature and arteriogenesis, the remodeling of small vessels into larger conduit vessels are both physiologically important aspects of vascular growth in adult tissues. These processes of vascular growth are required for beneficial processes such as tissue repair, wound healing, recovery from tissue ischemia and menstrual cycling. They are also required for the development of pathological conditions such as the growth of neoplasias, diabetic retinopathy, rheumatoid arthritis, psoriasis, certain forms of macular degeneration, and certain inflammatory pathologies. The inhibition of vascular growth in these contexts has also shown beneficial effects in preclinical animal models. For example, inhibition of angiogenesis by blocking vascular endothelial growth factor or its receptor has resulted in inhibition of tumor growth and in retinopathy. Also, the development of pathological pannus tissue in rheumatoid arthritis involves angiogenesis and might be blocked by inhibitors of angiogenesis.

The ability to stimulate vascular growth has potential utility for treatment of ischemia-induced pathologies such as myocardial infarction, coronary artery disease, peripheral vascular disease, and stroke. The sprouting of new vessels and/or the expansion of small vessels in ischemic tissues prevents ischemic tissue death and induces tissue repair. Certain diseases are

known to be associated with deregulated angiogenesis, for example ocular neovascularization, such as retinopathies (including diabetic retinopathy), age-related macular degeneration, psoriasis, hemangioblastoma, hemangioma, arteriosclerosis, inflammatory disease, such as a rheumatoid or rheumatic inflammatory disease, especially arthritis (including rheumatoid arthritis), or other chronic inflammatory disorders, such as chronic asthma, arterial or post-transplantational atherosclerosis, endometriosis, and neoplastic diseases, for example so-called solid tumors and liquid tumors (such as leukemias). Treatment of malaria and related viral diseases may also be mediated by HGF and cMet.

Elevated levels of HGF and c-Met have also been observed in non-oncological settings, such as hypertension, myocardial infarction and rheumatoid arthritis. It has been observed that levels of HGF increase in the plasma of patients with hepatic failure (Gohda et al., supra) and in the plasma (Hepatol., 13:734-750 (1991)) or serum (J. Biochem., 109:8-13 (1991)) of animals with experimentally induced liver damage. HGF has also been shown to be a mitogen for certain cell types, including melanocytes, renal tubular cells, keratinocytes, certain endothelial cells and cells of epithelial origin (Biochem. Biophys. Res. Commun., 176:45-51 (1991); Biochem. Biophys. Res. Commun., 174:831-838 (1991); Biochem., 30:9768-9780 (1991); Proc. Natl. Acad. Sci. USA, 88:415-419 (1991)). Both HGF and the c-Met proto-oncogene have been postulated to play a role in microglial reactions to CNS injuries (Oncogene, 8:219-222 (1993)).

Metastatic SCC cells overexpress c-Met and have enhanced tumoregenesis and metastasis in vivo [G. Gong et al., Oncogene, 23:6199-6208 (2004)]. C-Met is required for tumor cell survival [N. Shinomiya et al., Cancer Research, 64:7962-7970 (2004)]. For a general review see C. Birchmeier et al., Nature Reviews/Molecular Biology 4:915-925 (2003).

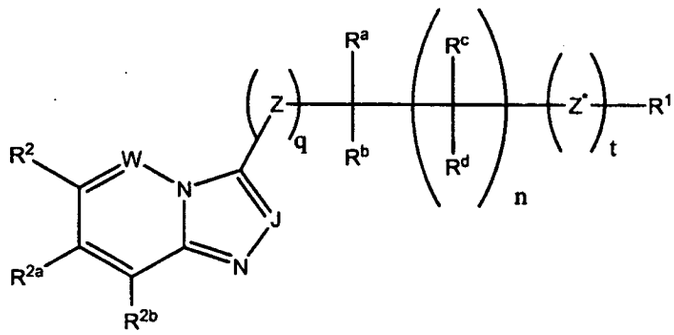
In view of the role of HGF and/or c-Met in potentiating or promoting such diseases or pathological conditions, it would be useful to have a means of substantially reducing or inhibiting one or more of the biological effects of HGF and its receptor. Thus a compound that reduces the effect of HGF would be a useful compound. Compounds of the current invention have not been previously described as inhibitors of angiogenesis such as for the treatment of cancer.

Sugen application WO 05/010005 describes certain Triazolotriazine compounds that are c-met inhibitors. Diamon Shamrock Corp. application WO 83/00864 discloses certain Triazolotriazine compounds that are useful as anti-inflammatory agents. Yamanouchi applications EP 1481955 and US 2005/0261297 disclose certain nitrogen-containing heterocyclic compounds that are therapeutic agents having a bone formation-stimulating effect.

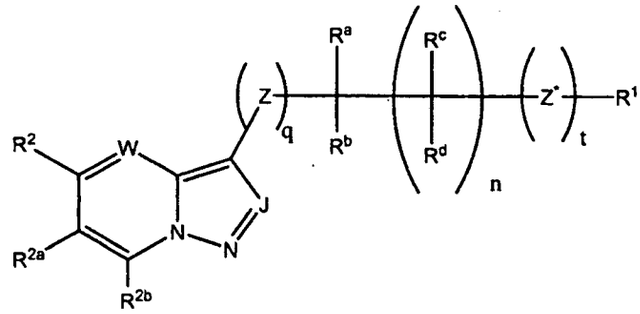
Compounds of the current invention are inhibitors of c-Met.

DESCRIPTION OF THE INVENTION

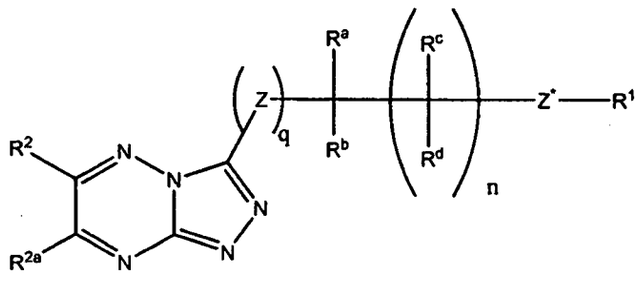
A class of compounds useful in treating cancer and angiogenesis is defined by Formulae I, II, III, IV, V, VI and VII



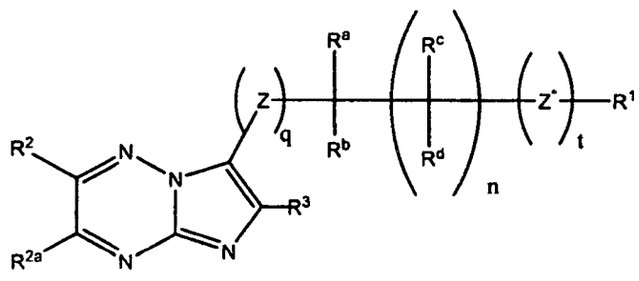
I



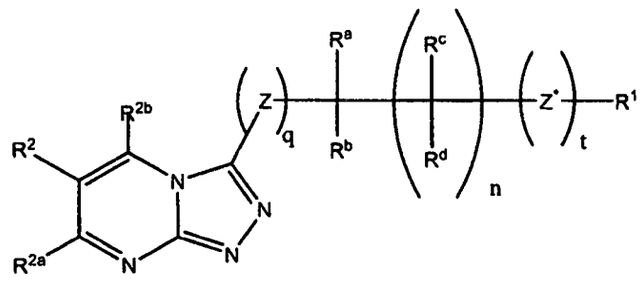
II



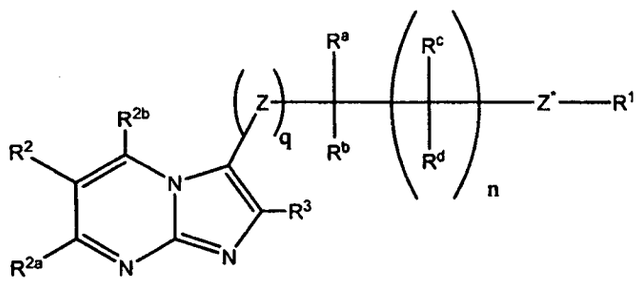
III



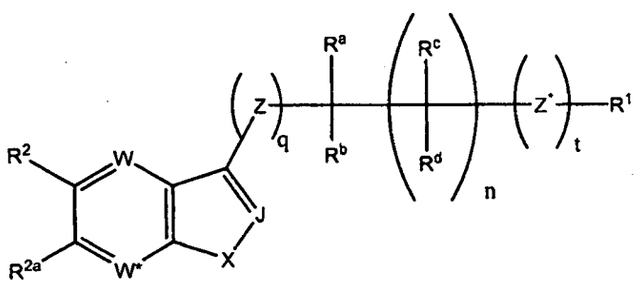
IV



V



VI



VII

enantiomers, diastereomers, salts and solvates thereof wherein

J is N or CR^3;

W is CR^{2b};

W* is N or CR^{2b};

X is O or S;

Z and Z* are independently -O-, $-S(O)_v-$, or $-NR^5-$;

R^a, R^b, R^c and R^d are each independently H, halo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, $-NO_2$, -CN, $-NR^5R^{5a}$, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$; $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-OC(=O)NR^5R^{5a}$, $-S(O)_vR^4$, $-S(O)_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$ any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

or R^a and R^b together with the carbon atom to which they are bonded may combine to form a 3-10 membered cycloalkyl, a 3-10membered cycloalkenyl ring, or a heterocyclo ring, any of which may be optionally substituted with one or more R^{10} groups as allowed by valance.;

or R^c and R^d together with the carbon atom to which they are bonded may combine to form a 3-10 membered cycloalkyl, a 3-10membered cycloalkenyl ring, or a heterocyclo ring, any of which may be optionally substituted with one or more R^{10} groups as allowed by valance;

or R^a and/or R^b may combine with any R^c or R^d to form a partially or fully saturated 3-8 membered cycloalkyl ring or heterocyclo ring, either of which may be optionally substituted with one or more R^{10} groups as allowed by valance;

or R^a and R^b may combine to form a carbonyl group;

or R^c and R^d attached to the same carbon atom may combine to form a carbonyl group;

R^1 is aryl, heteroaryl or heterocyclo any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

R^2 is

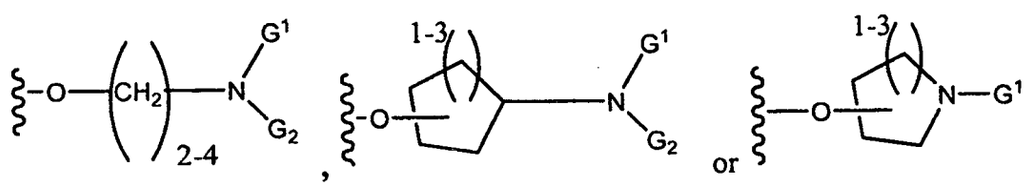
(i) H, halo, cyano, nitro, or

(ii) alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-OR^4$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, any of which may be optionally independently substituted with one or more R^{10} as allowed by valance,

provided that in compounds of formula I when W and J are both N, R^2 is other than

(a) $-NR^5R^{5a}$ where R^5 and R^{5a} are independently H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, and cycloalkylalkyl; and

(b) phenyl substituted with a group



where G^1 and G^2 are independently alkyl, cycloalkyl, or G^1 and G^2 together with the nitrogen atom to which they are attached combine to form a 5- to 8-membered heterocyclo ring;

R^{2a}, R^{2b} and R^3 are independently selected at each occurrence from H, halo, cyano, nitro, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl,

arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-OR^4$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

R^4 is independently selected at each occurrence from H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, and cycloalkylalkyl, any of which may be optionally independently substituted as allowed by valance with one or more R^{10} groups;

R^5 and R^{5a} are independently selected at each occurrence from H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, and cycloalkylalkyl, any of which may be optionally substituted as allowed by valance with one or more R^{10};

or R^5 and R^{5a} may combine to form a heterocyclo ring optionally substituted with one or more R^{10};

R^{10} at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-(alkylene)_m-OR^4$, $-(alkylene)_m-S(O)_vR^4$, $-(alkylene)_m-NR^5R^{5a}$, $-(alkylene)_m-C(=O)R^4$, $-(alkylene)_m-C(=S)R^4$, $-(alkylene)_m-C(=O)OR^4$, $-(alkylene)_m-OC(=O)R^4$, $-(alkylene)_m-C(=S)OR^4$, $-(alkylene)_m-C(=O)NR^5R^{5a}$, $-(alkylene)_m-C(=S)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=S)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)R^4$, $-(alkylene)_m-N(R^5)C(=S)R^4$, $-(alkylene)_m-OC(=O)NR^5R^{5a}$, $-(alkylene)_m-OC(=S)NR^5R^{5a}$, $-(alkylene)_m-SO_2NR^5R^{5a}$, $-(alkylene)_m-N(R^5)SO_2R^4$, $-(alkylene)_m-N(R^5)SO_2NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)OR^4$, $-(alkylene)_m-N(R^5)C(=S)OR^4$, or $-(alkylene)_m-N(R^5)SO_2R^4$;

wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more $-(alkylene)_m-OR^4$, $-(alkylene)_m-S(O)_vR^4$, $-(alkylene)_m-NR^5R^{5a}$, $-(alkylene)_m-C(=O)R^4$, $-(alkylene)_m-C(=S)R^4$, $-(alkylene)_m-C(=O)OR^4$, $-(alkylene)_m-OC(=O)R^4$, $-(alkylene)_m-C(=S)OR^4$, $-(alkylene)_m-C(=O)NR^5R^{5a}$, $-(alkylene)_m-C(=S)NR^5R^{5a}$,

-(alkylene)$_m$-N(R^5)C(=O)NR^5R^{5a}, -(alkylene)$_m$-N(R^5)C(=S)NR^5R^{5a},
-(alkylene)$_m$-N(R^5)C(=O)R^4, -(alkylene)$_m$-N(R^5)C(=S)R^4,
-(alkylene)$_m$-OC(=O)NR^5R^{5a}, -(alkylene)$_m$-OC(=S)NR^5R^{5a}, -(alkylene)$_m$-SO_2NR^5R^{5a},
-(alkylene)$_m$-N(R^5)SO_2R^4, -(alkylene)$_m$-N(R^5)SO_2NR^5R^{5a},
-(alkylene)$_m$-N(R^5)C(=O)OR^4, -(alkylene)$_m$-N(R^5)C(=S)OR^4, or
-(alkylene)$_m$-N(R^5)SO_2R^4;

and further wherein any two R^{10} groups attached to the same atom or attached to adjacent atoms may combine to form an optionally substituted 3- to 8 membered ring system;

m is 0 or 1;

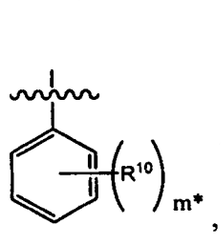
n is 0, 1 or 2;

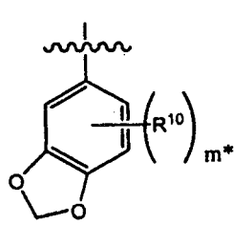
q and t are each independently 0 or 1;

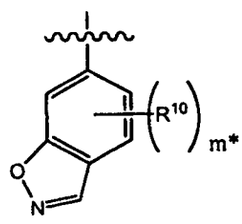
v is 0, 1 or 2.

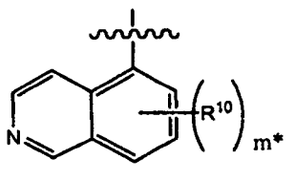
Preferred compounds include compounds wherein R^1 is phenyl, naphthyl, benzodioxolyl, benzooxazolyl, benzoisoxazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyrimidinyl, pyrazidinyl, isoquinolinyl, quinolinyl, quinazolinyl, quinazolinonyl, quinoxalinyl, naphthyridinyl, benzotriazinyl, triazolopyridinyl, triazolopyrimidinyl, triazolopyridazinyl, imidazopyridinyl, imidazopyrimidinyl, imidazopyridazinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, pyrrolopyridazinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrazolopyridazinyl, cinnolinyl, thienopyridinyl, thienopyrimidinyl, thienopyridazinyl, furopyridinyl, furopyrimidinyl, furopyrazidinyl, benzofuranyl, benzoimidazolyl, indolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, pyridopyrimidinyl, oxazolopyridinyl, thiazolopyridinyl, pyrazolopyrazinyl, triazolopyrazinyl and triazolopyridinyl any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance.

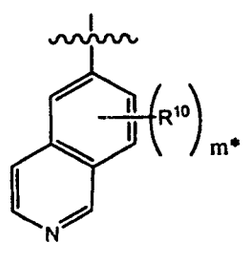
Preferred R^1 groups include

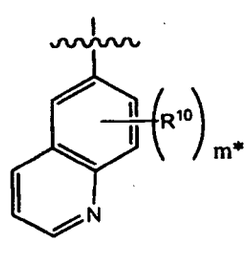


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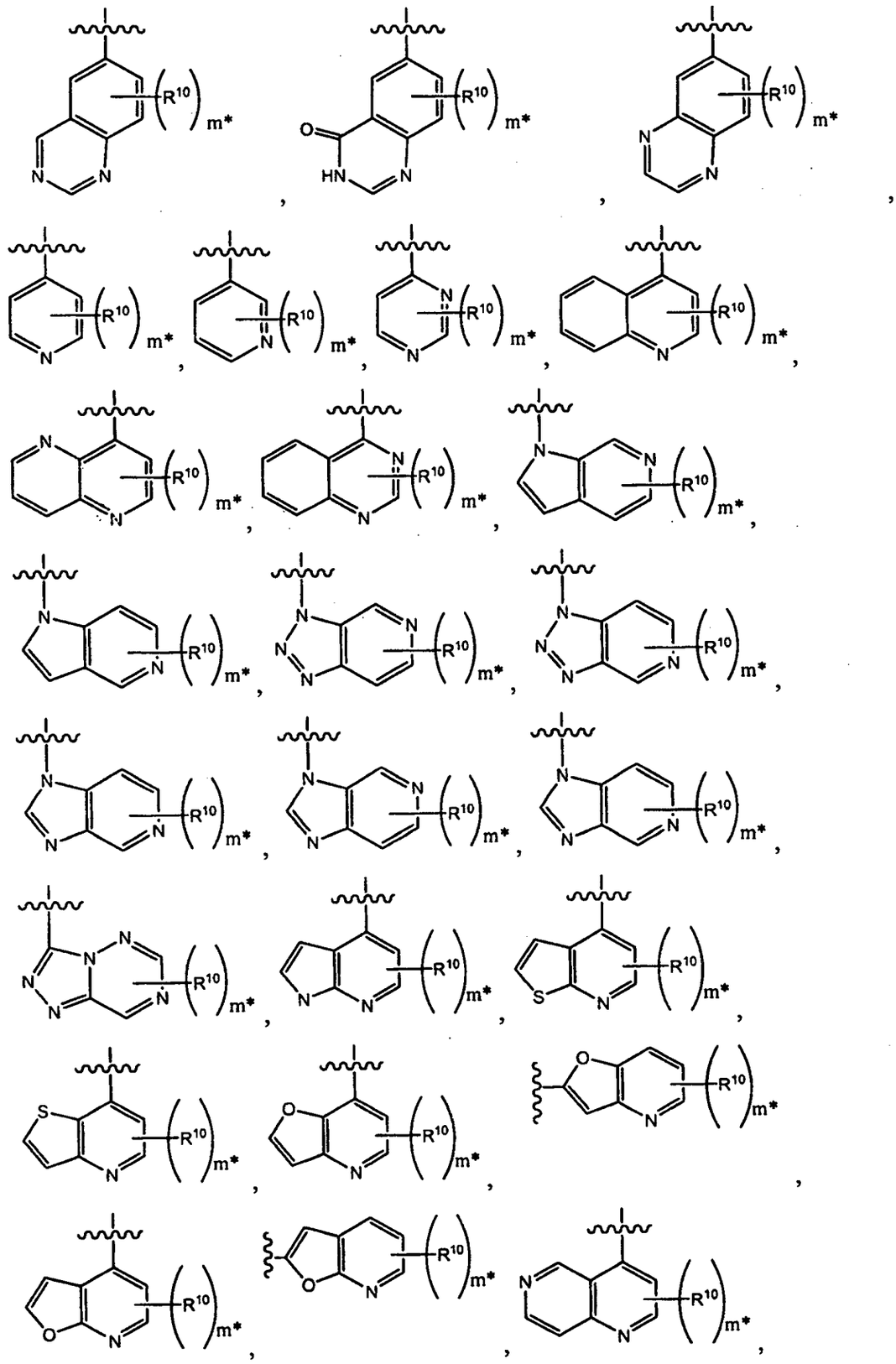
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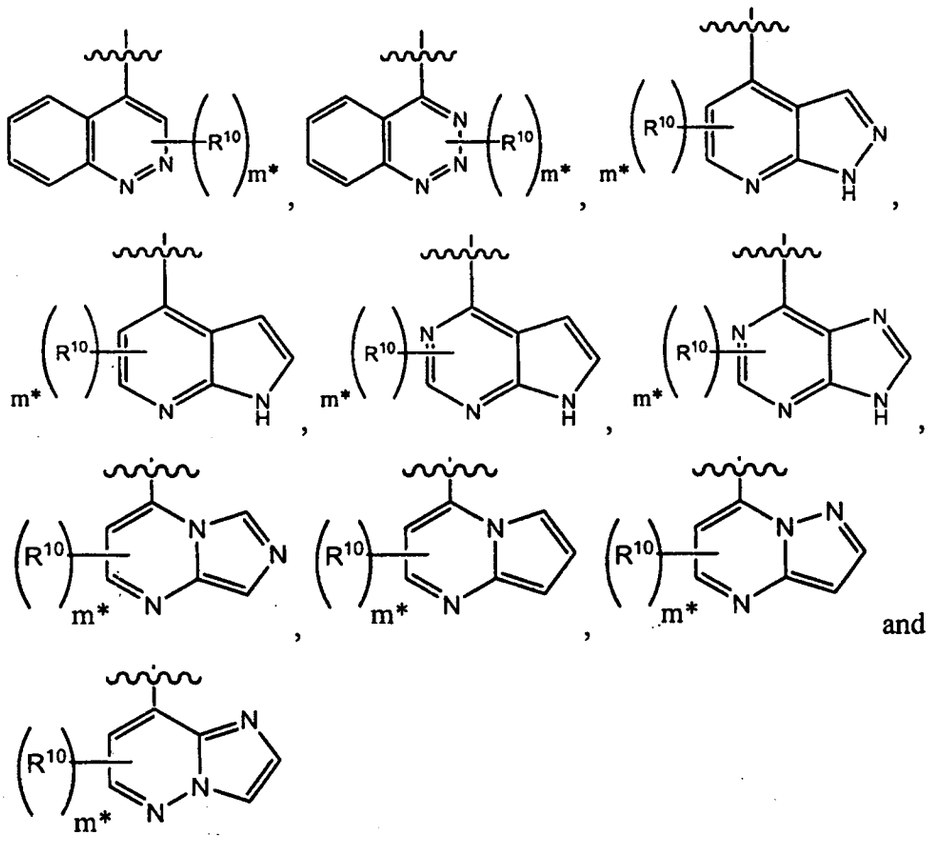
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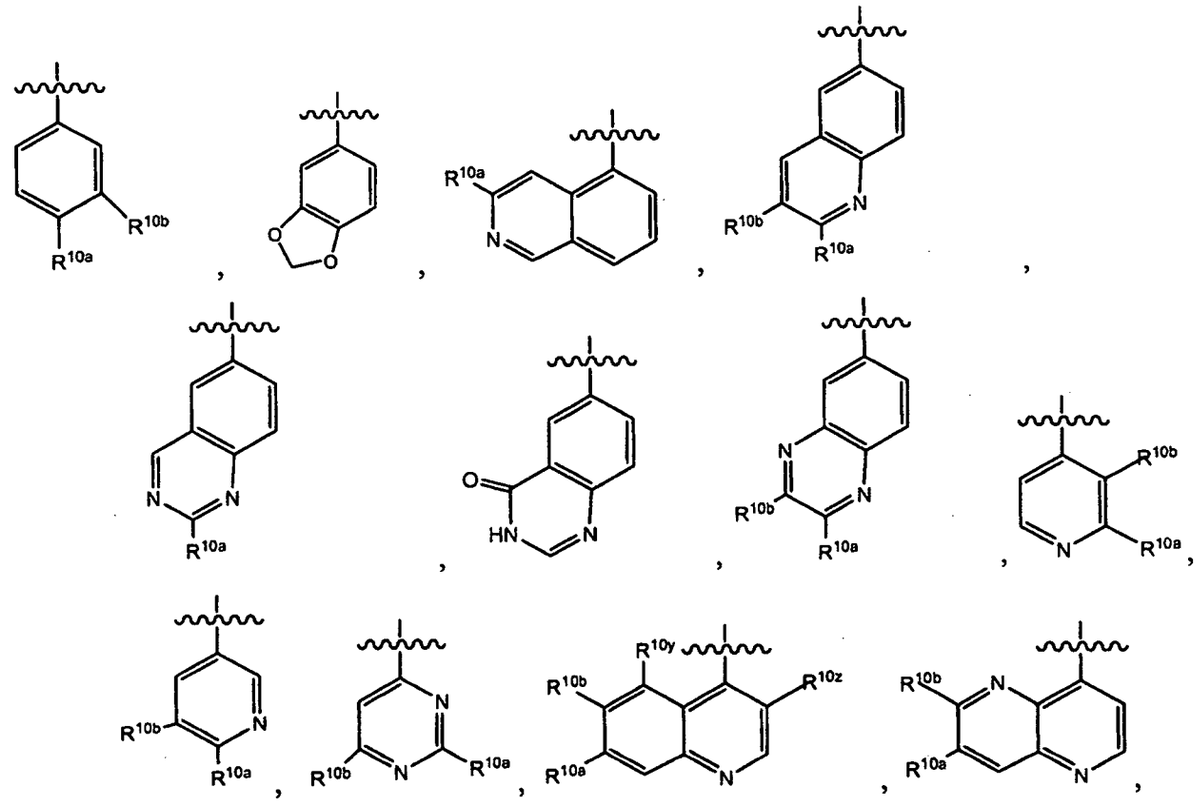
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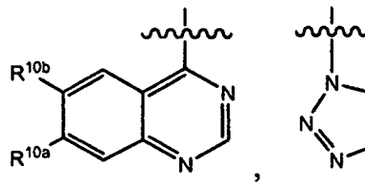
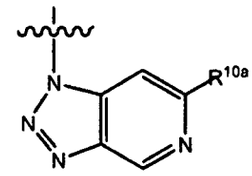
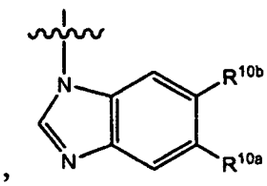
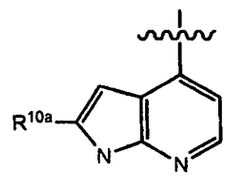
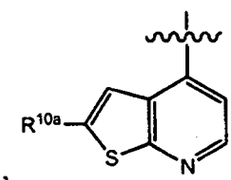
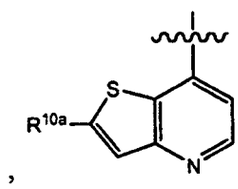
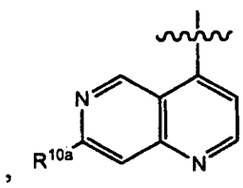
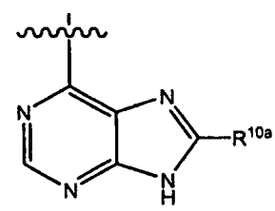




where m* is 0, 1, 2, 3, 4, 5 or 6, as allowed by valence.

Especially preferred R^1 groups include

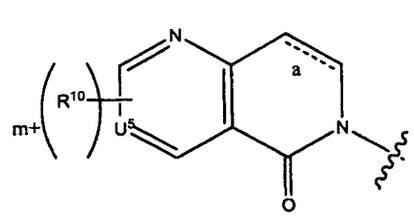
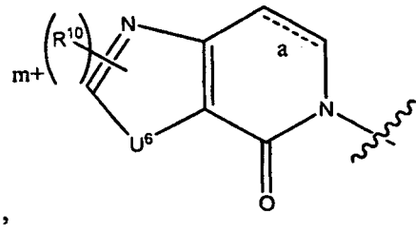
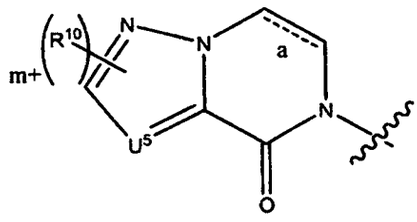
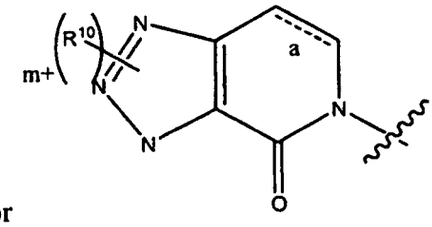



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and

where R^{10a}, R^{10b}. R^{10y} and R^{10z} are independently absent, halo, cyano, nitro, alkyl, alkenyl, alkynyl, haloalkyl, -(alkylene)$_m$-OR^4, -(alkylene)$_m$-NR^5R^{5a}, -(alkylene)$_m$-$C(=O)R^4$, -(alkylene)$_m$-$C(=O)OR^4$, -(alkylene)$_m$-$OC(=O)R^4$, -(alkylene)$_m$-$C(=O)NR^5R^{5a}$, -(alkylene)$_m$-$N(R^5)C(=O)NR^5R^{5a}$, -(alkylene)$_m$-$N(R^5)C(=O)R^4$, -(alkylene)$_m$-$OC(=O)NR^5R^{5a}$, or -(alkylene)$_m$-$N(R^5)C(=O)OR^4$;

or where R^{10a} and R^{10b} combine to form an optionally substituted 3- to 8-membered ring system.

Preferred R^1 groups further include


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, or

wherein a is a bond or is absent;

U^5 is C or N;

U^6 is NH, O or S; and

m+ is 0, 1, 2 or 3 .

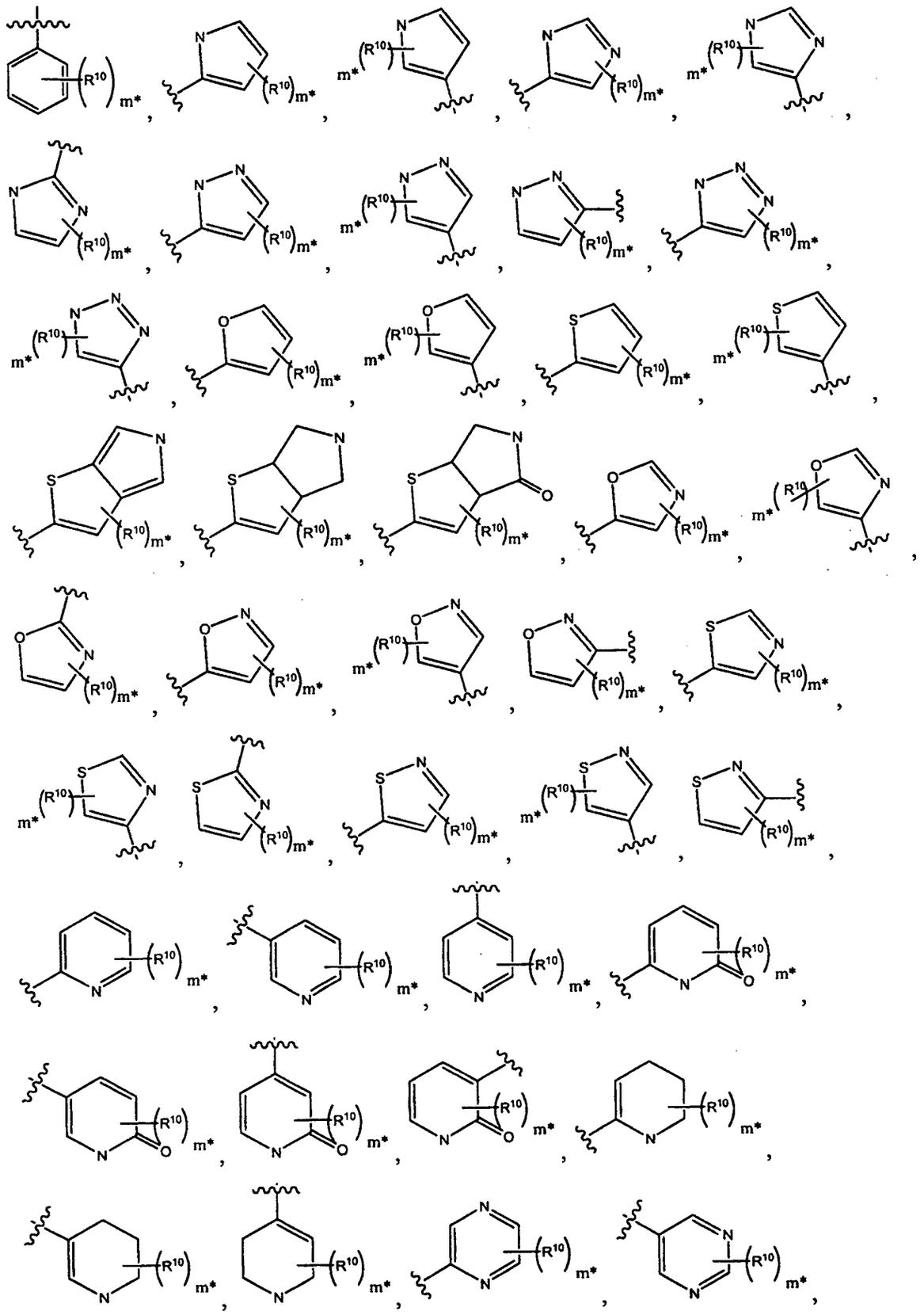
Most preferred R^1 groups include moieties that are either unsubstituted or independently substituted as allowed by valance with one or more halo, cyano, nitro, alkyl, alkenyl, alkynyl, haloalkyl, -(alkylene)$_m$-OR^4, -(alkylene)$_m$-NR^5R^{5a}, -(alkylene)$_m$-$C(=O)R^4$, -(alkylene)$_m$-$C(=O)OR^4$, -(alkylene)$_m$-$OC(=O)R^4$, —(alkylene)$_m$-$C(=O)NR^5R^{5a}$, -(alkylene)$_m$-$N(R^5)C(=O)NR^5R^{5a}$, -(alkylene)$_m$-$N(R^5)C(=O)R^4$, -(alkylene)$_m$-$OC(=O)NR^5R^{5a}$, or -(alkylene)$_m$-$N(R^5)C(=O)OR^4$.

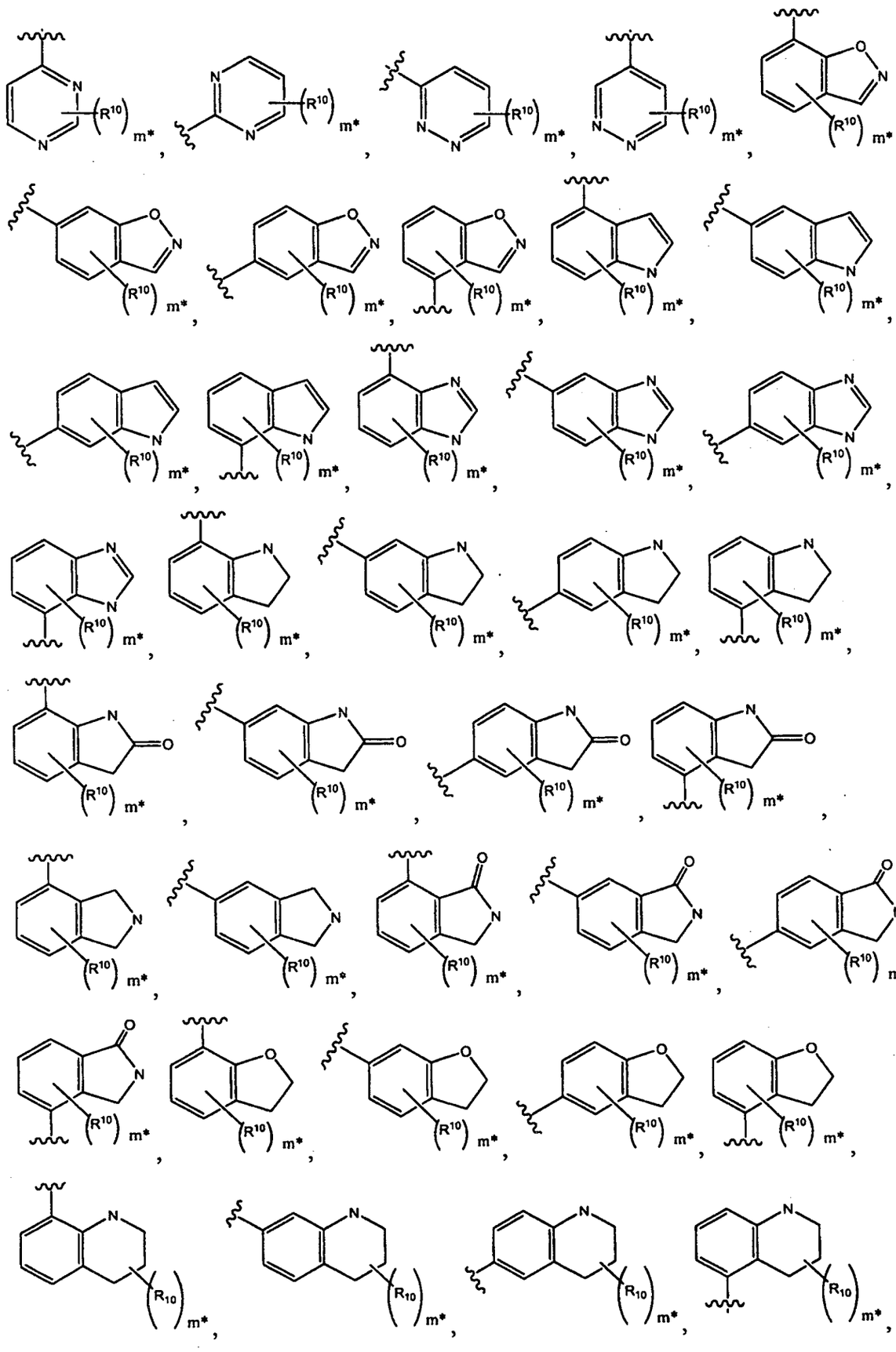
Preferred compounds of the present invention further include compounds wherein R^2 is H, halo, cyano, alkynyl, $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=O)OR^4$, phenyl, naphthyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, tetrahydropyridinyl, pyridinonyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, indolinyl, indolinonyl, isoidolinyl, isoindolinonyl, dihydrobenzofuranyl, dihydroisobenzofuranyl, benzofuranyl, isobenzofuranyl, quinolinyl, isoquinolinyl, quinazolinyl, quinazolinonyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, quinoxalinyl, tetrahydroquinoxalinyl, benzomorpholinyl, dihydrobenzodioxinyl, imidazopyridinyl, naphthyridinyl, benzotriazinyl, triazolopyridinyl, triazolopyrimidinyl, triazolopyridazinyl, imidazopyridinyl, imidazopyrimidinyl, imidazopyridazinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, pyrrolopyridazinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrazolopyridazinyl, cinnolinyl, thienopyrrolyl, tetrahydrothienopyrrolyl, dihydrothienopyrrolonyl, thienopyridinyl, thienopyrimidinyl, thienopyridazinyl, furopyridinyl, furopyrimidinyl, furopyrazidinyl, benzofuranyl, benzoimidazolyl, benzoisoxazolyl, benzothiazolyl, or benzoisothiazolyl any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance.

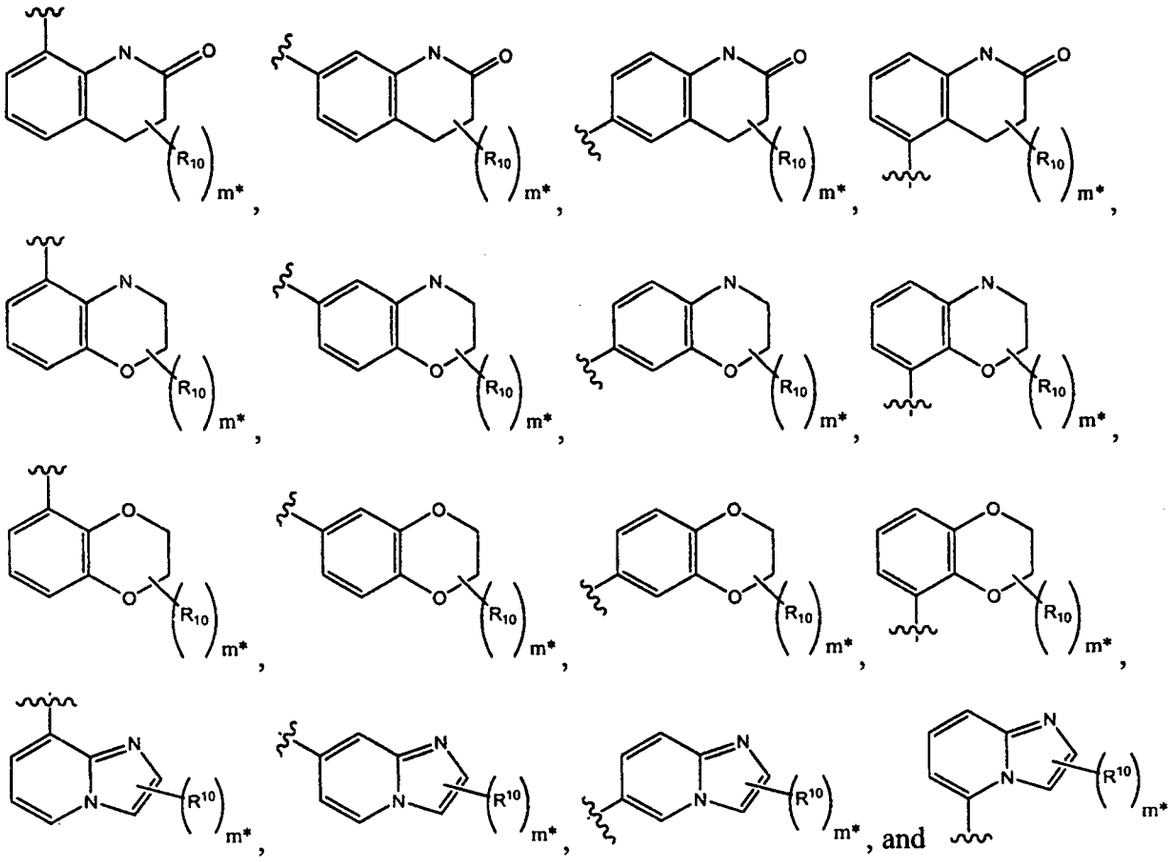
Preferred R^2 groups include

(a) halo, alkynyl, $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$ or $-N(R^5)C(=O)OR^4$ any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance; and

(b) an aryl, heteroaryl or heterocyclo ring system selected from





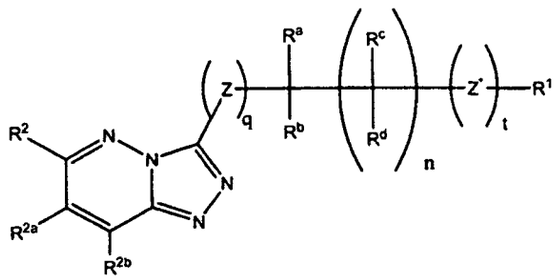


where m* is 0, 1, 2, 3, 4, 5 or 6, as allowed by valence.

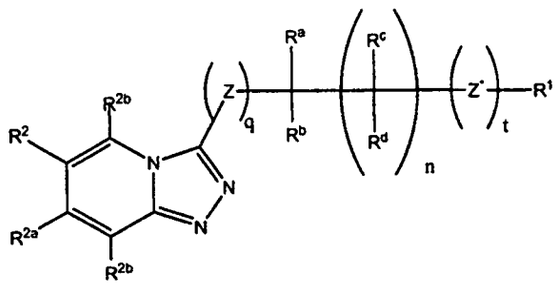
Preferred compounds of the present invention include compounds having either or both of preferred R^1 groups and preferred R^2 groups either alone or in any combination thereof..

Preferred compounds of the present invention include compounds wherein R^a, R^b, R^c and R^d groups are independently hydrogen, alkyl (especially methyl), and halogen (especially fluorine).

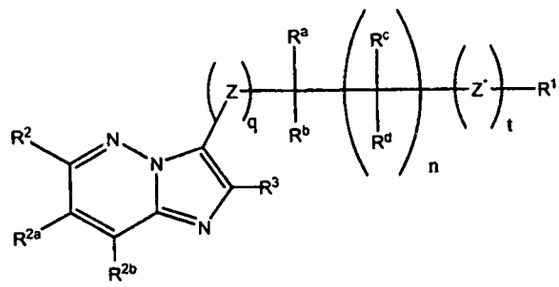
Preferred compounds within the scope of formula I and II include compounds of the following formualae IA, IB, IC, ID and IIA



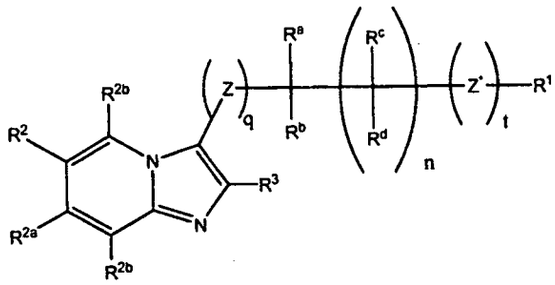
IA



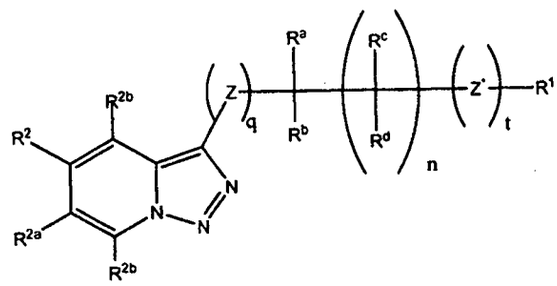
IB



IC



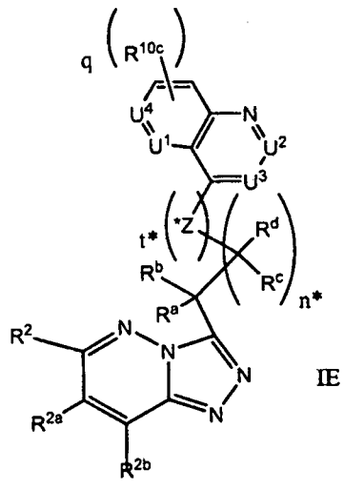
ID



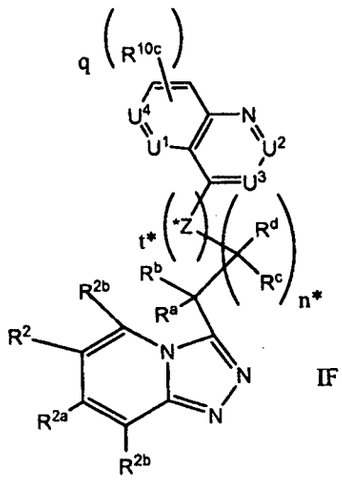
IIA

enantiomers, diastereomers, salts and solvates thereof, wherein variables R^a, R^b, R^c, R^d, R^1, R^2, R^{2a}, R^{2b}, R^3, Z, Z*, n, q and t are as previously defined above. Preferred compounds of formulae IA, IB, IC, ID and IIA include compounds having any of the preferred R^1 groups and R^2 groups, either alone or in any combination thereof.

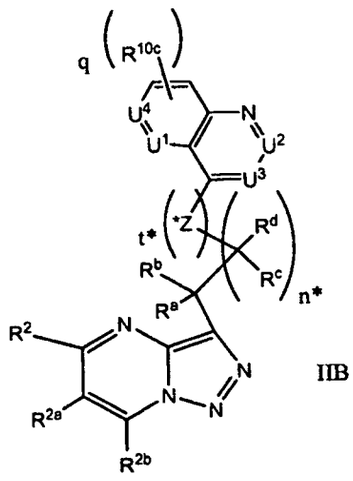
Preferred compounds within the scope of formula I and II also include compounds having the following formula IE, IF, IIB and IIC



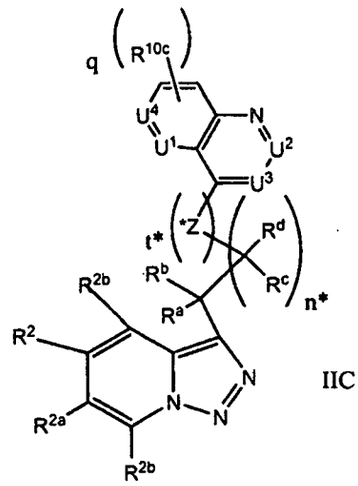
IE



IF



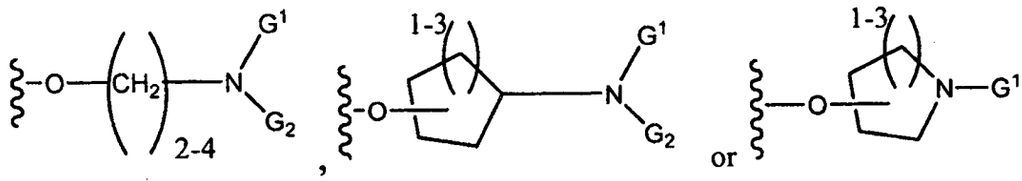
IIB



IIC

enantiomers, diastereomers, salts and solvates thereof

wherein variables R^a, R^b, R^c, R^d, R^2, R^{2a}, R^{2b}, and Z*, are as previously defined above, provided that in compounds of formula IE R^2 is not phenyl substituted with a group



where G^1 and G^2 are independently alkyl, cycloalkyl, or G^1 and G^2 together with the nitrogen atom to which they are attached combine to form a 5- to 8-membered heterocyclo ring; and further wherein

q is 0, 1, 2 or 3;

n* is 0, 1 or 2;

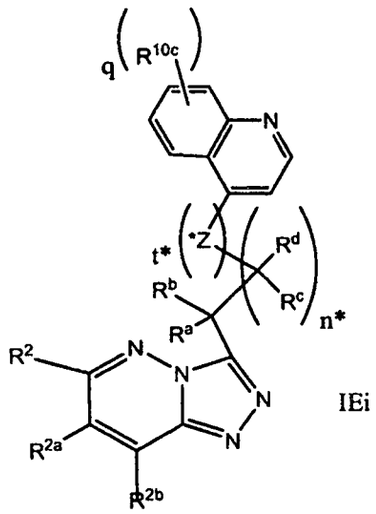
t* is 0 or 1

U^1, U^2, U^3 and U^4 are each independently C, or N; and

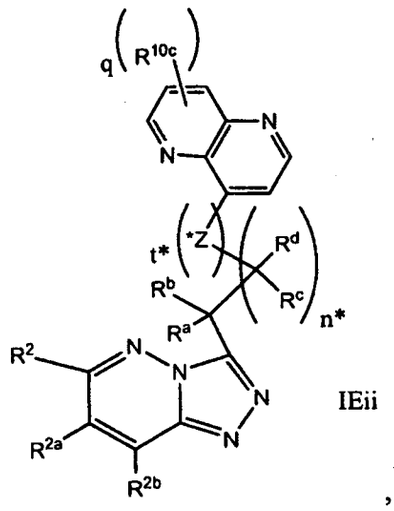
R^{10c} at each occurence is independently selected from the groups listed in the definition of R^{10} previously described above.

Preferred compounds of formulae IE, IF, IIB and IIC include compounds having any of the preferred R^2 groups described above.

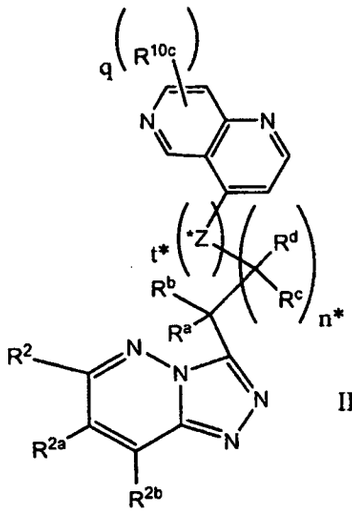
Preferred compounds within the scope of formulae IE and IF include compounds of the following formula IEi, IEii, IEiii, IEiv, IFi, IFii, IFiii and IFiv



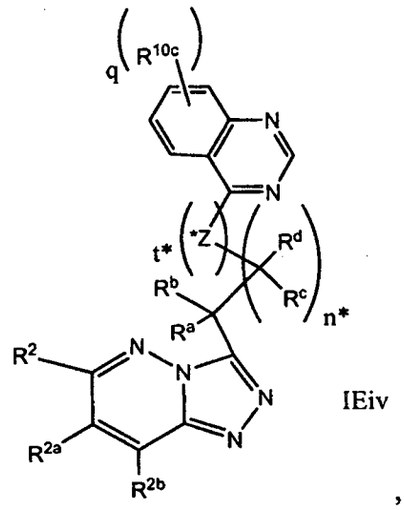
IEi ,



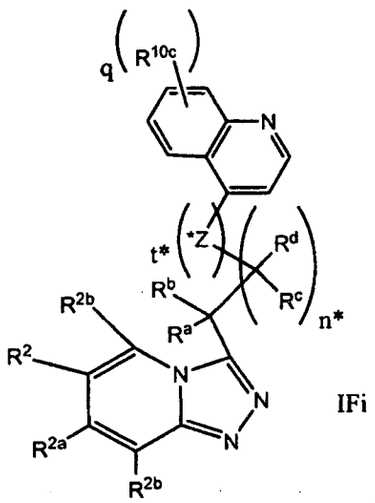
IEii ,



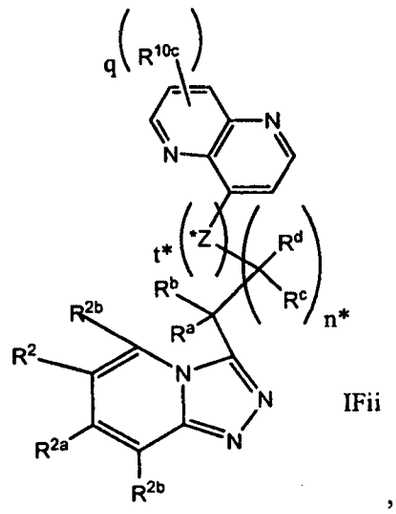
IEiii ,



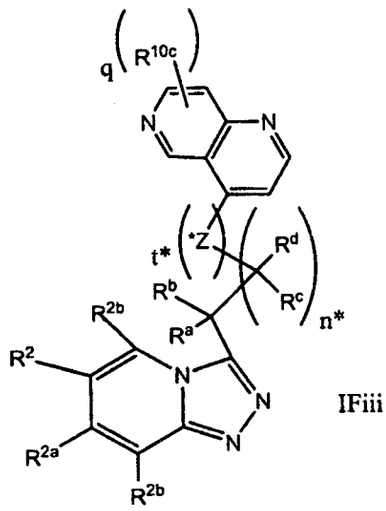
IEiv ,



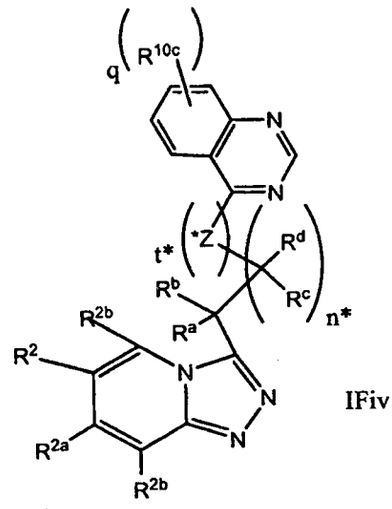
IFi ,



IFii ,



IFiii

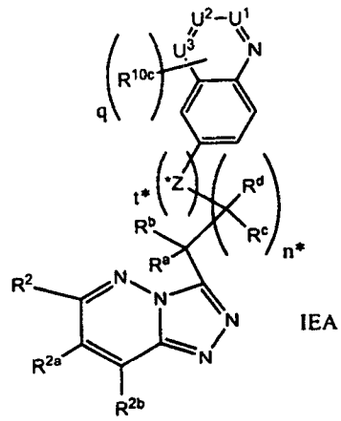


IFiv

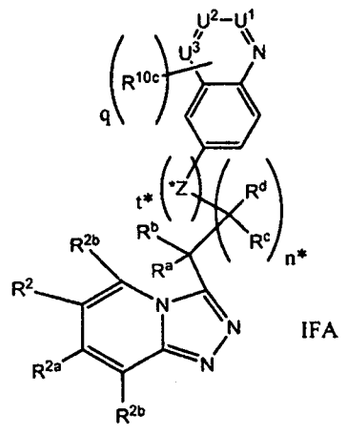
and

enantiomers, diastereomers, salts and solvates thereof.

Preferred compounds within the scope of formula I further include compounds of the following formula IEA and IFA

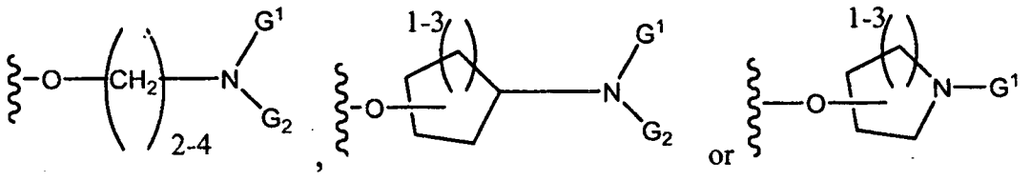


IEA



IFA

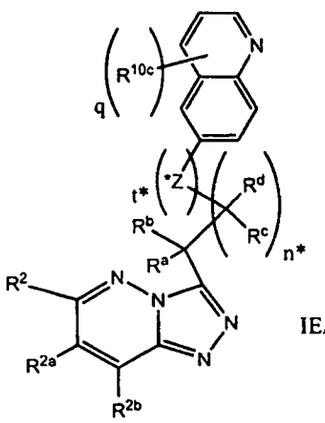
enantiomers, diastereomers, salts and solvates thereof wherein variables R^a, R^b, R^c, R^d, R^2, R^{2a}, R^{2b}, R^{10c}, U^1, U^2, U^3, Z*, n*, q, and t*are as previously defined above provided that in compounds of formula IEA R^2 is not phenyl substituted with a group

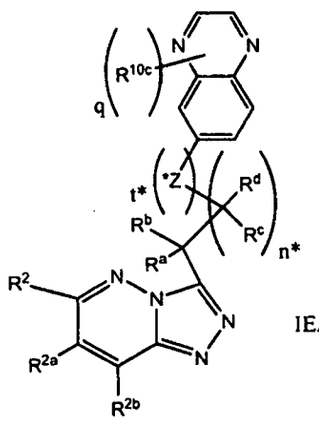


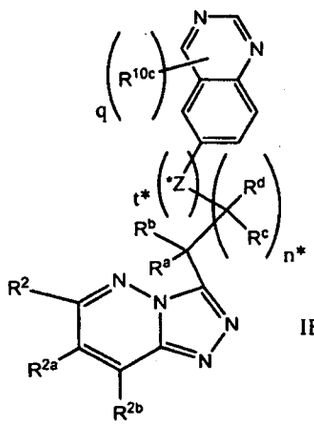
where G^1 and G^2 are independently alkyl, cycloalkyl, or G^1 and G^2 together with the nitrogen atom to which they are attached combine to form a 5- to 8-membered heterocyclo ring. .

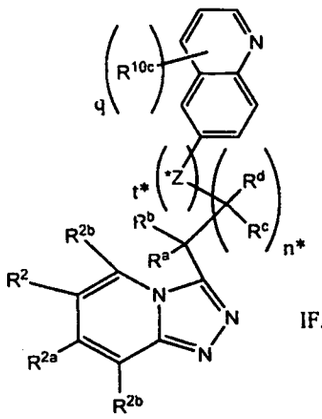
Preferred compounds of formulae IEA and IFA include compounds having any of the preferred R^2 groups described above.

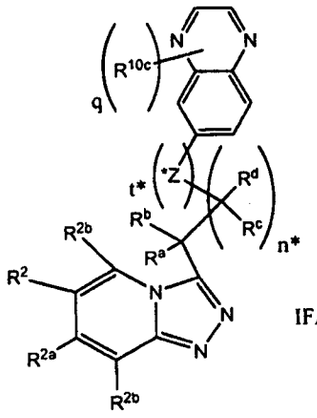
Preferred compounds of formulae IEA and IFA include compounds of formulae IEAi, IEAii, IEAiii, IFAi, IFAii and IFAiii

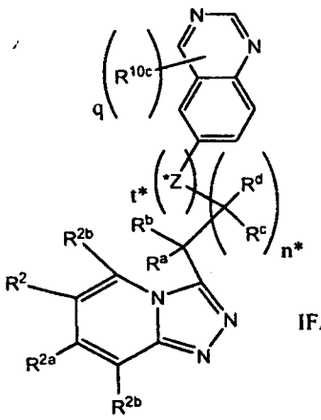

IEAi ,


IEAii ,


IEAiii ,

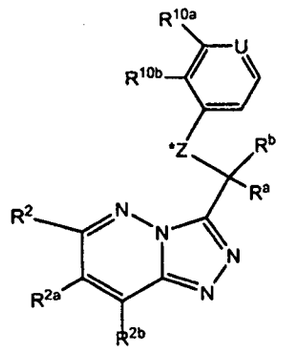

IFAi ,


IFAii ,

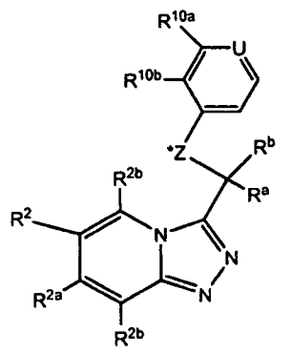

IFAiii

enantiomers, diastereomers, salts and solvates thereof.

Preferred compounds within the scope of formula I further include compounds of the following formula IG or IH



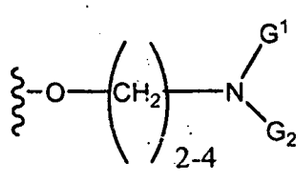
IG



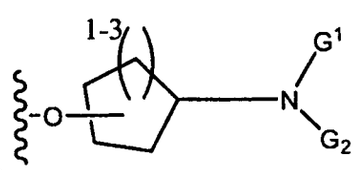
IH

,

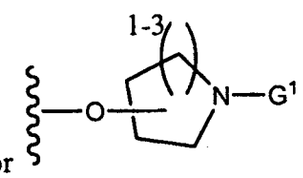
Wherein U is CR^{10c} or N, and variables R^a, R^b, R^2, R^{2a}, R^{2b}, R^{10a}, R^{10b}, R^{10c}, and Z*, are as previously defined above, provided that in compounds of formula IG R^2 is not phenyl substituted with a group



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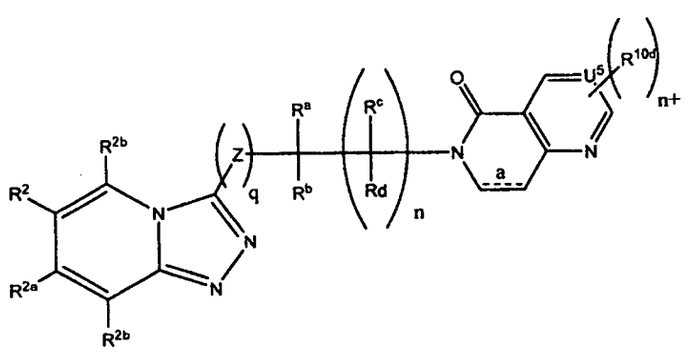


or

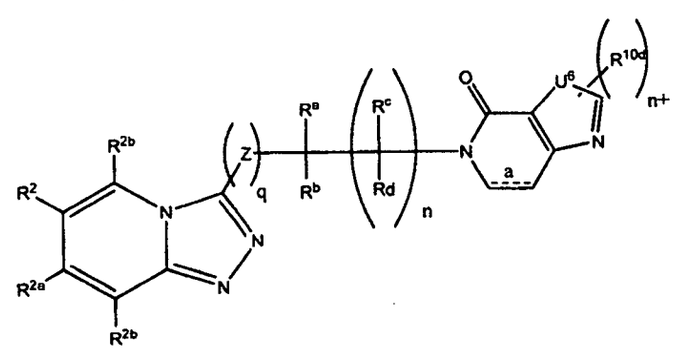


where G^1 and G^2 are independently alkyl, cycloalkyl, or G^1 and G^2 together with the nitrogen atom to which they are attached combine to form a 5- to 8-membered heterocyclo ring. Preferred compounds of formulae IG and IH include compounds having any of the preferred R^2 groups described above.

Preferred compounds within the scope of formula I further include compounds of the following formula IJ or IK



IJ



IK

Where a is a bond or is absent; U^5 is C or N; U^6 is NH, O or S; and m+ is 0, 1, 2 or 3. Preferred compounds of formulae IJ and IK include compounds having any of the preferred R^2 groups described above.

Preferred compounds of the present invention include the compounds exemplified herein.

The invention also relates to pharmaceutical compositions containing the above compounds, together with a pharmaceutically acceptable vehicle or carrier.

The invention also relates to a method of treating cancer in a subject using the above compounds.

The invention also relates to a method of reducing tumor size in a subject using the above compounds.

The invention also relates to a method of reducing metastasis in a tumor in a subject, using the above compounds.

The invention also relates to a method of treating HGF-mediated disorders in a subject using the above compounds.

INDICATIONS

Compounds of the present invention would be useful for, but not limited to, the prevention or treatment of angiogenesis related diseases. The compounds of the invention have c-Met inhibitory activity. The compounds of the invention are useful in therapy as antineoplasia agents or to minimize deleterious effects of HGF.

Compounds of the invention would be useful for the treatment of neoplasia including cancer and metastasis, including, but not limited to: carcinoma such as cancer of the bladder, breast, colon, kidney, liver, lung (including small cell lung cancer), esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin (including squamous cell carcinoma); hematopoietic tumors of lymphoid lineage (including leukemia, acute lymphocitic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma); hematopoietic tumors of myeloid lineage (including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia); tumors of mesenchymal origin (including fibrosarcoma and rhabdomyosarcoma, and other sarcomas, e.g. soft tissue and bone); tumors of the central and peripheral nervous system (including astrocytoma, neuroblastoma, glioma and schwannomas); and other tumors (including melanoma, seminoma,

teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma).

Preferably, the compounds are useful for the treatment of neoplasia selected from lung cancer, colon cancer and breast cancer.

The compounds also would be useful for treatment of ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, retrolental fibroplasia and neovascular glaucoma; retinal ischemia; vitreous hemorrhage; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemaginomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis. The compounds are also useful for the treatment of edema, and conditions of vascular hyperpermeability.

The compounds of the invention are useful in therapy of proliferative diseases. These compounds can be used for the treatment of an inflammatory rheumatoid or rheumatic disease, especially of manifestations at the locomotor apparatus, such as various inflammatory rheumatoid diseases, especially chronic polyarthritis including rheumatoid arthritis, juvenile arthritis or psoriasis arthropathy; paraneoplastic syndrome or tumor-induced inflammatory diseases, turbid effusions, collagenosis, such as systemic Lupus erythematosus, poly-myositis, dermato-myositis, systemic sclerodermia or mixed collagenosis; postinfectious arthritis (where no living pathogenic organism can be found at or in the affected part of the body), seronegative spondylarthritis, such as spondylitis ankylosans; vasculitis, sarcoidosis, or arthrosis; or further any combinations thereof. An example of an inflammation related disorder is (a) synovial inflammation, for example, synovitis, including any of the particular forms of synovitis, in particular bursal synovitis and purulent synovitis, as far as it is not crystal-induced. Such synovial inflammation may for example, be consequential to or associated with disease, e.g. arthritis, e.g. osteoarthritis, rheumatoid arthritis or arthritis deformans. The present invention is further applicable to the systemic treatment of inflammation, e.g. inflammatory diseases or conditions, of the joints or locomotor apparatus in the region of the tendon insertions and tendon sheaths. Such inflammation may be, for example, consequential to or associated with disease or further (in a broader sense of the invention) with surgical intervention, including, in particular conditions such as insertion endopathy, myofasciale syndrome and tendomyosis. The present invention is further especially applicable to the treatment of inflammation, e.g. inflammatory disease or condition, of connective tissues including dermatomyositis and myositis.

These compounds can be used as active agents against such disease states as arthritis, atherosclerosis, psoriasis, hemangiomas, myocardial angiogenesis, coronary and cerebral collaterals, ischemic limb angiogenesis, wound healing, peptic ulcer Helicobacter related diseases, fractures, cat scratch fever, rubeosis, neovascular glaucoma and retinopathies such as those associated with diabetic retinopathy or macular degeneration. In addition, some of these compounds can be used as active agents against solid tumors, malignant ascites, hematopoietic cancers and hyperproliferative disorders such as thyroid hyperplasia (especially Grave's disease), and cysts (such as hypervascularity of ovarian stroma, characteristic of polycystic ovarian syndrome (Stein-Leventhal syndrome)) since such diseases require a proliferation of blood vessel cells for growth and/or metastasis.

Further, some of these compounds can be used as active agents against burns, chronic lung disease, stroke, polyps, anaphylaxis, chronic and allergic inflammation, ovarian hyperstimulation syndrome, brain tumor-associated cerebral edema, high-altitude, trauma or hypoxia induced cerebral or pulmonary edema, ocular and macular edema, ascites, and other diseases where vascular hyperpermeability, effusions, exudates, protein extravasation, or edema is a manifestation of the disease. The compounds will also be useful in treating disorders in which protein extravasation leads to the deposition of fibrin and extracellular matrix, promoting stromal proliferation (e.g. fibrosis, cirrhosis and carpal tunnel syndrome).

The compounds of the present invention are also useful in the treatment of ulcers including bacterial, fungal, Mooren ulcers and ulcerative colitis.

The compounds of the present invention are also useful in the treatment of conditions wherein undesired angiogenesis, edema, or stromal deposition occurs in viral infections such as Herpes simplex, Herpes Zoster, AIDS, Kaposi's sarcoma, protozoan infections and toxoplasmosis, following trauma, radiation, stroke, endometriosis, ovarian hyperstimulation syndrome, systemic lupus, sarcoidosis, synovitis, Crohn's disease, sickle cell anemia, Lyme disease, pemphigoid, Paget's disease, hyperviscosity syndrome, Osler-Weber-Rendu disease, chronic inflammation, chronic occlusive pulmonary disease, asthma, and inflammatory rheumatoid or rheumatic disease. The compounds are also useful in the reduction of subcutaneous fat and for the treatment of obesity.

The compounds of the present invention are also useful in the treatment of ocular conditions such as ocular and macular edema, ocular neovascular disease, scleritis, radial keratotomy, uveitis, vitritis, myopia, optic pits, chronic retinal detachment, post-laser complications, glaucoma, conjunctivitis, Stargardt's disease and Eales disease in addition to retinopathy and macular degeneration.

The compounds of the present invention are also useful in the treatment of cardiovascular conditions such as atherosclerosis, restenosis, arteriosclerosis, vascular occlusion and carotid obstructive disease.

The compounds of the present invention are also useful in the treatment of cancer related indications such as solid tumors, sarcomas (especially Ewing's sarcoma and osteosarcoma), retinoblastoma, rhabdomyosarcomas, neuroblastoma, hematopoietic malignancies, including leukemia and lymphoma, tumor-induced pleural or pericardial effusions, and malignant ascites.

The compounds of the present invention are also useful in the treatment of diabetic conditions such as diabetic retinopathy and microangiopathy.

The compounds of the present invention are also useful in the reduction of blood flow in a tumor in a subject.

The compounds of the present invention are also useful in the reduction of metastasis of a tumor in a subject.

The compounds of this invention may also act as inhibitors of other protein kinases, e.g. tie-2, lck, src, fgf, c-Met, ron, ckit and ret, and thus be effective in the treatment of diseases associated with other protein kinases.

Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

As used herein, the compounds of the present invention include the pharmaceutically acceptable derivatives thereof.

Where the plural form is used for compounds, salts, and the like, this is taken to mean also a single compound, salt and the like.

DEFINITIONS

"Angiogenesis" is defined as any alteration of an existing vascular bed or the formation of new vasculature, which benefits tissue perfasion. This includes the formation of new vessels by sprouting of endothelial cells from existing blood vessels or the remodeling of existing vessels to alter size, maturity, direction or flow properties to improve blood perfusion of tissue.

As used herein, "HGF" refers to hepatocyte growth factor/scatter factor. This includes purified hepatocyte growth factor/scatter factor, fragments of hepatocyte growth factor/scatter factor, chemically synthesized fragments of hepatocyte growth factor/scatter factor, derivatives or mutated versions of hepatocyte growth factor/scatter factor, and fusion proteins comprising

hepatocyte growth factor/scatter factor and another protein. "HGF" as used herein also includes hepatocyte growth factor/scatter factor isolated from species other than humans.

As used herein "c-Met" refers to the receptor for HGF. This includes purified receptor, fragments of receptor, chemically synthesized fragments of receptor, derivatives or mutated versions of receptor, and fusion proteins comprising the receptor and another protein. "c-Met" as used herein also includes the HGF receptor isolated from a species other than humans.

As used herein, "HGF" refers to hepatocyte growth factor/scatter factor. This includes purified hepatocyte growth factor/scatter factor, fragments of hepatocyte growth factor/scatter factor, chemically synthesized fragments of hepatocyte growth factor/scatter factor, derivatives or mutated versions of hepatocyte growth factor/scatter factor, and fusion proteins comprising hepatocyte growth factor/scatter factor and another protein. "HGF" as used herein also includes hepatocyte growth factor/scatter factor isolated from species other than humans.

As used herein "c-Met" refers to the receptor for HGF. This includes purified receptor, fragments of receptor, chemically synthesized fragments of receptor, derivatives or mutated versions of receptor, and fusion proteins comprising the receptor and another protein. "c-Met" as used herein also includes the HGF receptor isolated from a species other than humans.

As used herein, the terms "hepatocyte growth factor" and "HGF" refer to a growth factor typically having a structure with six domains (finger, Kringle 1, Kringle 2, Kringle 3, Kringle 4 and serine protease domains). Fragments of HGF constitute HGF with fewer domains and variants of HGF may have some of the domains of HGF repeated; both are included if they still retain their respective ability to bind a HGF receptor. The terms "hepatocyte growth factor" and "HGF" include hepatocyte growth factor from humans ("huHGF") and any non-human mammalian species, and in particular rat HGF. The terms as used herein include mature, pre, pre-pro, and pro forms, purified from a natural source, chemically synthesized or recombinantly produced. Human HGF is encoded by the cDNA sequence published by Miyazawa et al. (1989), supra, or Nakamura et al. (1989), supra. The sequences reported by Miyazawa et al. and Nakamura et al. differ in 14 amino acids. The reason for the differences is not entirely clear; polymorphism or cloning artifacts are among the possibilities. Both sequences are specifically encompassed by the foregoing terms. It will be understood that natural allelic variations exist and can occur among individuals, as demonstrated by one or more amino acid differences in the amino acid sequence of each individual. The terms "hepatocyte growth factor" and "HGF" specifically include the delta 5 huHGF as disclosed by Seki et al., supra.

The terms "HGF receptor" and "c-Met" when used herein refer to a cellular receptor for HGF, which typically includes an extracellular domain, a transmembrane domain and an intracellular domain, as well as variants and fragments thereof which retain the ability to bind HGF. The terms "HGF receptor" and "c-Met" include the polypeptide molecule that comprises the full-length, native amino acid sequence encoded by the gene variously known as p190.sup.MET. The present definition specifically encompasses soluble forms of HGF receptor, and HGF receptor from natural sources, synthetically produced in vitro or obtained by genetic manipulation including methods of recombinant DNA technology. The HGF receptor variants or fragments preferably share at least about 65% sequence homology, and more preferably at least about 75% sequence homology with any domain of the human c-Met amino acid sequence published in Rodrigues et al., Mol. Cell. Biol., 11:2962-2970 (1991); Park et al., Proc. Natl. Acad. Sci., 84:6379-6383 (1987); or Ponzetto et al., Oncogene, 6:553-559 (1991).

The terms "agonist" and "agonistic" when used herein refer to or describe a molecule which is capable of, directly or indirectly, substantially inducing, promoting or enhancing HGF biological activity or HGF receptor activation.

The terms "cancer" and "cancerous" when used herein refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to, carcinoma, lymphoma, sarcoma, blastoma and leukemia. More particular examples of such cancers include squamous cell carcinoma, lung cancer, pancreatic cancer, cervical cancer, bladder cancer, hepatoma, breast cancer, colon carcinoma, and head and neck cancer. While the term "cancer" as used herein is not limited to any one specific form of the disease, it is believed that the methods of the invention will be particularly effective for cancers which are found to be accompanied by increased levels of HGF or expression of c-Met in the mammal.

The terms "treating," "treatment," and "therapy" as used herein refer to curative therapy, prophylactic therapy, and preventative therapy.

The term "mammal" as used herein refers to any mammal classified as a mammal, including humans, cows, horses, dogs and cats. In a preferred embodiment of the invention, the mammal is a human.

Given that elevated levels of c-Met and HGF are observed in hypertension, arteriosclerosis, myocardial infarction, and rheumatoid arthritis, nucleic acid ligands will serve as useful therapeutic agents for these diseases.

The term "treatment" includes therapeutic treatment as well as prophylactic treatment (either preventing the onset of disorders altogether or delaying the onset of a pre-clinically evident stage of disorders in individuals).

A "pharmaceutically-acceptable derivative " denotes any salt, ester of a compound of this invention, or any other compound which upon administration to a patient is capable of providing (directly or indirectly) a compound of this invention, or a metabolite or residue thereof, characterized by the ability to inhibit angiogenesis.

The phrase "therapeutically-effective" is intended to qualify the amount of each agent, which will achieve the goal of improvement in disorder severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies. For example, effective neoplastic therapeutic agents prolong the survivability of the patient, inhibit the rapidly proliferating cell growth associated with the neoplasm, or effect a regression of the neoplasm.

The term "H" denotes a single hydrogen atom. This radical may be attached, for example, to an oxygen atom to form a hydroxyl radical.

Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylamino", it embraces linear or branched radicals having one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isoamyl, hexyl and the like. Even more preferred are lower alkyl radicals having one or two carbon atoms. The term "alkylenyl" embraces bridging divalent alkyl radicals such as methylenyl and ethylenyl. The term "lower alkyl substituted with R^{2}" does not include an acetal moiety.

The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Most preferred lower alkenyl radicals are radicals having two to about four carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "alkynyl" denotes linear or branched radicals having at least one carbon-carbon triple bond and having two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about six carbon atoms. Most preferred are

lower alkynyl radicals having two to about four carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

Alkyl, alkylenyl, alkenyl, and alkynyl radicals may be optionally substituted with one or more functional groups such as halo, hydroxy, nitro, amino, cyano, haloalkyl, aryl, heteroaryl, heterocyclo and the like.

The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms.

The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals including perhaloalkyl. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Even more preferred are lower haloalkyl radicals having one to three carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Perfluoroalkyl" means alkyl radicals having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentafluoroethyl.

The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl. Even more preferred are lower hydroxyalkyl radicals having one to three carbon atoms.

The term "alkoxy" embraces linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-butoxy. Even more preferred are lower alkoxy radicals having one to three carbon atoms. Alkoxy radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Even more preferred are lower haloalkoxy radicals having one to three carbon atoms. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one or two rings wherein such rings may be attached together in a fused manner. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, indenyl, tetrahydronaphthyl, and indanyl. More preferred aryl is phenyl. Said "aryl" group may have 1 or more substituents such as lower alkyl, hydroxyl, halo, haloalkyl, nitro, cyano, alkoxy, lower alkylamino, and the like. Phenyl substituted with -O-CH_2-O- forms the aryl benzodioxolyl substituent.

The term "heterocyclyl" (or "heterocyclo") embraces saturated, and partially saturated and heteroatom-containing ring radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. It does not include rings containing -O-O-,-O-S- or -S-S- portions. Said "heterocyclyl" group may have 1 to 3 substituents such as hydroxyl, Boc, halo, haloalkyl, cyano, lower alkyl, lower aralkyl, oxo, lower alkoxy, amino, lower alkylamino, and the like.

Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, piperazinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl]. Examples of partially saturated heterocyclyl radicals include dihydrothienyl, dihydropyranyl, dihydrofuryl, dihydrothiazolyl, and the like.

Particular examples of partially saturated and saturated heterocyclyl include pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, pyrazolidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, thiazolidinyl, dihydrothienyl, 2,3-dihydro-benzo[1,4]dioxanyl, indolinyl, isoindolinyl, dihydrobenzothienyl, dihydrobenzofuryl, isochromanyl, chromanyl, 1,2-dihydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl, 1,2,3,4-tetrahydro-quinolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinolyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl, benzo[1,4]dioxanyl, 2,3-dihydro-1H-1λ'-benzo[d]isothiazol-6-yl, dihydropyranyl, dihydrofuryl and dihydrothiazolyl, and the like.

The term heterocyclyl, (or heterocyclo) also embraces radicals where heterocyclic radicals are fused/condensed with aryl radicals: unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl]; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl]; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g.,

benzothiazolyl, benzothiadiazolyl]; and saturated, partially unsaturated and unsaturated condensed heterocyclic group containing 1 to 2 oxygen or sulfur atoms [e.g. benzofuryl, benzothienyl, 2,3-dihydro-benzo[1,4]dioxinyl and dihydrobenzofuryl].

The term "heteroaryl" denotes aryl ring systems that contain one or more heteroatoms selected from the group O, N and S, wherein the ring nitrogen and sulfur atom(s) are optionally oxidized, and nitrogen atom(s) are optionally quarternized. Examples include unsaturated 5 to 6 membered heteromonocyclyl group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl]; unsaturated 5- to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl].

The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$.

The terms "sulfamyl," "aminosulfonyl" and "sulfonamidyl," denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2NH_2$).

The term "alkylaminosulfonyl" includes "N-alkylaminosulfonyl" where sulfamyl radicals are independently substituted with one or two alkyl radical(s). More preferred alkylaminosulfonyl radicals are "lower alkylaminosulfonyl" radicals having one to six carbon atoms. Even more preferred are lower alkylaminosulfonyl radicals having one to three carbon atoms. Examples of such lower alkylaminosulfonyl radicals include N-methylaminosulfonyl, and N-ethylaminosulfonyl.

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$.

The term "carbonyl", whether used alone or with other terms, such as "aminocarbonyl", denotes -(C=O)-.

The term "aminocarbonyl" denotes an amide group of the formula $-C(=O)NH_2$.

The terms "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" denote aminocarbonyl radicals independently substituted with one or two alkyl radicals, respectively.

More preferred are "lower alkylaminocarbonyl" having lower alkyl radicals as described above attached to an aminocarbonyl radical.

The terms "N-arylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl" denote aminocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl and one aryl radical.

The terms "heterocyclylalkylenyl" and "heterocyclylalkyl" embrace heterocyclic-substituted alkyl radicals. More preferred heterocyclylalkyl radicals are "5- or 6-membered heteroarylalkyl" radicals having alkyl portions of one to six carbon atoms and a 5- or 6-membered heteroaryl radical. Even more preferred are lower heteroarylalkylenyl radicals having alkyl portions of one to three carbon atoms. Examples include such radicals as pyridylmethyl and thienylmethyl.

The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are "phenylalkylenyl" attached to alkyl portions having one to three carbon atoms. Examples of such radicals include benzyl, diphenylmethyl and phenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, halkoalkyl and haloalkoxy.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower alkylthio radicals having one to three carbon atoms. An example of "alkylthio" is methylthio, (CH_3S-).

The term "haloalkylthio" embraces radicals containing a haloalkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. Even more preferred are lower haloalkylthio radicals having one to three carbon atoms. An example of "haloalkylthio" is trifluoromethylthio.

The term "alkylamino" embraces "N-alkylamino" and "N,N-dialkylamino" where amino groups are independently substituted with one alkyl radical and with two alkyl radicals, respectively. More preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Even more preferred are lower alkylamino radicals having one to three carbon atoms. Suitable alkylamino radicals may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino and the like.

The term "arylamino" denotes amino groups, which have been substituted with one or two aryl radicals, such as N-phenylamino. The arylamino radicals may be further substituted on the aryl ring portion of the radical.

The term "heteroarylamino" denotes amino groups, which have been substituted with one or two heteroaryl radicals, such as N-thienylamino. The "heteroarylamino" radicals may be further substituted on the heteroaryl ring portion of the radical.

The term "aralkylamino" denotes amino groups, which have been substituted with one or two aralkyl radicals. More preferred are phenyl-C_1-C_3-alkylamino radicals, such as N-benzylamino. The aralkylamino radicals may be further substituted on the aryl ring portion.

The terms "N-alkyl-N-arylamino" and "N-aralkyl-N-alkylamino" denote amino groups, which have been independently substituted with one aralkyl and one alkyl radical, or one aryl and one alkyl radical, respectively, to an amino group.

The term "aminoalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more amino radicals. More preferred aminoalkyl radicals are "lower aminoalkyl" radicals having one to six carbon atoms and one or more amino radicals. Examples of such radicals include aminomethyl, aminoethyl, aminopropyl, aminobutyl and aminohexyl. Even more preferred are lower aminoalkyl radicals having one to three carbon atoms.

The term "alkylaminoalkyl" embraces alkyl radicals substituted with alkylamino radicals. More preferred alkylaminoalkyl radicals are "lower alkylaminoalkyl" radicals having alkyl radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkyl radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkyl radicals may be mono or dialkyl substituted, such as N-methylaminomethyl, N,N-dimethyl-aminoethyl, N,N-diethylaminomethyl and the like.

The term "alkylaminoalkoxy" embraces alkoxy radicals substituted with alkylamino radicals. More preferred alkylaminoalkoxy radicals are "lower alkylaminoalkoxy" radicals having alkoxy radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkoxy radicals having alkyl radicals of one to three carbon atoms. Suitable alkylaminoalkoxy radicals may be mono or dialkyl substituted, such as N-methylaminoethoxy, N,N-dimethylaminoethoxy, N,N-diethylaminoethoxy and the like.

The term "alkylaminoalkoxyalkoxy" embraces alkoxy radicals substituted with alkylaminoalkoxy radicals. More preferred alkylaminoalkoxyalkoxy radicals are "lower alkylaminoalkoxyalkoxy" radicals having alkoxy radicals of one to six carbon atoms. Even more preferred are lower alkylaminoalkoxyalkoxy radicals having alkyl radicals of one to three

carbon atoms. Suitable alkylaminoalkoxyalkoxy radicals may be mono or dialkyl substituted, such as N-methylaminomethoxyethoxy, N-methylaminoethoxyethoxy, N,N-dimethylaminoethoxyethoxy, N,N-diethylaminomethoxymethoxy and the like.

The term "carboxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more carboxy radicals. More preferred carboxyalkyl radicals are "lower carboxyalkyl" radicals having one to six carbon atoms and one carboxy radical. Examples of such radicals include carboxymethyl, carboxypropyl, and the like. Even more preferred are lower carboxyalkyl radicals having one to three CH_2 groups.

The term "halosulfonyl" embraces sulfonyl radicals substituted with a halogen radical. Examples of such halosulfonyl radicals include chlorosulfonyl and fluorosulfonyl.

The term "arylthio" embraces aryl radicals of six to ten carbon atoms, attached to a divalent sulfur atom. An example of "arylthio" is phenylthio.

The term "aralkylthio" embraces aralkyl radicals as described above, attached to a divalent sulfur atom. More preferred are phenyl-C_1-C_3-alkylthio radicals. An example of "aralkylthio" is benzylthio.

The term "aryloxy" embraces optionally substituted aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy.

The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals having optionally substituted phenyl radicals attached to lower alkoxy radical as described above.

The term "heteroaryloxy" embraces optionally substituted heteroaryl radicals, as defined above, attached to an oxygen atom.

The term "heteroarylalkoxy" embraces oxy-containing heteroarylalkyl radicals attached through an oxygen atom to other radicals. More preferred heteroarylalkoxy radicals are "lower heteroarylalkoxy" radicals having optionally substituted heteroaryl radicals attached to lower alkoxy radical as described above.

The term "cycloalkyl" includes saturated carbocyclic groups. Preferred cycloalkyl groups include C_3-C_6 rings. More preferred compounds include, cyclopentyl, cyclopropyl, and cyclohexyl.

The term "cycloalkylalkyl" embraces cycloalkyl-substituted alkyl radicals. Preferable cycloalkylalkyl radicals are "lower cycloalkylalkyl" radicals having cycloalkyl radicals attached to alkyl radicals having one to six carbon atoms. Even more preferred are "5-6-

membered cycloalkylalkyl" attached to alkyl portions having one to three carbon atoms. Examples of such radicals include cyclohexylmethyl. The cycloalkyl in said radicals may be additionally substituted with halo, alkyl, alkoxy and hydroxy.

The term "cycloalkenyl" includes carbocyclic groups having one or more carbon-carbon double bonds including "cycloalkyldienyl" compounds. Preferred cycloalkenyl groups include C_3-C_6 rings. More preferred compounds include, for example, cyclopentenyl, cyclopentadienyl, cyclohexenyl and cycloheptadienyl.

The term "comprising" is meant to be open ended, including the indicated component but not excluding other elements.

The term(s) "Formulas I, II, III, IV, V, VI and VII" either alone or in combination includes any sub formulas.

The compounds of the invention are endowed with c-Met inhibitory activity.

The present invention also comprises the use of a compound of the invention, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment either acutely or chronically of an angiogenesis mediated disease state, including those described previously. The compounds of the present invention are useful in the manufacture of an anti-cancer medicament. The compounds of the present invention are also useful in the manufacture of a medicament to attenuate or prevent disorders through inhibition of c-Met.

The present invention comprises a pharmaceutical composition comprising a therapeutically effective amount of a compound of the current invention in association with a least one pharmaceutically acceptable carrier, adjuvant or diluent.

The present invention also comprises a method of treating angiogenesis related disorders in a subject having or susceptible to such disorder, the method comprising treating the subject with a therapeutically effective amount of a compound of the current invention.

COMBINATIONS

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more compounds of the invention or other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions that are administered at the same time or sequentially at different times, or the therapeutic agents can be given as a single composition.

The phrase "co-therapy" (or "combination-therapy"), in defining use of a compound of the present invention and another pharmaceutical agent, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a

substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent.

Specifically, the administration of compounds of the present invention may be in conjunction with additional therapies known to those skilled in the art in the prevention or treatment of neoplasia, such as with radiation therapy or with cytostatic or cytotoxic agents.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the accepted dosage ranges. Compounds of the current invention may also be administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of the invention may be administered either prior to, simultaneous with or after administration of the known anticancer or cytotoxic agent.

Currently, standard treatment of primary tumors consists of surgical excision followed by either radiation or IV administered chemotherapy. The typical chemotherapy regime consists of either DNA alkylating agents, DNA intercalating agents, CDK inhibitors, or microtubule poisons. The chemotherapy doses used are just below the maximal tolerated dose and therefore dose limiting toxicities typically include, nausea, vomiting, diarrhea, hair loss, neutropenia and the like.

There are large numbers of antineoplastic agents available in commercial use, in clinical evaluation and in pre-clinical development, which would be selected for treatment of neoplasia by combination drug chemotherapy. Such antineoplastic agents fall into several major categories, namely, antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents and a category of miscellaneous agents.

A first family of antineoplastic agents, which may be used in combination with compounds of the present invention, consists of antimetabolite-type/thymidilate synthase inhibitor antineoplastic agents. Suitable antimetabolite antineoplastic agents may be selected from but not limited to the group consisting of 5-FU-fibrinogen, acanthifolic acid, aminothiadiazole, brequinar sodium, carmofur, Ciba-Geigy CGP-30694, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, Lilly DATHF, Merrel Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine, Wellcome EHNA, Merck & Co. EX-015, fazarabine, floxuridine, fludarabine phosphate, 5-fluorouracil, N-(2'-furanidyl)-5-fluorouracil, Daiichi Seiyaku FO-152, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, methotrexate, Wellcome MZPES, norspermidine, NCI NSC-127716, NCI NSC-264880, NCI NSC-39661, NCI NSC-612567,

Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical PL-AC, Takeda TAC-788, thioguanine, tiazofurin, Erbamont TIF, trimetrexate, tyrosine kinase inhibitors, Taiho UFT and uricytin.

A second family of antineoplastic agents, which may be used in combination with compounds of the present invention, consists of alkylating-type antineoplastic agents. Suitable alkylating-type antineoplastic agents may be selected from but not limited to the group consisting of Shionogi 254-S, aldo-phosphamide analogues, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bestrabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine, Chinoin-139, Chinoin-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558, Sanofi CY-233, cyplatate, Degussa D-19-384, Sumimoto DACHP(Myr)2, diphenylspiromustine, diplatinum cytostatic, Erba distamycin derivatives, Chugai DWA-2114R, ITI E09, elmustine, Erbamont FCE-24517, estramustine phosphate sodium, fotemustine, Unimed G-6-M, Chinoin GYKI-17230, hepsul-fam, ifosfamide, iproplatin, lomustine, mafosfamide, mitolactol, Nippon Kayaku NK-121, NCI NSC-264395, NCI NSC-342215, oxaliplatin, Upjohn PCNU, prednimustine, Proter PTT-119, ranimustine, semustine, SmithKline SK&F-101772, Yakult Honsha SN-22, spiromus-tine, Tanabe Seiyaku TA-077, tauromustine, temozolomide, teroxirone, tetraplatin and trimelamol.

A third family of antineoplastic agents which may be used in combination with compounds of the present invention consists of antibiotic-type antineoplastic agents. Suitable antibiotic-type antineoplastic agents may be selected from but not limited to the group consisting of Taiho 4181-A, aclarubicin, actinomycin D, actinoplanone, Erbamont ADR-456, aeroplysinin derivative, Ajinomoto AN-201-II, Ajinomoto AN-3, Nippon Soda anisomycins, anthracycline, azino-mycin-A, bisucaberin, Bristol-Myers BL-6859, Bristol-Myers BMY-25067, Bristol-Myers BMY-25551, Bristol-Myers BMY-26605, Bristol-Myers BMY-27557, Bristol-Myers BMY-28438, bleomycin sulfate, bryostatin-1, Taiho C-1027, calichemycin, chromoximycin, dactinomycin, daunorubicin, Kyowa Hakko DC-102, Kyowa Hakko DC-79, Kyowa Hakko DC-88A, Kyowa Hakko DC89-A1, Kyowa Hakko DC92-B, ditrisarubicin B, Shionogi DOB-41, doxorubicin, doxorubicin-fibrinogen, elsamicin-A, epirubicin, erbstatin, esorubicin, esperamicin-A1, esperamicin-Alb, Erbamont FCE-21954, Fujisawa FK-973, fostriecin, Fujisawa FR-900482, glidobactin, gregatin-A, grincamycin, herbimycin, idarubicin, illudins, kazusamycin, kesarirhodins, Kyowa Hakko KM-5539, Kirin Brewery KRN-8602, Kyowa Hakko KT-5432, Kyowa Hakko KT-5594, Kyowa Hakko KT-6149, American Cyanamid LL-D49194, Meiji Seika ME 2303, menogaril, mitomycin, mitoxantrone, SmithKline M-TAG, neoenactin, Nippon Kayaku NK-313, Nippon Kayaku NKT-01, SRI

International NSC-357704, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, porothramycin, pyrindanycin A, Tobishi RA-I, rapamycin, rhizoxin, rodorubicin, sibanomicin, siwenmycin, Sumitomo SM-5887, Snow Brand SN-706, Snow Brand SN-07, sorangicin-A, sparsomycin, SS Pharmaceutical SS-21020, SS Pharmaceutical SS-7313B, SS Pharmaceutical SS-9816B, steffimycin B, Taiho 4181-2, talisomycin, Takeda TAN-868A, terpentecin, thrazine, tricrozarin A, Upjohn U-73975, Kyowa Hakko UCN-10028A, Fujisawa WF-3405, Yoshitomi Y-25024 and zorubicin.

A fourth family of antineoplastic agents which may be used in combination with compounds of the present invention consists of a miscellaneous family of antineoplastic agents, including tubulin interacting agents, topoisomerase II inhibitors, topoisomerase I inhibitors and hormonal agents, selected from but not limited to the group consisting of α-carotene, α-difluoromethyl-arginine, acitretin, Biotec AD-5, Kyorin AHC-52, alstonine, amonafide, amphethinile, amsacrine, Angiostat, ankinomycin, anti-neoplaston A10, antineoplaston A2, antineoplaston A3, antineoplaston A5, antineoplaston AS2-1, Henkel APD, aphidicolin glycinate, asparaginase, Avarol, baccharin, batracylin, benfluron, benzotript, Ipsen-Beaufour BIM-23015, bisantrene, Bristol-Myers BMY-40481, Vestar boron-10, bromofosfamide, Wellcome BW-502, Wellcome BW-773, caracemide, carmethizole hydrochloride, Ajinomoto CDAF, chlorsulfaquinoxalone, Chemes CHX-2053, Chemex CHX-100, Warner-Lambert CI-921, Warner-Lambert CI-937, Warner-Lambert CI-941, Warner-Lambert CI-958, clanfenur, claviridenone, ICN compound 1259, ICN compound 4711, Contracan, Yakult Honsha CPT-11, crisnatol, curaderm, cytochalasin B, cytarabine, cytocytin, Merz D-609, DABIS maleate, dacarbazine, datelliptinium, didemnin-B, dihaematoporphyrin ether, dihydrolenperone, dinaline, distamycin, Toyo Pharmar DM-341, Toyo Pharmar DM-75, Daiichi Seiyaku DN-9693, docetaxel elliprabin, elliptinium acetate, Tsumura EPMTC, the epothilones, ergotamine, etoposide, etretinate, fenretinide, Fujisawa FR-57704, gallium nitrate, genkwadaphnin, Chugai GLA-43, Glaxo GR-63178, grifolan NMF-5N, hexadecylphosphocholine, Green Cross HO-221, homoharringtonine, hydroxyurea, BTG ICRF-187, ilmofosine, isoglutamine, isotretinoin, Otsuka JI-36, Ramot K-477, Otsuak K-76COONa, Kureha Chemical K-AM, MECT Corp KI-8110, American Cyanamid L-623, leukoregulin, lonidamine, Lundbeck LU-23-112, Lilly LY-186641, NCI (US) MAP, marycin, Merrel Dow MDL-27048, Medco MEDR-340, merbarone, merocyanlne derivatives, methylanilinoacridine, Molecular Genetics MGI-136, minactivin, mitonafide, mitoquidone mopidamol, motretinide, Zenyaku Kogyo MST-16, N-(retinoyl)amino acids, Nisshin Flour Milling N-021, N-acylated-dehydroalanines, nafazatrom, Taisho NCU-190, nocodazole

derivative, Normosang, NCI NSC-145813, NCI NSC-361456, NCI NSC-604782, NCI NSC-95580, ocreotide, Ono ONO-112, oquizanocine, Akzo Org-10172, paclitaxel, pancratistatin, pazelliptine, Warner-Lambert PD-111707, Warner-Lambert PD-115934, Warner-Lambert PD-131141, Pierre Fabre PE-1001, ICRT peptide D, piroxantrone, polyhaematoporphyrin, polypreic acid, Efamol porphyrin, probimane, procarbazine, proglumide, Invitron protease nexin I, Tobishi RA-700, razoxane, Sapporo Breweries RBS, restrictin-P, retelliptine, retinoic acid, Rhone-Poulenc RP-49532, Rhone-Poulenc RP-56976, SmithKline SK&F-104864, Sumitomo SM-108, Kuraray SMANCS, SeaPharm SP-10094, spatol, spirocyclopropane derivatives, spirogermanium, Unimed, SS Pharmaceutical SS-554, strypoldinone, Stypoldione, Suntory SUN 0237, Suntory SUN 2071, superoxide dismutase, Toyama T-506, Toyama T-680, taxol, Teijin TEI-0303, teniposide, thaliblastine, Eastman Kodak TJB-29, tocotrienol, topotecan, Topostin, Teijin TT-82, Kyowa Hakko UCN-01, Kyowa Hakko UCN-1028, ukrain, Eastman Kodak USB-006, vinblastine sulfate, vincristine, vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, withanolides and Yamanouchi YM-534.

Alternatively, the present compounds may also be used in co-therapies with other anti-neoplastic agents, such as acemannan, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, amifostine, aminolevulinic acid, amrubicin, amsacrine, anagrelide, anastrozole, ANCER, ancestim, ARGLABIN, arsenic trioxide, BAM 002 (Novelos), bexarotene, bicalutamide, broxuridine, capecitabine, celmoleukin, cetrorelix, cladribine, clotrimazole, cytarabine ocfosfate, DA 3030 (Dong-A), daclizumab, denileukin diftitox, deslorelin, dexrazoxane, dilazep, docetaxel, docosanol, doxercalciferol, doxifluridine, doxorubicin, bromocriptine, carmustine, cytarabine, fluorouracil, HIT diclofenac, interferon alfa, daunorubicin, doxorubicin, tretinoin, edelfosine, edrecolomab, eflornithine, emitefur, epirubicin, epoetin beta, etoposide phosphate, exemestane, exisulind, fadrozole, filgrastim, finasteride, fludarabine phosphate, formestane, fotemustine, gallium nitrate, gemcitabine, gemtuzumab zogamicin, gimeracil/oteracil/tegafur combination, glycopine, goserelin, heptaplatin, human chorionic gonadotropin, human fetal alpha fetoprotein, ibandronic acid, idarubicin, (imiquimod, interferon alfa, interferon alfa, natural, interferon alfa-2, interferon alfa-2a, interferon alfa-2b, interferon alfa-N1, interferon alfa-n3, interferon alfacon-1, interferon alpha, natural, interferon beta, interferon beta-1a, interferon beta-1b, interferon gamma, natural interferon gamma-1a, interferon gamma-1b, interleukin-1 beta, iobenguane, irinotecan, irsogladine, lanreotide, LC 9018 (Yakult), leflunomide, lenograstim, lentinan sulfate, letrozole, leukocyte alpha interferon, leuprorelin, levamisole + fluorouracil, liarozole, lobaplatin, lonidamine, lovastatin, masoprocol, melarsoprol, metoclopramide, mifepristone,

miltefosine, mirimostim, mismatched double stranded RNA, mitoguazone, mitolactol, mitoxantrone, molgramostim, nafarelin, naloxone + pentazocine, nartograstim, nedaplatin, nilutamide, noscapine, novel erythropoiesis stimulating protein, NSC 631570 octreotide, oprelvekin, osaterone, oxaliplatin, paclitaxel, pamidronic acid, pegaspargase, peginterferon alfa-2b, pentosan polysulfate sodium, pentostatin, picibanil, pirarubicin, rabbit antithymocyte polyclonal antibody, polyethylene glycol interferon alfa-2a, porfimer sodium, raloxifene, raltitrexed, rasburicase, rhenium Re 186 etidronate, RII retinamide, rituximab, romurtide, samarium (153 Sm) lexidronam, sargramostim, sizofiran, sobuzoxane, sonermin, strontium-89 chloride, suramin, tasonermin, tazarotene, tegafur, temoporfin, temozolomide, teniposide, tetrachlorodecaoxide, thalidomide, thymalfasin, thyrotropin alfa, topotecan, toremifene, tositumomab-iodine 131, trastuzumab, treosulfan, tretinoin, trilostane, trimetrexate, triptorelin, tumor necrosis factor alpha, natural, ubenimex, bladder cancer vaccine, Maruyama vaccine, melanoma lysate vaccine, valrubicin, verteporfin, vinorelbine, VIRULIZIN, zinostatin stimalamer, or zoledronic acid; abarelix; AE 941 (Aeterna), ambamustine, antisense oligonucleotide, bcl-2 (Genta), APC 8015 (Dendreon), cetuximab, decitabine, dexaminoglutethimide, diaziquone, EL 532 (Elan), EM 800 (Endorecherche), eniluracil, etanidazole, fenretinide, filgrastim SD01 (Amgen), fulvestrant, galocitabine, gastrin 17 immunogen, HLA-B7 gene therapy (Vical), granulocyte macrophage colony stimulating factor, histamine dihydrochloride, ibritumomab tiuxetan, ilomastat, IM 862 (Cytran), interleukin-2, iproxifene, LDI 200 (Milkhaus), leridistim, lintuzumab, CA 125 MAb (Biomira), cancer MAb (Japan Pharmaceutical Development), HER-2 and Fc MAb (Medarex), idiotypic 105AD7 MAb (CRC Technology), idiotypic CEA MAb (Trilex), LYM-1-iodine 131 MAb (Techniclone), polymorphic epithelial mucin-yttrium 90 MAb (Antisoma), marimastat, menogaril, mitumomab, motexafin gadolinium, MX 6 (Galderma), nelarabine, nolatrexed, P 30 protein, pegvisomant, pemetrexed, porfiromycin, prinomastat, RL 0903 (Shire), rubitecan, satraplatin, sodium phenylacetate, sparfosic acid, SRL 172 (SR Pharma), SU 5416 (SUGEN), TA 077 (Tanabe), tetrathiomolybdate, thaliblastine, thrombopoietin, tin ethyl etiopurpurin, tirapazamine, cancer vaccine (Biomira), melanoma vaccine (New York University), melanoma vaccine (Sloan Kettering Institute), melanoma oncolysate vaccine (New York Medical College), viral melanoma cell lysates vaccine (Royal Newcastle Hospital), or valspodar.

Alternatively, the present compounds may also be used in co-therapies with VEGFR inhibitors including:

AMG 706 (motesanib diphosphate);

N-(4-chlorophenyl)-4-(4-pyridinylmethyl)-1-phthalazinamine;

4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl-2-pyridinecarboxamide;

N-[2-(diethylamino)ethyl]-5-[(5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide;

3-[(4-bromo-2,6-difluorophenyl)methoxy]-5-[[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-4-isothiazolecarboxamide;

N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methyl-4-piperidinyl)methoxy]-4-quinazolinamine;

3-[5,6,7,13-tetrahydro-9-[(1-methylethoxy)methyl]-5-oxo-12H-indeno[2,1-a]pyrrolo[3,4-c]carbazol-12-yl]propyl ester N,N-dimethyl-glycine;

N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide;

N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[5-[[[2-(methylsulfonyl)ethyl]amino]methyl]-2-furanyl]-4-quinazolinamine

4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide

N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]-4-quinazolinamine

N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine

N-(3-((((2R)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-2-((3-(1,3-oxazol-5-yl)phenyl)amino)-3-pyridinecarboxamide;

2-(((4-fluorophenyl)methyl)amino)-N-(3-((((2R)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;

N-[3-(Azetidin-3-ylmethoxy)-5-trifluoromethyl-phenyl]-2-(4-fluoro-benzylamino)-nicotinamide.

6-fluoro-N-(4-(1-methylethyl)phenyl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;

2-((4-pyridinylmethyl)amino)-N-(3-(((2S)-2-pyrrolidinylmethyl)oxy)-5-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;

N-(3-(1,1-dimethylethyl)-1H-pyrazol-5-yl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;

N-(3,3-dimethyl-2,3-dihydro-1-benzofuran-6-yl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;

N-(3-((((2S)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;

2-((4-pyridinylmethyl)amino)-N-(3-((2-(1-pyrrolidinyl)ethyl)oxy)-4-(trifluoromethyl)phenyl)-3-pyridinecarboxamide;

N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;

N-(4-(pentafluoroethyl)-3-(((2S)-2-pyrrolidinylmethyl)oxy)phenyl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;

N-(3-((3-azetidinylmethyl)oxy)-5-(trifluoromethyl)phenyl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide;

N-(3-(4-piperidinyloxy)-5-(trifluoromethyl)phenyl)-2-((2-(3-pyridinyl)ethyl)amino)-3-pyridinecarboxamide;

N-(4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-(1H-indazol-6-ylamino)-nicotinamide;

2-(1H-indazol-6-ylamino)-N-[3-(1-methylpyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide;

N-[1-(2-dimethylamino-acetyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl]-2-(1H-indazol-6-ylamino)-nicotinamide;

2-(1H-indazol-6-ylamino)-N-[3-(pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide;

N-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(1H-indazol-6-ylamino)-nicotinamide;

N-(4,4-dimethyl-1-oxo-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-(1H-indazol-6-ylamino)-nicotinamide;

N-[4-(tert-butyl)-3-(3-piperidylpropyl)phenyl][2-(1H-indazol-6-ylamino)(3-pyridyl)]carboxamide;

N-[5-(tert-butyl)isoxazol-3-yl][2-(1H-indazol-6-ylamino)(3-pyridyl)]carboxamide; and

N-[4-(tert-butyl)phenyl][2-(1H-indazol-6-ylamino)(3-pyridyl)]carboxamide.

Other compounds described in the following patents and patent applications can be used in combination therapy: US 6,258,812, US 2003/0105091, WO 01/37820, US 6,235,764, WO 01/32651, US 6,630,500, US 6,515,004, US 6,713,485, US 5,521,184, US 5,770,599, US 5,747,498, WO 02/68406, WO 02/66470, WO 02/55501, WO 04/05279, WO 04/07481, WO 04/07458, WO 04/09784, WO 02/59110, WO 99/45009, WO 00/59509, WO 99/61422, US 5,990,141, WO 00/12089 and WO 00/02871.

In some embodiments, the combination comprises a composition of the present invention in combination with at least one anti-angiogenic agent. Agents are inclusive of, but not limited to, *in vitro* synthetically prepared chemical compositions, antibodies, antigen binding regions, radionuclides, and combinations and conjugates thereof. An agent can be an agonist, antagonist, allosteric modulator, toxin or, more generally, may act to inhibit or

stimulate its target (e.g., receptor or enzyme activation or inhibition), and thereby promote cell death or arrest cell growth.

Exemplary anti-tumor agents include HERCEPTIN™ (trastuzumab), which may be used to treat breast cancer and other forms of cancer, and RITUXAN™ (rituximab), ZEVALIN™ (ibritumomab tiuxetan), and LYMPHOCIDE™ (epratuzumab), which may be used to treat non-Hodgkin's lymphoma and other forms of cancer, GLEEVAC™ which may be used to treat chronic myeloid leukemia and gastrointestinal stromal tumors, and BEXXAR™ (iodine 131 tositumomab) which may be used for treatment of non-Hodgkins's lymphoma.

Exemplary anti-angiogenic agents include ERBITUX™ (IMC-C225), KDR (kinase domain receptor) inhibitory agents (e.g., antibodies and antigen binding regions that specifically bind to the kinase domain receptor), anti-VEGF agents (e.g., antibodies or antigen binding regions that specifically bind VEGF, or soluble VEGF receptors or a ligand binding region thereof) such as AVASTIN™ or VEGF-TRAP™, and anti-VEGF receptor agents (e.g., antibodies or antigen binding regions that specifically bind thereto), EGFR inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto) such as ABX-EGF (panitumumab), IRESSA™ (gefitinib), TARCEVA™ (erlotinib), anti-Ang1 and anti-Ang2 agents (e.g., antibodies or antigen binding regions specifically binding thereto or to their receptors, e.g., Tie2/Tek), and anti-Tie2 kinase inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto). The pharmaceutical compositions of the present invention can also include one or more agents (e.g., antibodies, antigen binding regions, or soluble receptors) that specifically bind and inhibit the activity of growth factors, such as antagonists of hepatocyte growth factor (HGF, also known as Scatter Factor), and antibodies or antigen binding regions that specifically bind its receptor "c-met".

Other anti-angiogenic agents include Campath, IL-8, B-FGF, Tek antagonists (Ceretti et al., US Publication No. 2003/0162712; US Patent No. 6,413,932), anti-TWEAK agents (e.g., specifically binding antibodies or antigen binding regions, or soluble TWEAK receptor antagonists; see, Wiley, US Patent No. 6,727,225), ADAM distintegrin domain to antagonize the binding of integrin to its ligands (Fanslow et al., US Publication No. 2002/0042368), specifically binding anti-eph receptor and/or anti-ephrin antibodies or antigen binding regions (US Patent Nos. 5,981,245; 5,728,813; 5,969,110; 6,596,852; 6,232,447; 6,057,124 and patent family members thereof), and anti-PDGF-BB antagonists (e.g., specifically binding antibodies or antigen binding regions) as well as antibodies or antigen binding regions specifically binding to PDGF-BB ligands, and PDGFR kinase inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto).

Additional anti-angiogenic/anti-tumor agents include: SD-7784 (Pfizer, USA); cilengitide.(Merck KGaA, Germany, EPO 770622); pegaptanib octasodium, (Gilead Sciences, USA); Alphastatin, (BioActa, UK); M-PGA, (Celgene, USA, US 5712291); ilomastat, (Arriva, USA, US 5892112); emaxanib, (Pfizer, USA, US 5792783); vatalanib, (Novartis, Switzerland); 2-methoxyestradiol, (EntreMed, USA); TLC ELL-12, (Elan, Ireland); anecortave acetate, (Alcon, USA); alpha-D148 Mab, (Amgen, USA); CEP-7055,(Cephalon, USA); anti-Vn Mab, (Crucell, Netherlands) DAC:antiangiogenic, (ConjuChem, Canada); Angiocidin, (InKine Pharmaceutical, USA); KM-2550, (Kyowa Hakko, Japan); SU-0879, (Pfizer, USA); CGP-79787, (Novartis, Switzerland, EP 970070); ARGENT technology, (Ariad, USA); YIGSR-Stealth, (Johnson & Johnson, USA); fibrinogen-E fragment, (BioActa, UK); angiogenesis inhibitor, (Trigen, UK); TBC-1635, (Encysive Pharmaceuticals, USA); SC-236, (Pfizer, USA); ABT-567, (Abbott, USA); Metastatin, (EntreMed, USA); angiogenesis inhibitor, (Tripep, Sweden); maspin, (Sosei, Japan); 2-methoxyestradiol, (Oncology Sciences Corporation, USA); ER-68203-00, (IVAX, USA); Benefin, (Lane Labs, USA); Tz-93, (Tsumura, Japan); TAN-1120, (Takeda, Japan); FR-111142, (Fujisawa, Japan, JP 02233610); platelet factor 4, (RepliGen, USA, EP 407122); vascular endothelial growth factor antagonist, (Borean, Denmark); cancer therapy, (University of South Carolina, USA); bevacizumab (pINN), (Genentech, USA); angiogenesis inhibitors, (SUGEN, USA); XL 784, (Exelixis, USA); XL 647, (Exelixis, USA); MAb, alpha5beta3 integrin, second generation, (Applied Molecular Evolution, USA and MedImmune, USA); gene therapy, retinopathy, (Oxford BioMedica, UK); enzastaurin hydrochloride (USAN), (Lilly, USA); CEP 7055, (Cephalon, USA and Sanofi-Synthelabo, France); BC 1, (Genoa Institute of Cancer Research, Italy); angiogenesis inhibitor, (Alchemia, Australia); VEGF antagonist, (Regeneron, USA); rBPI 21 and BPI-derived antiangiogenic, (XOMA, USA); PI 88, (Progen, Australia); cilengitide (pINN), (Merck KGaA, German; Munich Technical University, Germany, Scripps Clinic and Research Foundation, USA); cetuximab (INN), (Aventis, France); AVE 8062, (Ajinomoto, Japan); AS 1404, (Cancer Research Laboratory, New Zealand); SG 292, (Telios, USA); Endostatin, (Boston Childrens Hospital, USA); ATN 161, (Attenuon, USA); ANGIOSTATIN, (Boston Childrens Hospital, USA); 2-methoxyestradiol, (Boston Childrens Hospital, USA); ZD 6474, (AstraZeneca, UK); ZD 6126, (Angiogene Pharmaceuticals, UK); PPI 2458, (Praecis, USA); AZD 9935, (AstraZeneca, UK); AZD 2171, (AstraZeneca, UK); vatalanib (pINN), (Novartis, Switzerland and Schering AG, Germany); tissue factor pathway inhibitors, (EntreMed, USA); pegaptanib (Pinn), (Gilead Sciences, USA); xanthorrhizol, (Yonsei University, South Korea); vaccine, gene-based, VEGF-2, (Scripps Clinic and Research

Foundation, USA); SPV5.2, (Supratek, Canada); SDX 103, (University of California at San Diego, USA); PX 478, (ProlX, USA); METASTATIN, (EntreMed, USA); troponin I, (Harvard University, USA); SU 6668, (SUGEN, USA); OXI 4503, (OXiGENE, USA); o-guanidines, (Dimensional Pharmaceuticals, USA); motuporamine C, (British Columbia University, Canada); CDP 791, (Celltech Group, UK); atiprimod (pINN), (GlaxoSmithKline, UK); E 7820, (Eisai, Japan); CYC 381, (Harvard University, USA); AE 941, (Aeterna, Canada); vaccine, angiogenesis, (EntreMed, USA); urokinase plasminogen activator inhibitor, (Dendreon, USA); oglufanide (pINN), (Melmotte, USA); HIF-1alfa inhibitors, (Xenova, UK); CEP 5214, (Cephalon, USA); BAY RES 2622, (Bayer, Germany); Angiocidin, (InKine, USA); A6, (Angstrom, USA); KR 31372, (Korea Research Institute of Chemical Technology, South Korea); GW 2286, (GlaxoSmithKline, UK); EHT 0101, (ExonHit, France); CP 868596, (Pfizer, USA); CP 564959, (OSI, USA); CP 547632, (Pfizer, USA); 786034, (GlaxoSmithKline, UK); KRN 633, (Kirin Brewery, Japan); drug delivery system, intraocular, 2-methoxyestradiol, (EntreMed, USA); anginex, (Maastricht University, Netherlands, and Minnesota University, USA); ABT 510, (Abbott, USA); AAL 993, (Novartis, Switzerland); VEGI, (ProteomTech, USA); tumor necrosis factor-alpha inhibitors, (National Institute on Aging, USA); SU 11248, (Pfizer, USA and SUGEN USA); ABT 518, (Abbott, USA); YH16, (Yantai Rongchang, China); S-3APG , (Boston Childrens Hospital, USA and EntreMed, USA); MAb, KDR, (ImClone Systems, USA); MAb, alpha5 beta1, (Protein Design, USA); KDR kinase inhibitor, (Celltech Group, UK, and Johnson & Johnson, USA); GFB 116, (South Florida University, USA and Yale University, USA); CS 706, (Sankyo, Japan); combretastatin A4 prodrug, (Arizona State University, USA); chondroitinase AC, (IBEX, Canada); BAY RES 2690, (Bayer, Germany); AGM 1470, (Harvard University, USA, Takeda, Japan, and TAP, USA); AG 13925, (Agouron, USA); Tetrathiomolybdate, (University of Michigan, USA); GCS 100, (Wayne State University, USA) CV 247, (Ivy Medical, UK); CKD 732, (Chong Kun Dang, South Korea); MAb, vascular endothelium growth factor, (Xenova, UK); irsogladine (INN), (Nippon Shinyaku, Japan); RG 13577, (Aventis, France); WX 360, (Wilex, Germany); squalamine (pINN), (Genaera, USA); RPI 4610, (Sirna, USA); cancer therapy, (Marinova, Australia); heparanase inhibitors, (InSight, Israel); KL 3106, (Kolon, South Korea); Honokiol, (Emory University, USA); ZK CDK, (Schering AG, Germany); ZK Angio, (Schering AG, Germany); ZK 229561, (Novartis, Switzerland, and Schering AG, Germany); XMP 300, (XOMA, USA); VGA 1102, (Taisho, Japan); VEGF receptor modulators, (Pharmacopeia, USA); VE-cadherin-2 antagonists , (ImClone Systems, USA); Vasostatin, (National Institutes of Health, USA);vaccine, Flk-1, (ImClone Systems, USA); TZ 93, (Tsumura, Japan);

TumStatin, (Beth Israel Hospital, USA); truncated soluble FLT 1 (vascular endothelial growth factor receptor 1), (Merck & Co, USA); Tie-2 ligands, (Regeneron, USA); and, thrombospondin 1 inhibitor, (Allegheny Health, Education and Research Foundation, USA).

Alternatively, the present compounds may also be used in co-therapies with other anti-neoplastic agents, such as VEGF antagonists, other kinase inhibitors including p38 inhibitors, KDR inhibitors, EGF inhibitors and CDK inhibitors, TNF inhibitors, metallomatrix proteases inhibitors (MMP), COX-2 inhibitors including celecoxib, NSAID's, or $\alpha_v\beta_3$ inhibitors.

The present invention comprises processes for the preparation of a compound of Formula I, II, III, IV, V, VI and VII.

Also included in the family of compounds of the current are the pharmaceutically acceptable salts and solvates thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts of compounds of the current invention may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, arylaliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, adipic, butyric, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, ethanedisulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, camphoric, camphorsulfonic, digluconic, cyclopentanepropionic, dodecylsulfonic, glucoheptanoic, glycerophosphonic, heptanoic, hexanoic, 2-hydroxy-ethanesulfonic, nicotinic, 2-naphthalenesulfonic, oxalic, palmoic, pectinic, persulfuric, 2-phenylpropionic, picric, pivalic propionic, succinic, tartaric, thiocyanic, mesylic, undecanoic, stearic, algenic, β-hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of the current invention include metallic salts, such as salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc, or salts made from organic bases including primary, secondary and tertiary amines, substituted amines including cyclic amines, such as caffeine, arginine, diethylamine, N-ethyl piperidine, aistidine, glucamine, isopropylamine, lysine, morpholine, N-ethyl morpholine, piperazine, piperidine, triethylamine, trimethylamine. All of these salts may be prepared by conventional means from the corresponding compound of the

invention by reacting, for example, the appropriate acid or base with the compound of the current invention. When a basic group and an acid group are present in the same molecule, a compound of the current invention may also form internal salts.

GENERAL SYNTHETIC PROCEDURES

The compounds of the invention can be synthesized according to the general procedures described in WO 08/008539 (the entirety of which is incorporated herein by reference) as well as those illustrated in the example compounds described below.

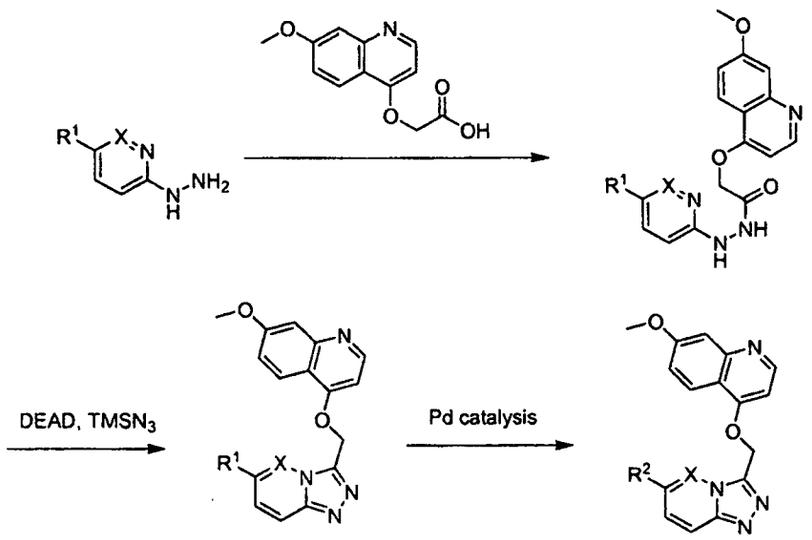
The following abbreviations are used throughout the specification:

HOAc	-	acetic acid
MeCN, CH_3CN	-	acetonitrile
NH_3	-	ammonia
NH_4Cl	-	ammonium chloride
Ar	-	argon
HBTA	-	O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
HATU	-	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
PyBop	-	benzotriazol-1-yl-oxy-tripyrrolidino-phosphonium hexafluorophosphate
$Pd_2(dba)_3$	-	bis(dibenzylideneacetone) palladium
BINAP	-	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
TEAC	-	bis(tetra-ethylammonium)carbonate
BBr_3	-	boron tribromide
BSA	-	bovine serum albumin
Br_2	-	bromine
BOC	-	butyloxycarbonyl
Cs_2CO_3	-	cesium carbonate
$CHCl_3$	-	chloroform
$CDCl_3$	-	chloroform deuterated
Cu	-	copper
CuI	-	copper(I) iodide
Et_2O	-	diethyl ether
DBU	-	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	-	diisobutylaluminum hydride

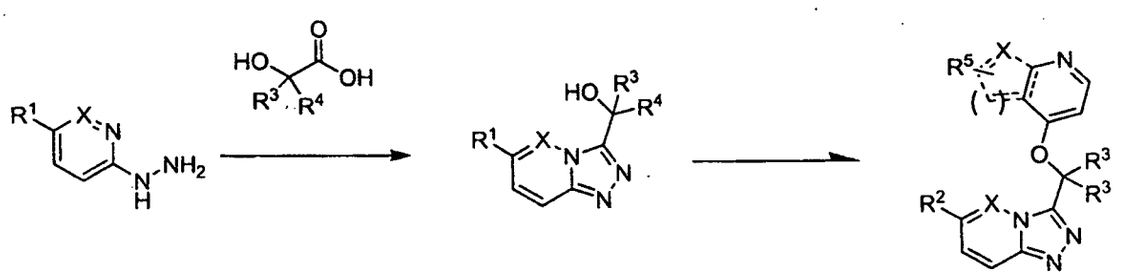
	DIAD	-	diisopropyl azodicarboxylate
	DIEA	-	diisopropylethylamine
	DMF	-	dimethylformamide
	DMAP	-	4-dimethylaminopyridine
	DMSO	-	dimethylsulfoxide
	EDC, EDCI	-	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
	dppa	-	diphenylphosphoryl azide
	EtOAc	-	ethyl acetate
	FBS	-	fetal bovine serum
	g	-	gram
	h	-	hour
	HBr	-	hydrobromic acid
	HCl	-	hydrochloric acid
	HOBt	-	1-hydroxybenzotriazole hydrate
	H_2	-	hydrogen
	H_2O_2	-	hydrogen peroxide
	Fe	-	iron
	LiHMDS	-	lithium bis(trimethylsilyl)-amide
	LDA	-	Lithium diisopropylamide
	MCPBA	-	*meta*-chloroperbenzoic acid
	$MgSO_4$	-	magnesium sulfate
	MeOH, CH_3OH	-	methanol
	MeI	-	methyl iodide
	CH_2Cl_2, DCM	-	methylene chloride
	NMP	-	N-methylpyrrolidinone
	ML, ml	-	milliliter
	N_2	-	nitrogen
	Pd/C	-	palladium on carbon
	$Pd(OAc)_2$	-	palladium acetate
	$Pd(OH)_2$	-	palladium hydroxide
	$Pd(PPh_3)_4$	-	palladium tetrakis triphenylphosphine
	$Pd(dppf)Cl_2$	-	1,1-bis(diphenylphosphino)ferrocene palladium chloride
	PBS	-	phosphate buffered saline
	$POCl_3$	-	phosphorous oxychloride

	K_2CO_3	-	potassium carbonate
	KOH	-	potassium hydroxide
	RT	-	room temperature
	$NaHCO_3$	-	sodium bicarbonate
5	$NaBH_4$	-	sodium borohydride
	$NaBH_3CN$	-	sodium cyanoborohydride
	NaOtBu	-	sodium tert-butoxide
	NaOH	-	sodium hydroxide
	$NaClO_2$	-	sodium chlorite
10	NaCl	-	sodium chloride
	$NaHPO_4$	-	sodium biphospate
	NaH	-	sodium hydride
	NaI	-	sodium iodide
	Na_2SO_4	-	sodium sulfate
15	TBTU	-	O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate
	THF	-	tetrahydrofuran
	Et_3N, TEA	-	triethylamine
	TFA	-	trifluoroacetic acid
20	P(*t*-bu)$_3$	-	tri(tert-butyl)phosphine
	H_2O	-	water

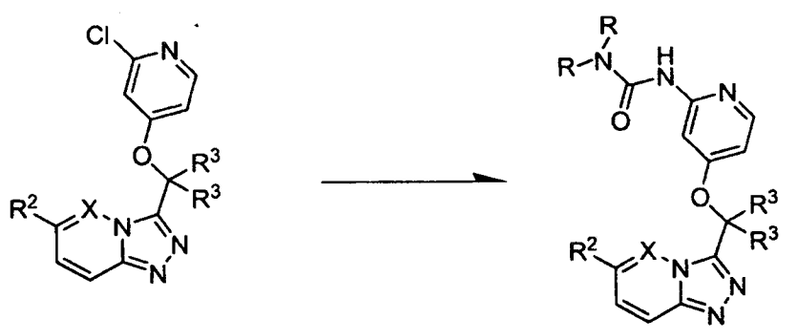
General Method A



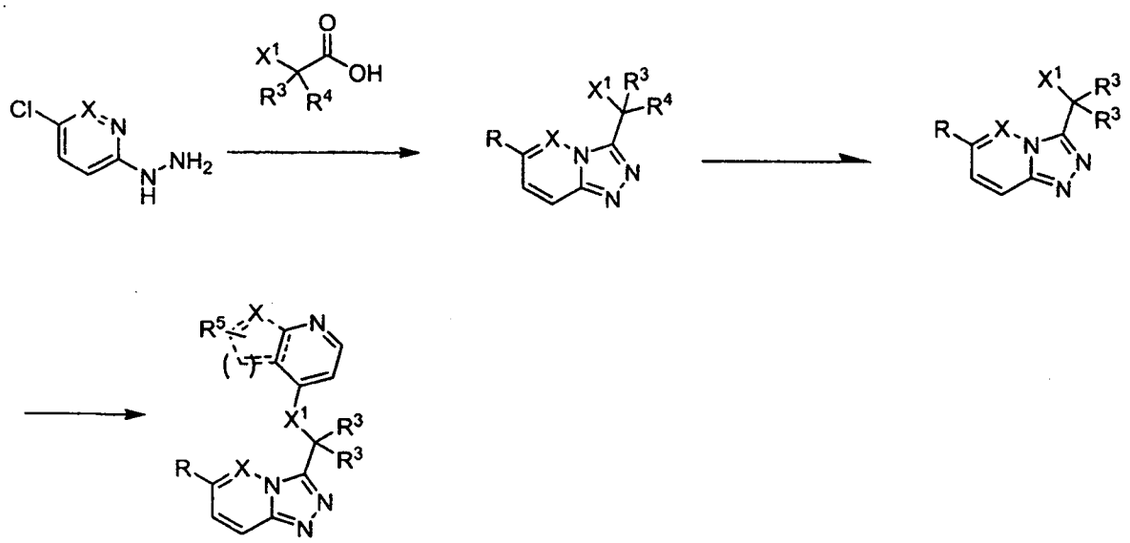
General Method B



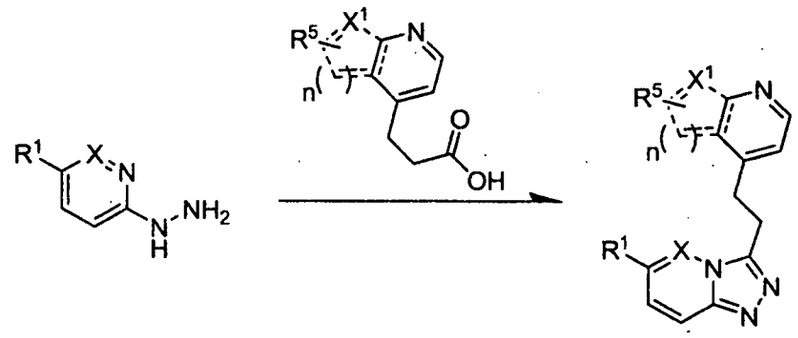
General Method C



General Method D

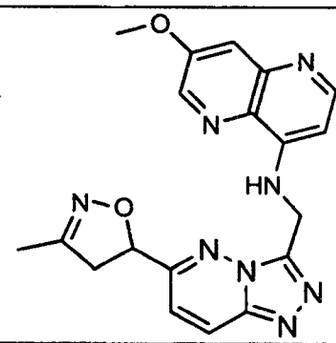


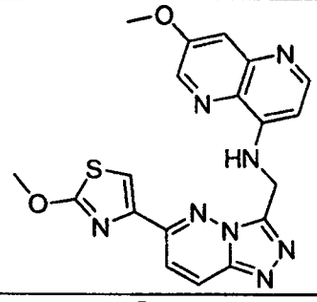
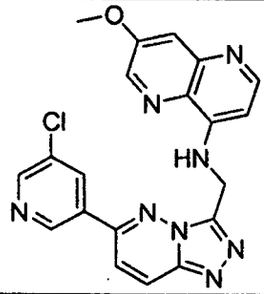
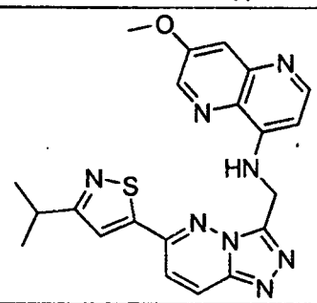
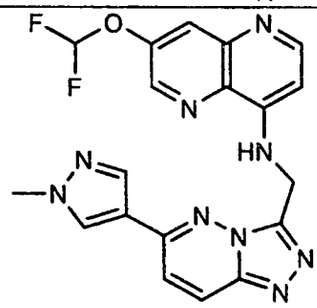
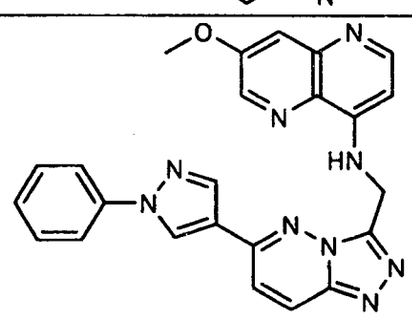
General Method E

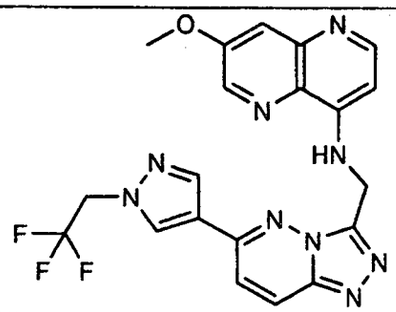
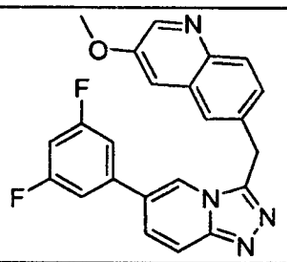
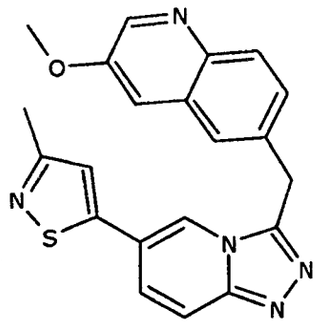
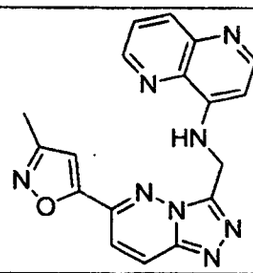
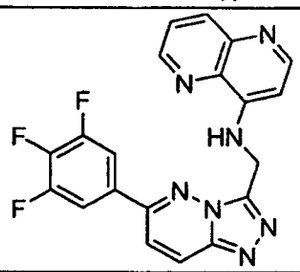


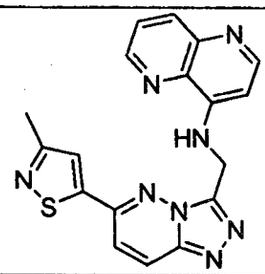
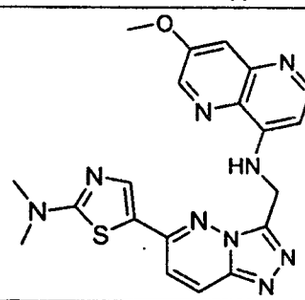
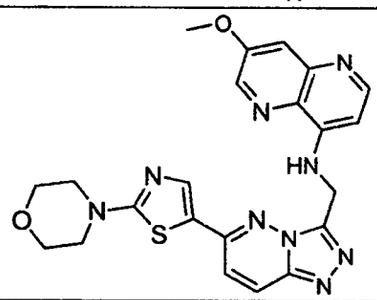
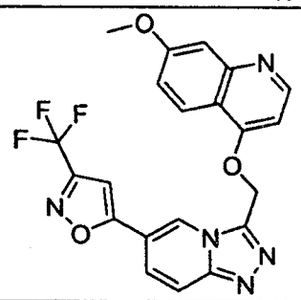
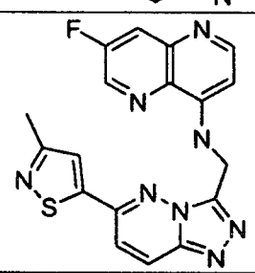
Examples 1-343

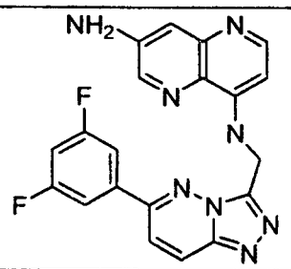
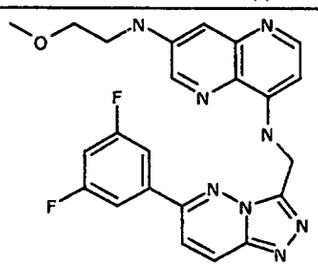
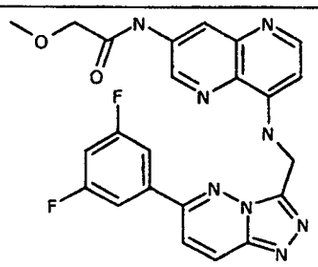
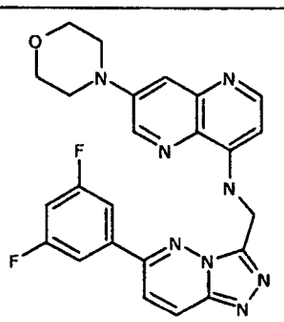
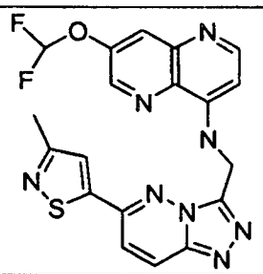
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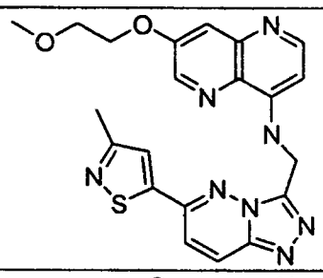
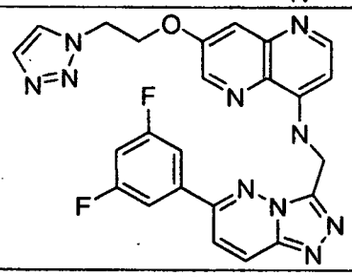
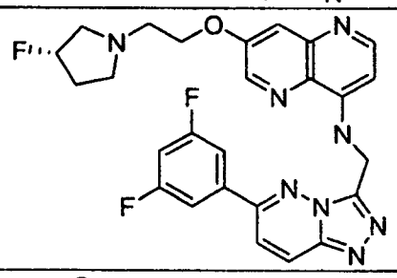
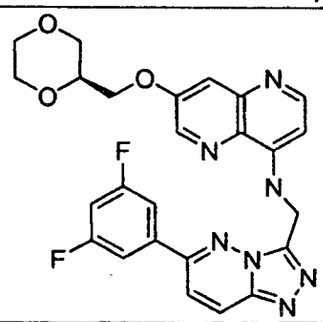
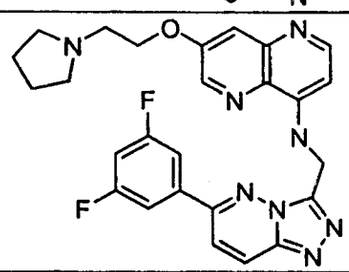
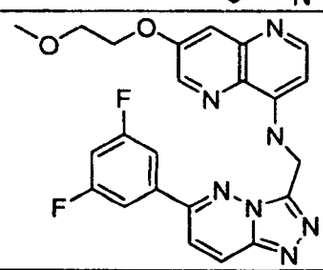
EX.	Structure	MW	Mass Found	General Method
344		390	391	D

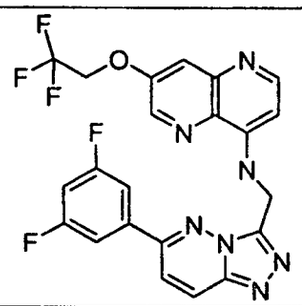
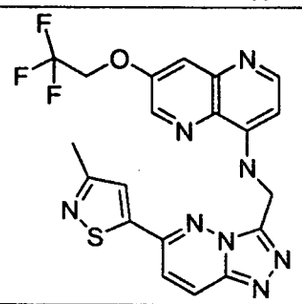
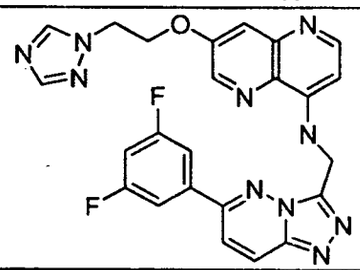
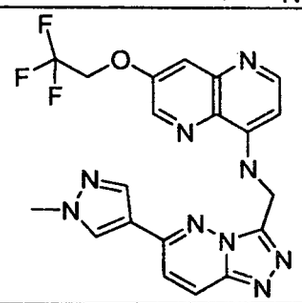
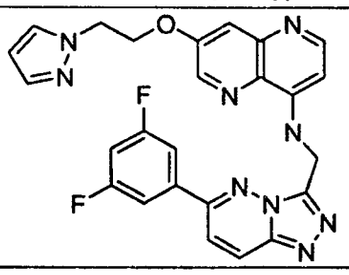
EX.	Structure	MW	Mass Found	General Method
345		420	421	D
346		418	419	D
347		432	433	D
348		423	424	D
349		449	450	D

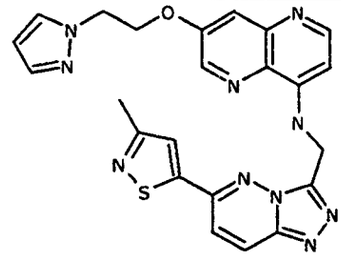
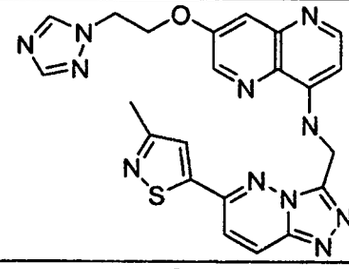
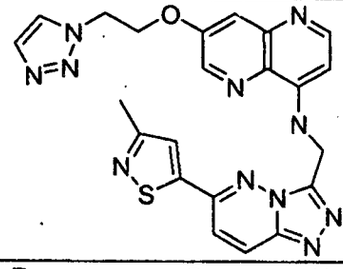
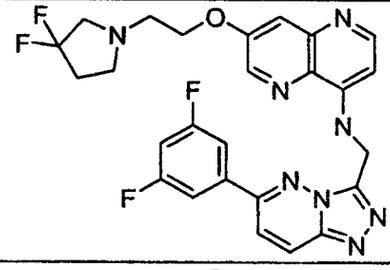
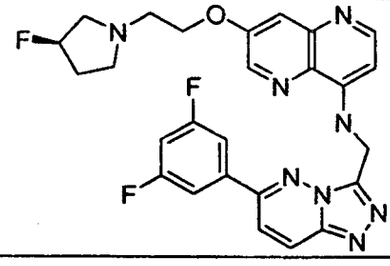
EX.	Structure	MW	Mass Found	General Method
350		455	456	D
351		402	403	A
352		387	388	A
353		358	359	D
354		407	408	D

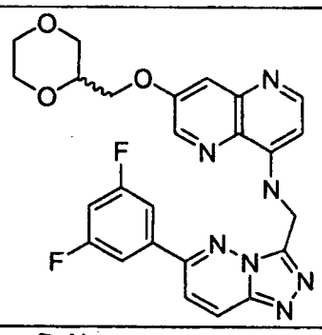
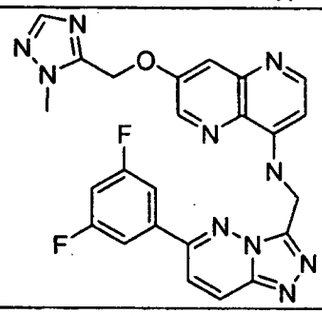
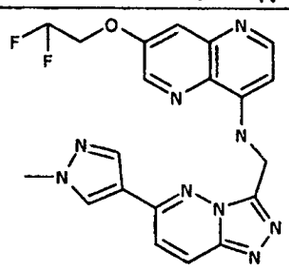
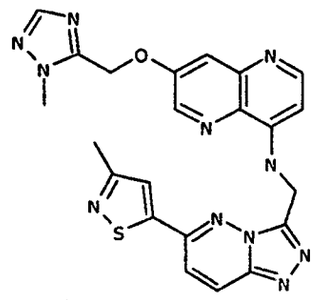
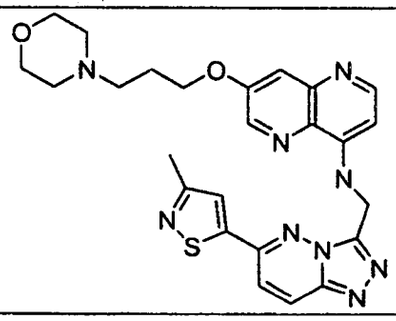
EX.	Structure	MW	Mass Found	General Method
355		374	375	D
356		433	434	D
357		475	476	D
358		441	442	A
359		392	393	D

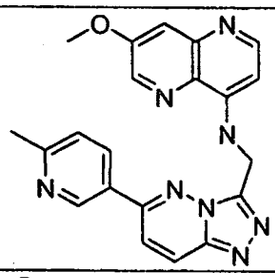
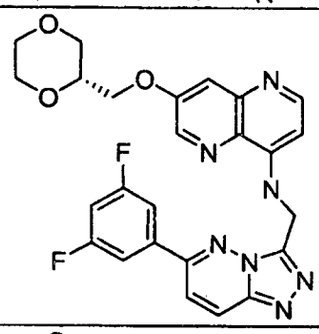
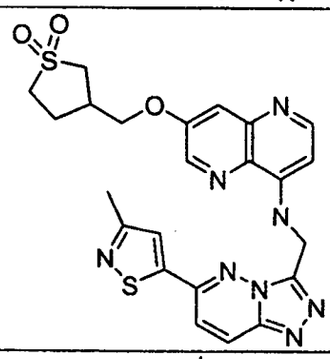
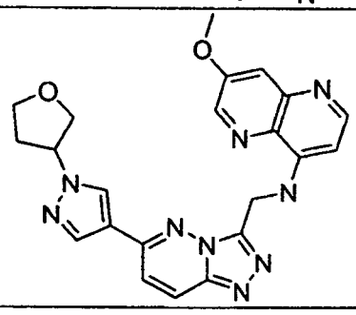
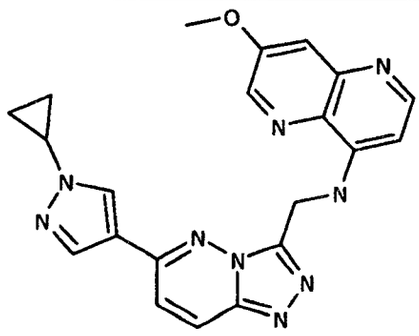
EX.	Structure	MW	Mass Found	General Method
360		404	405	D
361		462	463	D
362		476	477	D
363		474	475	D
364		440	441	D

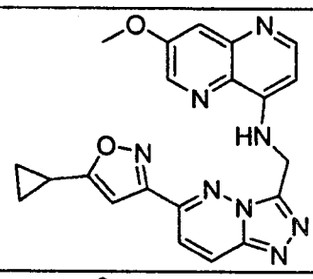
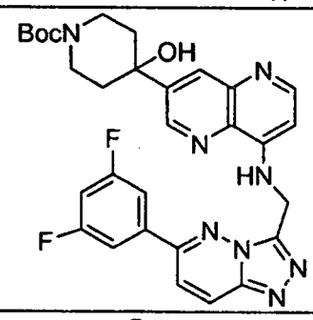
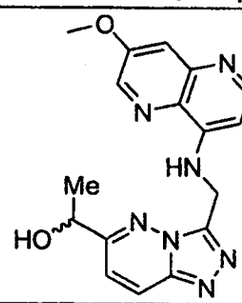
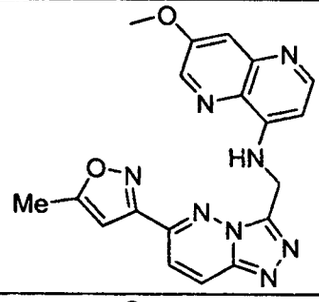
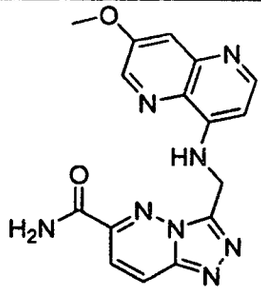
EX.	Structure	MW	Mass Found	General Method
365		448	449	D
366		500	501	D
367		520	521	D
368		505	506	D
369		502	503	D
370		463	464	D

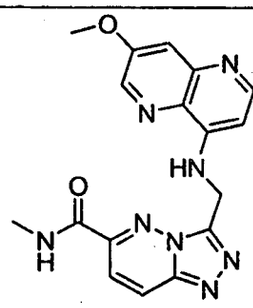
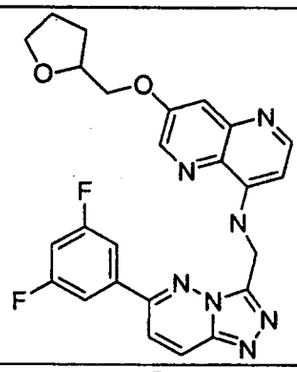
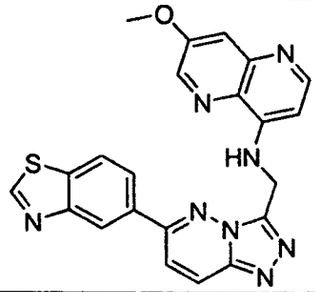
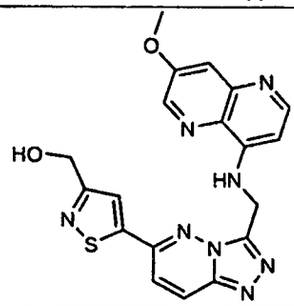
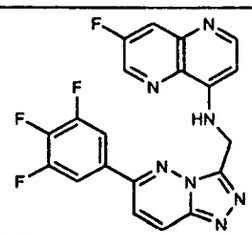
EX.	Structure	MW	Mass Found	General Method
371		487	488	D
372		472	473	D
373		500	501	D
374		455	456	D
375		499	500	D

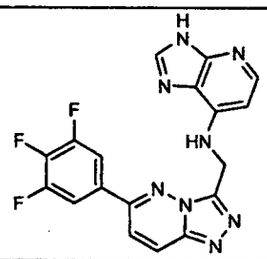
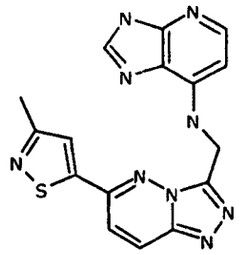
EX.	Structure	MW	Mass Found	General Method
376		484	485	D
377		485	486	D
378		485	485	D
379		538	539	D
380		520	521	D

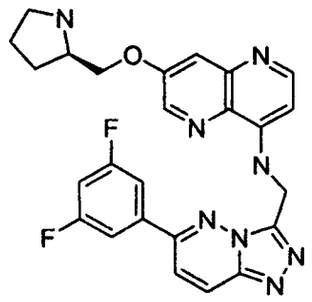
EX.	Structure	MW	Mass Found	General Method
381		505	506	D
382		500	501	D
383		437	438	D
384		485	486	D
385		517	518	D

EX.	Structure	MW	Mass Found	General Method
386		398	399	D
387		505	506	D
388		522	523	D
389		443	444	D
390		413	414	D

EX.	Structure	MW	Mass Found	General Method
391		414	415	D
392		488	489	D
393		351	352	D
394		388	388	D
395		350	351	D

EX.	Structure	MW	Mass Found	General Method
396		364	365	D
397		489	490	D
398		440	441	D
399		420	421	D
400		425	426	D

EX.	Structure	MW	Mass Found	General Method
401		396	397	D
402		363	364	D

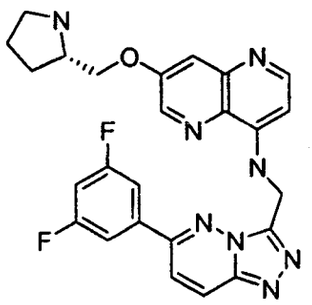


Example 403

(R)-N-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-(pyrrolidin-2-ylmethoxy)-1,5-naphthyridin-4-amine

a) (R)-tert-butyl 2-((8-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylamino)-1,5-naphthyridin-3-yloxy)methyl)pyrrolidine-1-carboxylate was prepared according to method D.

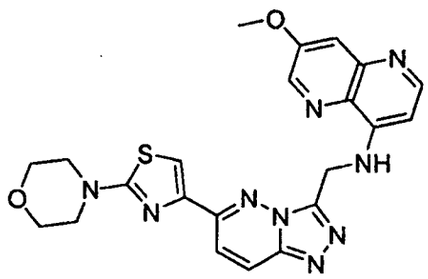
b) (R)-N-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-(pyrrolidin-2-ylmethoxy)-1,5-naphthyridin-4-amine. The title compound was prepared from (R)-tert-butyl 2-((8-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylamino)-1,5-naphthyridin-3-yloxy)methyl)pyrrolidine-1-carboxylate following the procedure used to make 7-methoxy-4-((6-(6-(piperazin-1-yl)pyridin-3-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methoxy)quinoline. *m/z*: 489 (M+H). Calc'd. for $C_{25}H_{22}F_2N_8O$ – 488.



Example 404

(S)-N-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-(pyrrolidin-2-ylmethoxy)-1,5-naphthyridin-4-amine

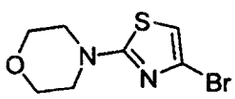
The title compound was prepared in the same manner as (R)-N-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-(pyrrolidin-2-ylmethoxy)-1,5-naphthyridin-4-amine. *m/z*: 489 (M+H). Calc'd. for $C_{25}H_{22}F_2N_8O$ – 488.



Example 405

7-methoxy-*N*-((6-(2-morpholinothiazol-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methyl)-1,5-naphthyridin-4-amine

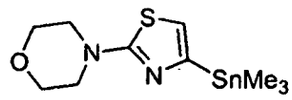
1) 4-(4-bromothiazol-2-yl)morpholine



To a microwave vial was added *N,N*-diisopropylethylamine (0.86 ml, 4.9 mmol), 2,4-dibromothiazole (1.00 g, 4.1 mmol), and morpholine (0.43 ml, 4.9 mmol) in EtOH (4 mL). The mixture was heated under microwave irradiation at 140 °C for 35 minutes. The reaction mixture was concentrated in vacuo. The crude material was dissolved in minimal

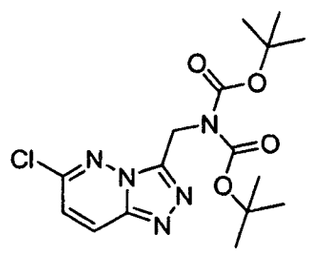
DCM/MeOH and purified via MPLC (eluting with 0-30% EtOAc in hexnaes) to yield 4-(4-bromothiazol-2-yl)morpholine (0.700 g, 68% yield) as a white solid.

2) 4-(4-(trimethylstannyl)thiazol-2-yl)morpholine



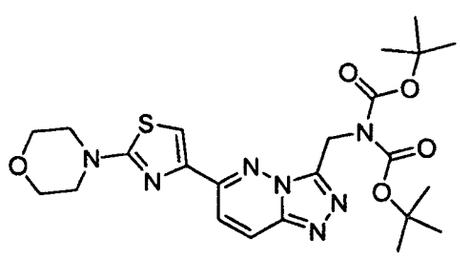
Prepared in a method similar to 3-methyl-5-trimethylstannyl)isothiazole.

3) Bis-tert-butyl(6-chloro-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methylcarbamate



Di-tert-butyl dicarbonate (24.42 g, 111.9 mmol) was added to a stirred suspension of tert-butyl (6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (10.58 g, 37.3 mmol) in acetonitrile (200 mL) at 0°C followed by 4-dimethylaminopyridine (4.556 g, 37.3 mmol). Stirring was continued at 0°C for ~10 min then the cooling bath was removed and stirring was continued at room temperature overnight. The reaction mixture was concentrated in vacuo, diluted with EtOAc and washed with water. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. Purification via MPLC (EtOAc/MeOH: 100/0 to 90/10) afforded the title compound (14.3g, 37.3 mmol, 100% yield).

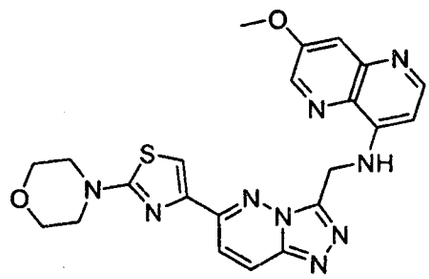
4) (6-(2-morpholinothiazol-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl di-tert-butyl carbamate



To a pressure vessel purged with argon was added palladium (II) acetate (0.0029 g, 0.013 mmol), Xantphos (0.015 g, 0.026 mmol) and bis-tert-butyl(6-chloro-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methylcarbamate (0.100 g, 0.26 mmol) in 1,4-dioxane (0.17 M, 1.5 mL). 4-

(4-(trimethylstannyl)thiazol-2-yl)morpholine (0.13 g, 0.39 mmol) and degassed water (0.0094 ml, 0.52 mmol) were added, once more purging the flask with argon. The reaction mixture was stirred at 100 °C for 4h until complete consumption of the starting material. The reaction mixture was concentrated in vacuo. The crude material was dissolved in minimal EtOAc and purified via MPLC (eluting with 100% EtOAc). (6-(2-morpholinothiazol-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl di-tert-butyl carbamate (0.086 g, 64% yield) was obtained as a solid. The material was carried forward without further purification.

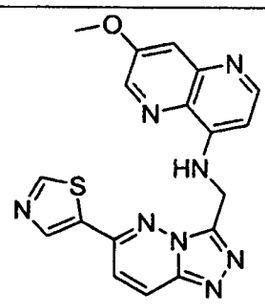
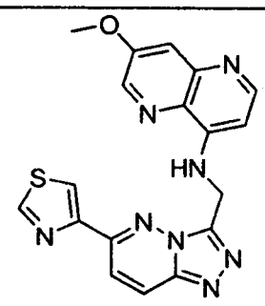
5) 7-methoxy-*N*-((6-(2-morpholinothiazol-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methyl)-1,5-naphthyridin-4-amine



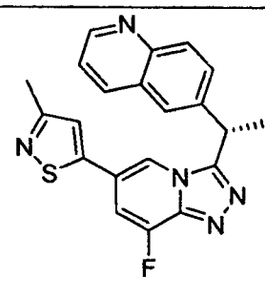
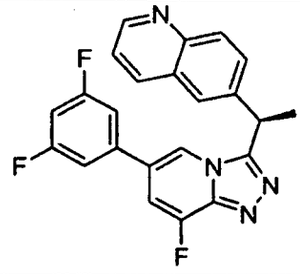
To a microwave vial was added (6-(2-morpholinothiazol-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl di-tert-butyl carbamate (0.086 g, 0.17 mmol) and 8-chloro-3-methoxy-1,5-naphthyridine (0.036 g, 0.18 mmol) in 2-butanol (1.0 mL). The vial was sealed and heated under microwave irradiation at 120 °C for 6 h. The reaction was concentrated in vacuo. The crude material was dissolved in 2M ammonia in methanol and purified via MPLC (eluting with 0-10% 1% NH_4OH/ in DCM). 7-methoxy-N-((6-(2-morpholinothiazol-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-1,5-naphthyridin-4-amine (0.031 g, 39% yield) was obtained as a yellow solid. *m/z*: 476.0 (M+H). Calc'd. for $C_{22}H_{21}N_9O_2S$ – 475.53.

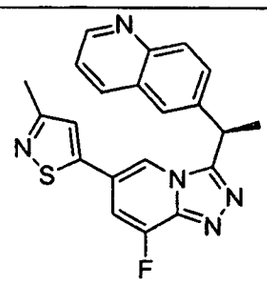
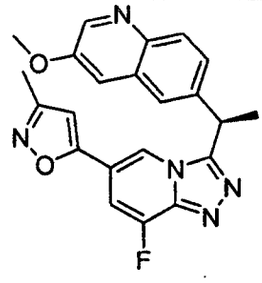
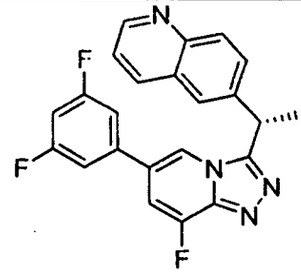
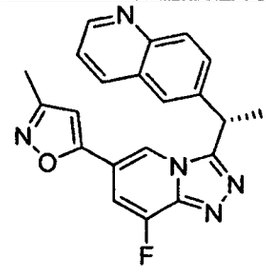
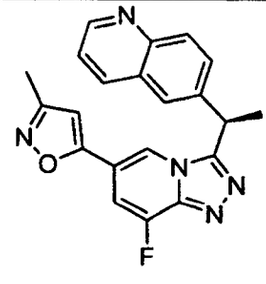
The following example compounds 406 and 407 were prepared using the method to make 7-methoxy-*N*-((6-(2-morpholinothiazol-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methyl)-1,5-naphthyridin-4-amine:

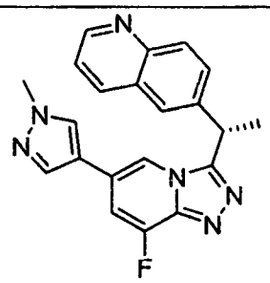
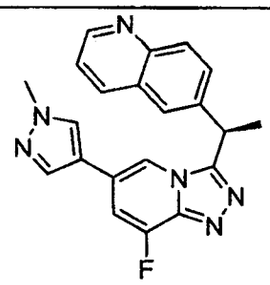
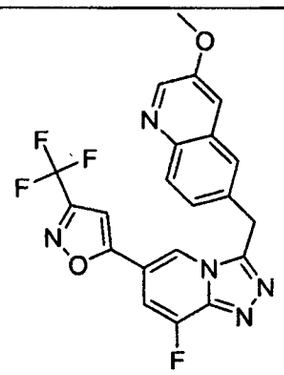
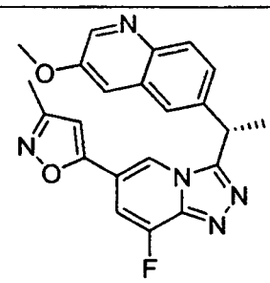
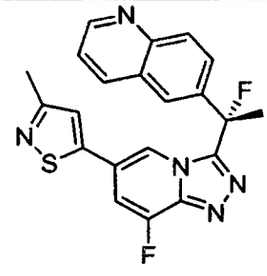
Ex	Structure	MW	Mass Found

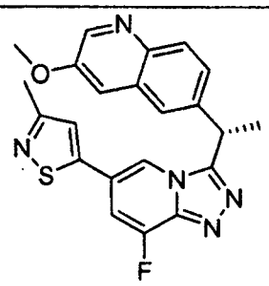
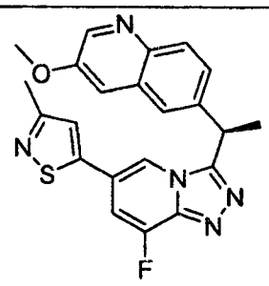
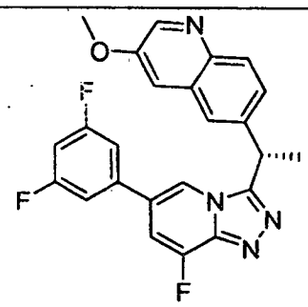
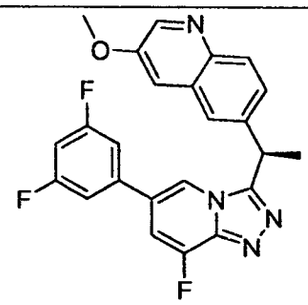
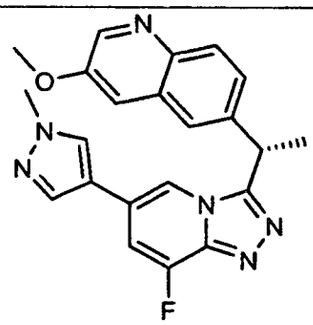
406		390	391
407		390	391

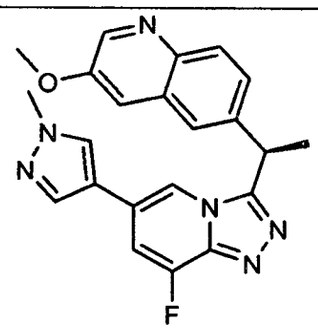
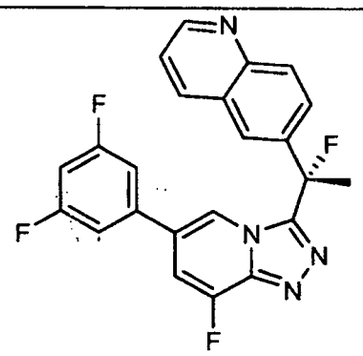
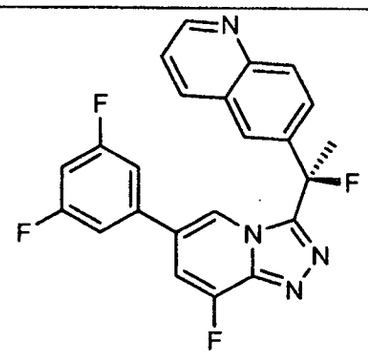
The following example compounds 408-428 were prepared using steps 1 and 2 of Method A. Where applicable, enantiomer was obtained via SFC:

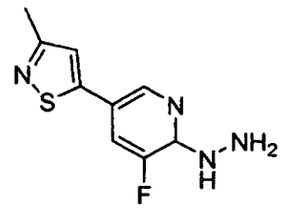
Ex	Structure	MW	Mass Found
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409		404	405

410		389	389
411		403	404
412		404	405
413		407	408
414		373	374
415		373	374

416		372	373
417		372	373
418		443	444
419		403	404
420		407	408

421		419	420
422		419	420
423		434	435
424		434	435
425		402	403

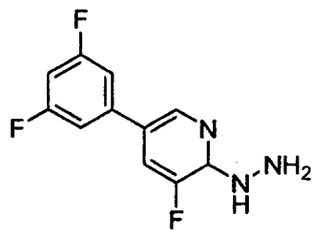
426		402	403
427		422	423
428		422	423



1-(3-fluoro-5-(3-methylisothiazol-5-yl)pyridin-2-yl)hydrazine

5-chloro-2,3-difluoropyridine (0.069 ml, 0.67 mmol), X-Phos (0.045 g, 0.094 mmol) and palladium (II) acetate (0.011 g, 0.047 mmol) were combined in 1,4-dioxane (0.2 M, 3.4 mL). To the reaction vessel was added 3-methyl-5-(trimethylstannyl)isothiazole (0.53 g, 2.0 mmol) and, after purging with argon, the reaction was stirred at 100 °C for 2h and then concentrated in vacuo. The crude material was dissolved in minimal DCM and purified via MPLC (eluting first with 100% EtOAc followed by 20% EtOAc in hexanes -isocratic) to yield 2,3-difluoro-5-(3-methylisothiazol-5-yl)pyridine (0.139 g, 98% yield) as a yellow solid. 2,3-difluoro-5-(3-

methylisothiazol-5-yl)pyridine was converted to the title compound using a procedure similar to 1-(4-methyl-6-phenylpyridazin-3-yl)hydrazine.



1-(5-(3,5-difluorophenyl)-3-fluoropyridin-2-yl)hydrazine

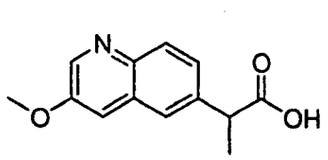
A mixture of palladium (II) acetate (0.0375 g, 0.167 mmol), potassium phosphate (2.13 g, 10.0 mmol), 3,5-difluorophenylboronic acid (1.58 g, 10.0 mmol), X-Phos (0.159 g, 0.334 mmol) and 5-chloro-2,3-difluoropyridine (0.347 ml, 3.34 mmol) was diluted with 1,4-dioxane (0.1M, 33.4 mL) and water (0.3M, 11.0 mL) and was heated under nitrogen at 100 °C for 45 minutes. The reaction was concentrated in vacuo. The concentrated material was triturated with water, filtered and rinsed with MeCN. The crude solid was taken up in dichloromethane and filtered over a plug of Celite to eliminate residual palladium. The material was dissolved in minimal DCM, and purified via MPLC (eluting with 0-10% EtOAc in hexanes) to yield 5-(3,5-difluorophenyl)-2,3-difluoropyridine. The material was converted to the hydrazine in a method similar to that in the synthesis of (*S*)-6-(1-(8-fluoro-6-(3-methylisothiazol-5-yl)-[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)ethyl)quinoline.

The following compounds were prepared using a similar method as 1-(5-(3,5-difluorophenyl)-3-fluoropyridin-2-yl)hydrazine:

1) 1-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)hydrazin

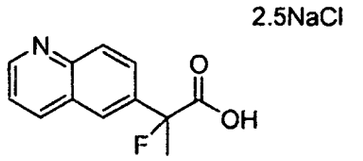
The following compounds were prepared using a similar method (using either the trimethyl- or tributyl- stannnane) as 1-(3-fluoro-5-(3-methylisothiazol-5-yl)pyridin-2-yl)hydrazine:

1-(3-fluoro-5-(3-methylisoxazol-5-yl)pyridin-2-yl)hydrazine; and
1-(3-fluoro-5-(3-trifluoromethylisoxazol-5-yl)pyridin-2-yl)hydrazine.



2-(3-methoxyquinolin-6-yl)propanoic acid hydrochloride

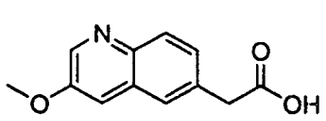
Tert-butyl 2-(3-methoxyquinolin-6-yl)propanoate (0.865 g, 3.01 mmol) was dissolved in EtOAc (0.2M, 15 mL), and HCl (g) (0.0915 ml, 3.01 mmol) was bubbled through the solution for approximately 5 minutes. The reaction vessel was sealed and the reaction was stirred at room temperature for 1.5h until completion. The reaction mixture was concentrated in vacuo to yield 2-(3-methoxyquinolin-6-yl)propanoic acid hydrochloride (0.805 g, 99.9% yield) as an orange solid.



2-fluoro-2-(quinolin-6-yl)propanoic acid

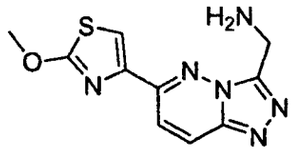
To a solution of methyl 2-(quinolin-6-yl)propanoate (0.868 g, 4.03 mmol) in THF (1.1M, 3.7 mL) at -78 °C was added LiHMDS (1M in THF) (5.24 ml, 5.24 mmol). The reaction was stirred at -78 °C for ~15 minutes, then to it was added a solution of N-fluorobenzenesulfonimide (1.40 g, 4.44 mmol) in THF(1.0M, 4.5 mL). The reaction was allowed to warm to -10 °C over 2h. The reaction was filtered through a plug of Celite, washed with EtOAc and the filtrate was then concentrated in vacuo. The concentrated material was rediluted with EtOAc and washed with saturated NH_4Cl solution. The aqueous layer was then extracted with EtOAc, and the organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was dissolved in minimal DCM and purified via MPLC (eluting with isocratic 40% EtOAc:Hexanes to yield methyl 2-fluoro-2-(quinolin-6-yl)propanoate (0.709 g, 75.4% yield) as a yellow oil.

To synthesize the corresponding acid, methyl 2-fluoro-2-(quinolin-6-yl)propanoate was saponified in a method similar to that of 2-(quinolin-6-yl)propanoic acid.



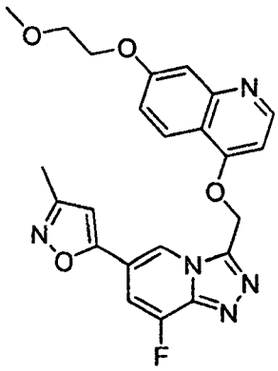
2-(3-methoxyquinolin-6-yl)acetic acid hydrochloride

tert-Butyl 2-(3-methoxyquinolin-6-yl)acetate was saponified in a method similar to 2-(3-methoxyquinolin-6-yl)propanoic acid hydrochloride.



(6-(2-methoxythiazol-4-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methanamine

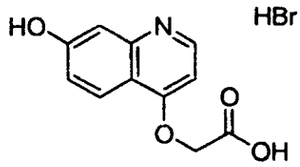
The di-tert-butyl carbonate precursor ((6-(2-methoxy-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl di-tert-butyl carbamate) was synthesized in a method similar to (6-(2-morpholinothiazol-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl di-tert-butyl carbamate, using 2-methoxy-4-(tributylstannyl)thiazole as the organostannane, followed by TFA deprotection similar to the method described for (6-(3-methylisothiazol-5-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methanamine.



Example 429

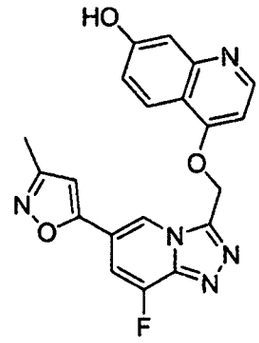
4-((8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)methoxy)-7-(2-methoxyethoxy)quinoline

1) 2-(7-hydroxyquinolin-4-yloxy)acetic acid hydrobromide



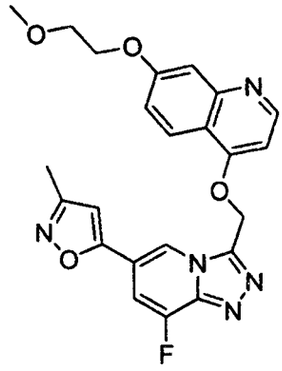
To a pressure vial was added 2-(7-methoxyquinolin-4-yloxy)acetic acid (1.00 g, 4.29 mmol) in DCE (0.6 M, 7 mL). The vial was cooled in an ice bath and to the solution was added BBr_3 (1.62 ml, 17.2 mmol). The reaction was allowed to warm to room temperature and stirred overnight. While some starting material remained, the reaction was stopped and diluted with DCM (keep in hood due to fuming). The solids were filtered and dried over high vacuum to yield a light brown crude solid (~1.8g). The material was used without further purification.

2) 4-((8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)quinolin-7-ol

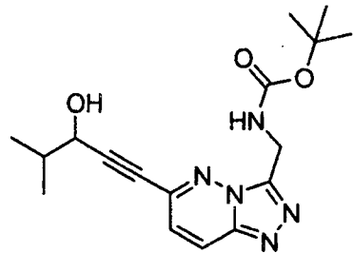


The material was prepared using general method A (with 2-(7-hydroxyquinolin-4-yloxy)acetic acid hydrobromide and 1-(3-fluoro-5-(3-methylisoxazol-5-yl)pyridin-2-yl)hydrazine

3) 4-((8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)-7-(2-methoxyethoxy)quinoline

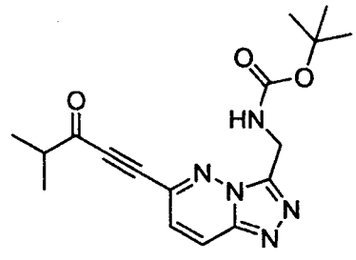


4-((8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)quinolin-7-ol (0.110 g, 0.28 mmol), PPh_3 (polymer supported: 2.3 mmol/g) (1.2 g, 2.8 mmol) and 2-methoxyethanol (0.11 ml, 1.3 mmol) were combined in DCM (11 ml, 0.28 mmol). The mixture was cooled to 0 °C, and DEAD (0.089 ml, 0.56 mmol) was added dropwise. The reaction was removed from the ice bath, and stirred at RT for 1h. The material was diluted with DCM, and the PS-PPh_3 was filtered off and washed thoroughly with DCM. The filtrate was concentrated in vacuo. The crude material was dissolved in minimal DCM and purified via MPLC (eluting with 0-100% 90:10:1 DCM:MeOH:NH_4OH in DCM) to yield 4-((8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)-7-(2-methoxyethoxy)quinoline (0.070 g, 55% yield) as a white solid. MS (ESI pos. ion) m/z: 450.0 (M+H). Calc'd Exact Mass for $C_{23}H_{20}FN_5O_4$: 449.44



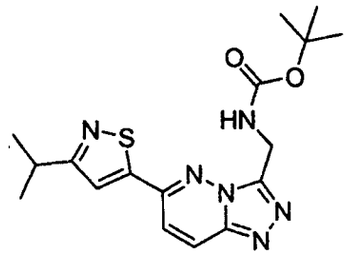
tert-Butyl (6-(3-hydroxy-4-methylpent-1-ynyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate

In a 15-mL sealed tube flushed with nitrogen, tert-butyl (6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (2.00 g, 7.0 mmol), $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.58 g, 0.70 mmol), and copper (I) iodide (0.34 g, 1.8 mmol) were diluted in MeCN (70 mL). To the reaction mixture was first added 4-methylpent-1-yn-3-ol (3.7 ml, 35 mmol), followed by triethylamine (25 ml, 176 mmol). The reaction was then heated at 50 °C for 7.5 h. The crude material was dissolved in minimal DCM and purified via MPLC (twice)(eluting with 0-10% MeOH/NH_4OH:DCM) to yield tert-butyl (6-(3-hydroxy-4-methylpent-1-ynyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (1.823 g, 75% yield) as a light brown solid.



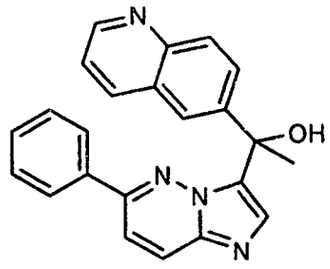
tert-Butyl (6-(4-methyl-3-oxopent-1-ynyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate

tert-Butyl (6-(3-hydroxy-4-methylpent-1-ynyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (1.82 g, 5.27 mmol) and manganese dioxide (activated) (9.16 g, 105 mmol) were dissolved in DCM (263 mL) and stirred at room temperature over two days. Additional manganese dioxide (activated) (4.58 g, 52.7 mmol) was added and stirring continued overnight. The reaction mixture was filtered over a plug of Celite and washed with DCM to yield tert-butyl (6-(4-methyl-3-oxopent-1-ynyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (0.917 g, 50.7% yield) after concentration in vacuo.



tert-Butyl (6-(3-isopropylisothiazol-5-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate

An aqueous mixture of tert-butyl (6-(4-methyl-3-oxopent-1-ynyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (0.800 g, 2.33 mmol) and hydroxylamine-O-sulfonic acid (0.263 g, 2.33 mol) in water (8.0 mL) and 1,4-dioxane (8.0 mL) was stirred at 0 °C until complete consumption of the organic starting material was observed. The mixture was then carefully treated with solid sodium bicarbonate (0.196 g, 2.33 mmol), followed by treatment with 1.4 M aqueous sodium hydrosulfide (1.83 ml, 2.56 mmol). The reaction was stirred at room temperature overnight. The reaction mixture was diluted with water (20 mL) and extracted with DCM (40 mL), dried over sodium sulfate, filtered and concentrated in vacuo. The concentrated crude material was dissolved in minimal DCM and was purified via MPLC (eluting with 0-10% MeOH/NH_4OH in DCM) to yield tert-butyl (6-(3-isopropylisothiazol-5-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (0.196 g, 22.5% yield) with 82% purity. MS (ESI pos. ion) m/z: 433.0 (M+H). Calc'd Exact Mass for $C_{21}H_{20}N_8OS$: 432.51.



Example 430

1-(6-Phenylimidazo[1,2-b]pyridazin-3-yl)-1-(quinolin-6-yl)ethanol

a) N-methoxy-N-methylquinoline-6-carboxamide

A 250 mL RB flask was charged with quinoline-6-carboxylic acid (5.00 g, 28.9 mmol), DCM (100 ml, 1554 mmol), oxalyl chloride (3.79 ml, 43.3 mmol), and a few drops of DMF and stirred at RT for 2 hours, then concentrated. The residue was taken up in DCM (100 ml, 1554 mmol), cooled to 0°C, then Hunig's Base (17.7 ml, 101 mmol) and N-methoxymethanamine hydrochloride (2.96 g, 30.3 mmol) were added slowly. The mixture was stirred at room

temperature for 16 hours (91463-3-1). The mixture was diluted with DCM (200 mL), then washed with water (250 mL), sat. $NaHCO_3$ (250 mL), and brine (250 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated to give a brown oil, which was purified by MPLC eluting with 2-6% MeOH/DCM to give N-methoxy-N-methylquinoline-6-carboxamide (5.943 g, 95.2% yield) as a brown oil.

b) 1-(quinolin-6-yl)ethanone

A 250 mL RB flask was charged with N-methoxy-N-methylquinoline-6-carboxamide (5.943 g, 27.5 mmol) and THF (100 ml, 1220 mmol), then cooled to 0 C. Methylmagnesium bromide (18.3 ml, 55.0 mmol) was added dropwise and the mixture was allowed to warm to room temperature and stirred for 3 hours. The reaction was not quite complete, so additional MeMgBr (3 mL) was added and the mixture was stirred overnight. The mixture was then neutralized using 2N HCl and the aqueous layer was extracted with DCM (200 mL x 2) and EtOAc (200 mL x 2). The organic layer was dried with $MgSO_4$, filtered, and concentrated to give a yellow oil. The aqueous layer contained some product, so the layer was concentrated and then filtered thru a reverse phase C_{18} column, first eluting with water than with MeOH. The MeOH layer was concentrated to give a yellow oil which was combined with the yellow oil from the organic layer. The combined portions were purified by MPLC eluting with a gradient of 2-6% MeOH/DCM. 1-(quinolin-6-yl)ethanone (4.074 g, 86.6% yield) was isolated as a yellow oil which solidified upon standing.

c) 2-bromo-1-(quinolin-6-yl)ethanone hydrobromide

A 250 mL RB flask was charged with 1-(quinolin-6-yl)ethanone (3.82 g, 22.3 mmol) and 30% HBr/AcOH (45.0 ml). Bromine (1.14 ml, 22.1 mmol) was added slowly. This was stirred at room temperature for 4 hours, at which point full conversion to product (with a small amount of dibrominated side product) was observed. The reaction mixture was filtered and the solid was washed with Et_2O to give 2-bromo-1-(quinolin-6-yl)ethanone hydrobromide (5.6359 g, 76.3% yield). The compound was used in the next step without further purification.

d) (E)-N'-(6-chloropyridazin-3-yl)-N,N-dimethylformamidine

A 500 mL RB flask was charged with 6-chloropyridazin-3-amine (10.0 g, 77.2 mmol) and dimethoxy-N,N-dimethylmethanamine (206 ml, 1544 mmol), equipped with a reflux condenser, then heated to 110°C for 3 hours then left at room temperature for 16 hours. The precipitate was collected by filtration. The mother liqour was concentrated down to give an

yellow solid, which was triturated with EtOAc and collected. The solids were combined to give (E)-N'-(6-chloropyridazin-3-yl)-N,N-dimethylformamidine (11.81 g, 82.9% yield) as a white solid

e) (6-Chloroimidazo[1,2-b]pyridazin-3-yl)(quinolin-6-yl)methanone

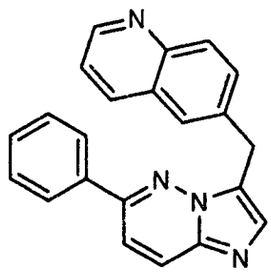
A 100 mL RB flask was charged with 2-bromo-1-(quinolin-6-yl)ethanone (0.7011 g, 2.80 mmol), (E)-N'-(6-chloropyridazin-3-yl)-N,N-dimethylformamidine (0.518 g, 2.80 mmol), and DMF (10.0 ml, 129 mmol), equipped with a reflux condenser, then heated at 105°C for 3 hours. The reaction mixture was concentrated, then triturated with MeOH to yield (6-chloroimidazo[1,2-b]pyridazin-3-yl)(quinolin-6-yl)methanone (0.530 g, 1.72 mmol, 61%) as a brown solid.

f) (6-Phenylimidazo[1,2-b]pyridazin-3-yl)(quinolin-6-yl)methanone

A 48 mL sealed tube was charged with (6-chloroimidazo[1,2-b]pyridazin-3-yl)(quinolin-6-yl)methanone (0.530 g, 1.72 mmol), phenylboronic acid (0.314 g, 2.58 mmol), cesium carbonate (1.68 g, 5.15 mmol), $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.0701 g, 0.0858 mmol), 1,4-dioxane (6.31 ml, 73.8 mmol), and water (1.11 ml, 61.8 mmol), flushed with argon, sealed, then placed in an 80°C oil bath for 8 hours. The mixture was concentrated then triturated with water, followed by MeOH/DCM to give (6-phenylimidazo[1,2-b]pyridazin-3-yl)(quinolin-6-yl)methanone as a reddish brown solid.

g) 1-(6-Phenylimidazo[1,2-b]pyridazin-3-yl)-1-(quinolin-6-yl)ethanol

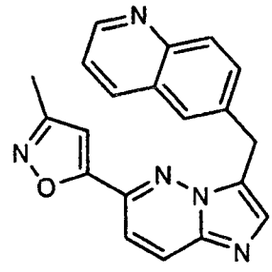
A 25 mL RB flask was charged with (6-phenylimidazo[1,2-b]pyridazin-3-yl)(quinolin-6-yl)methanone (0.200 g, 0.57 mmol) and THF (2.00 ml, 24 mmol), then cooled to 0°C. methylmagnesium bromide (0.76 ml, 2.2 mmol) was added dropwise and the mixture was stirred at room temperature for 5 hours. This was diluted with 2 N HCl (1 mL) and water (25 mL), then extracted with DCM (25 mL x 2) and EtOAc (25 mL). The combined organics were washed with brine and dried with $MgSO_4$, filtered, and concentrated. The resulting oil was purified by MPLC using a 40 g RediSep column, eluting with 2-6% MeOH/DCM over 40 minutes. 1-(6-phenylimidazo[1,2-b]pyridazin-3-yl)-1-(quinolin-6-yl)ethanol (0.082 g, 39% yield) was isolated as a tan solid. MS (ESI pos. ion) m/z: 367 (MH+). Calc'd exact mass for $C_{23}H_{18}N_4O$: 366.



Example 431

6-((6-Phenylimidazo[1,2-b]pyridazin-3-yl)methyl)quinoline

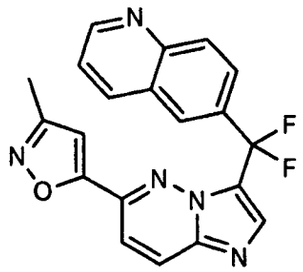
A 10-20 mL microwave vial was charged with hydrazine hydrate (0.0312 ml, 0.642 mmol), (6-phenylimidazo[1,2-b]pyridazin-3-yl)(quinolin-6-yl)methanone (0.150 g, 0.428 mmol), KOH (0.0961 g, 1.71 mmol), and diethylene glycol (4.09 ml, 42.8 mmol), sealed, then placed in a Personal Chemistry microwave at 130°C for 20 minutes after a 5 minute pre-stir. The mixture was diluted with water (75 mL), then extracted with DCM (2 x 75 mL). The combined organics were washed with brine (75 mL), then dried with $MgSO_4$, filtered, and concentrated to give a brown solid, then purified by prep HPLC to give the product as the formic acid salt. MS (ESI pos. ion) m/z: 337 (MH+). Calc'd exact mass for $C_{22}H_{16}N_4$: 336.



Example 432

6-((6-(3-Methylisoxazol-5-yl)imidazo[1,2-b]pyridazin-3-yl)methyl)quinoline

A 16 mm test tube was charged with hydrazine hydrate (0.0273 ml, 0.563 mmol), (6-(3-methylisoxazol-5-yl)imidazo[1,2-b]pyridazin-3-yl)(quinolin-6-yl)methanone (prepared using a similar procedure as (6-phenylimidazo[1,2-b]pyridazin-3-yl)(quinolin-6-yl)methanone) (0.100 g, 0.281 mmol), sodium tert-butoxide (0.0406 g, 0.422 mmol), and 1-butanol (0.670 ml, 7.32 mmol), sealed, then heated to 150°C for 2 hours (96979-1-1). The mixture was diluted with water, neutralized with 2 N HCl, then extracted with DCM (3 x 30 mL). The combined organics were dried with $MgSO_4$, filtered, then concentrated. 6-((6-(3-methylisoxazol-5-yl)imidazo[1,2-b]pyridazin-3-yl)methyl)quinoline was purified by prep HPLC and isolated as the TFA salt. MS (ESI pos. ion) m/z: 341 (MH+). Calc'd exact mass for $C_{20}H_{15}N_5O$: 341.

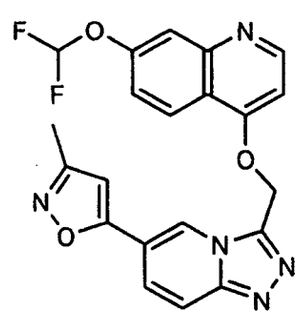


Example 433

6-(difluoro(6-(3-methylisoxazol-5-yl)imidazo[1,2-b]pyridazin-3-yl)methyl)quinoline

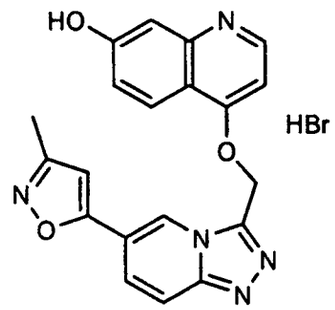
A 25 mm test tube was charged with 2,2-difluoro-1,3-dimethylimidazolidine (DFI) (0.24 g, 1.8 mmol), (6-(3-methylisoxazol-5-yl)imidazo[1,2-b]pyridazin-3-yl)(quinolin-6-yl)methanone (0.125 g, 0.35 mmol), and MeCN (2.00 ml, 38 mmol), sealed, then heated at 84°C for 36 hours, adding additional 2,2-difluoro-1,3-dimethylimidazolidine (DFI) (0.24 g, 1.8 mmol) after 16 hours. The mixture was diluted with water (50 mL), then extracted with DCM (2 x 40 mL). The combined organics were washed with brine (40 mL), dried with $MgSO_4$, filtered, then concentrated to give a brown residue. This was purified by MPLC using a 40 g RediSep column, eluting with 20 - 50% (90:10:1 DCM:MeOH:NH_4OH mixture) in EtOAc over 40 minutes. The purest fractions were collected—these still contained DFI, so the residue was triturated with EtOAc and decanted. 6-(difluoro(6-(3-methylisoxazol-5-yl)imidazo[1,2-b]pyridazin-3-yl)methyl)quinoline was isolated as a light yellow solid.

MS (ESI pos. ion) m/z: 378 (MH+). Calc'd exact mass for $C_{20}H_{13}F_2N_5O$: 377.



Example 434

7-(difluoromethoxy)-4-((6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)quinoline

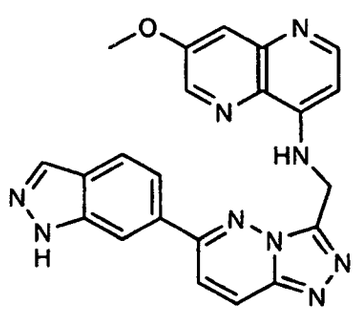


1) 4-((6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)quinolin-7-ol hydrobromide.

A 150 mL tube was charged with 7-methoxy-4-((6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)quinoline (1.44 g, 3.72 mmol) and HBr (30.3 ml, 558 mmol), sealed, then placed in a 120°C for 5 hours. The reaction mixture was slowly neutralized with 6N NaOH until a precipitate crashed out of solution (pH ~5)--the solid was collected to give 4-((6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)quinolin-7-ol hydrobromide.

2) 7-(difluoromethoxy)-4-((6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)quinoline.

A 48 mL tube was charged with sodium 2-chloro-2,2-difluoroacetate (0.15 g, 1.0 mmol), 4-((6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)quinolin-7-ol hydrobromide (0.200 g, 0.44 mmol), cesium carbonate (0.43 g, 1.3 mmol), and DMF (1.7 ml, 22 mmol), flushed with argon, sealed, then placed in a 100°C oil bath for 5 hours. The reaction mixture was concentrated, then diluted with DCM and chloroform. This was washed with water, sat. $NaHCO_3$, and brine, then dried with $MgSO_4$, filtered, and concentrated to give a brown oil. This was purified by HPLC to give 7-(difluoromethoxy)-4-((6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methoxy)quinoline (0.025 g, 13% yield) as the formic acid salt. MS (ESI pos. ion) m/z: 424 (MH+). Calc'd exact mass for $C_{21}H_{15}F_2N_5O_3$: 423.



Example 435

N-((6-(1H-indazol-6-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-methoxy-1,5-naphthyridin-4-amine

a) 6-(3-((7-Methoxy-1,5-naphthyridin-4-ylamino)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-1H-indazole-1-carboxylate. A tube was charged with N-((6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-methoxy-1,5-naphthyridin-4-amine (0.250 g, 0.732 mmol), tert-butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole-1-carboxylate (0.378 g, 1.10 mmol), PdCl2(dppf)-CH2Cl2Adduct (0.0597 g, 0.0732 mmol), potassium carbonate (0.303 g, 2.19 mmol), DMF (5.01 ml, 64.4 mmol), and water (1.16 ml, 64.4 mmol), flushed with argon, sealed, then placed in a 60°C oil bath for 6 hours. The reaction mixture was concentrated, then triturated with water to give a black solid. The material was used directly in the next step.

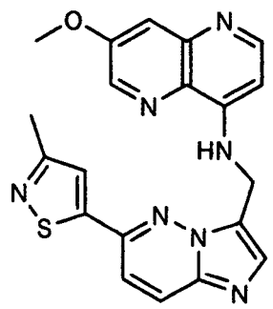
b) N-((6-(1H-indazol-6-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-methoxy-1,5-naphthyridin-4-amine. The title compound was prepared in the same manner as 7-methoxy-4-((6-(6-(piperazin-1-yl)pyridin-3-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methoxy)quinoline MS (ESI pos. ion) m/z: 424 (MH+). Calc'd exact mass for $C_{22}H_{17}N_9O$: 423.

4-bromo-1-(2,2,2-trifluoroethyl)-1H-pyrazole

A 250 mL RB flask was charged with 4-bromo-1H-pyrazole (2.00 g, 13.6 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (2.35 ml, 17.0 mmol), cesium carbonate (8.87 g, 27.2 mmol), and 1,4-dioxane (40.0 ml, 468 mmol), capped, and stirred at room temperature for 20 hours. The reaction mixture was filtered and the solid washed with dioxane; the filtrate was then concentrated to give 4-bromo-1-(2,2,2-trifluoroethyl)-1H-pyrazole (2.402 g, 77.1% yield) as a crude oil.

4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)-1H-pyrazole.

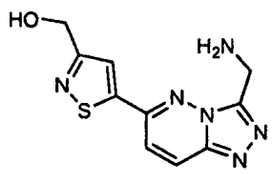
The title compound was prepared in the same manner as 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole starting with 4-bromo-1-(2,2,2-trifluoroethyl)-1H-pyrazole.



Example 436

7-methoxy-N-((6-(3-methylisothiazol-5-yl)imidazo[1,2-b]pyridazin-3-yl)methyl)-1,5-naphthyridin-4-amine.

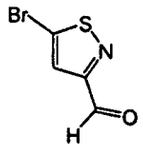
The title compound was prepared in the same manner as 7-Methoxy-N-((6-(3,4,5-trifluorophenyl)imidazo[1,2-b]pyridazin-3-yl)methyl)-1,5-naphthyridin-4-amine. MS (ESI pos. ion) m/z: 404 (MH+). Calc'd exact mass for $C_{20}H_{17}N_7OS$: 403.



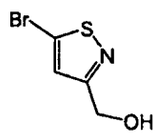
(5-(3-(aminomethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)isothiazol-3-yl)methanol.



1) 5-bromo-3-(dibromomethyl) isothiazole. 5-Bromo-3-methylisothiazole (2.15 g, 12 mmol) was dissolved in dichloroethane (20 mL) then added N-bromosuccinimide (4.5 g, 25 mmol) and AIBN (0.50 g, 3.0 mmol). The reaction mixture was heated at 100 °C for 4 hours. Additional AIBN (0.50 g, 3.0 mmol) and bromine (0.062 ml, 1.2 mmol) were added to the mixture and continued heating at 100 °C for 4 hours. N-bromosuccinimide (4.5 g, 25 mmol) and AIBN (0.50 g, 3.0 mmol) were added then continued heating at 100 °C for 4 hours. Again, N-bromosuccinimide (4.5 g, 25 mmol) and AIBN (0.30 g, 1.8 mmol) were added and the mixture was heated at 100 °C for 4 hours. The reaction mixture was diluted with ethyl acetate and washed with water, saturated sodium bicarbonate and brine. The organic layer was dried over sodium sulfate and concentrated under vacuum. The sample was purified by flash chromatography eluting with 0-10% ethyl acetate/hexane to afford 5-bromo-3-(dibromomethyl)isothiazole (2.07 g, 51% yield) as a colorless liquid.

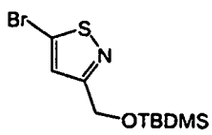


2) 5-bromoisothiazole-3-carbaldehyde. 5-Bromo-3-(dibromomethyl)isothiazole (1.00 g, 3.0 mmol) was dissolved in DME (10 mL) then added a solution of silver nitrate (0.56 g, 3.3 mmol) in water (1.6 mL). A white precipitate formed. The reaction mixture was heated at 100 °C for 1.5 hours. Additional silver nitrate (0.56 g, 3.3 mmol) in water (1.6 mL) was added and heating was continued at 100 °C for 2.5 hours. The reaction mixture was filtered through a pad of Celite washing with THF then ethyl acetate. The filtrate was concentrated under vacuum and the remaining oil was diluted with ethyl acetate. The organic layer was washed with water then dried over sodium sulfate and concentrated under vacuum to afford 5-bromoisothiazole-3-carbaldehyde (0.536 g, 94% yield) as alight yellow oil.



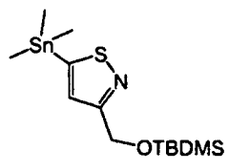
3)(5-bromoisothiazol-3-yl)methanol. 5-Bromoisothiazole-3-carbaldehyde (0.533 g, 2.8 mmol) was dissolved in ethanol (40 mL) then added sodium borohydride (0.11 g, 2.8 mmol). The reaction mixture was stirred at room temperature for 3 hours. Added more sodium borohydride (0.026 g, 0.69 mmol) and continued stirring at room temperature for 4.5 hours. Additional sodium borohydride (0.11 g, 2.8 mmol) was added once again and stirring was continued at room temperature overnight. The reaction was quenched with saturated aqueous ammonium chloride then concentrated under vacuum. The remaining aqueous layer was diluted with water then extracted with ethyl acetate (2x). The organic layer was dried over sodium sulfate and concentrated under vacuum to afford (5-bromoisothiazol-3-yl)methanol (0.430 g, 80% yield) as an orange oil.

MS (ESI pos. ion) m/z: 194.0 and 196.0 (MH^+).

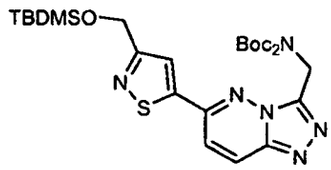


4) 5-bromo-3-((tert-butyldimethylsilyl oxy)methyl)isothiazole. (5-Bromoisothiazol-3-yl) methanol (0.380 g, 1.96 mmol) was dissolved in DMF (4 mL) then added tert-butyldimthylsilyl chloride (0.443 g, 2.94 mmol) and imidazole (0.400 g, 5.87 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was combined with previous reactions and concentrated under vacuum. The sample was purified by flash chromatography

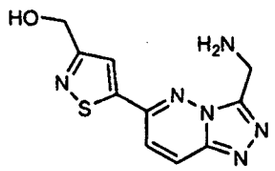
eluting with 0-15% ethyl acetate/hexane to afford 5-bromo-3-((tert-butyldimethylsilyloxy)methyl)isothiazole as a pale yellow liquid. MS (ESI pos. ion) m/z: 308.0 and 310.0 (MH^+).



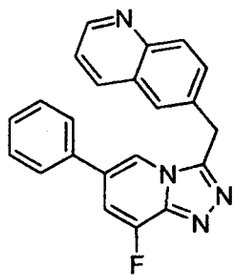
5) 3-((tert-butyldimethylsilyloxy) methyl)-5-(trimethylstannyl)isothiazole. 5-Bromo-3-((tert-butyldimethylsilyloxy)methyl)isothiazole (0.100 g, 0.324 mmol) was dissolved in THF (1 mL) then cooled to -78 °C and added 1.6 M n-BuLi in hexane (0.223 ml, 0.357 mmol) dropwise via syringe. The reaction mixture became yellow and stirring was continued at -78 °C for 45 minutes. 1M Trimethyltin chloride in THF (0.324 ml, 0.324 mmol) was added to the mixture dropwise via syringe. No color change was observed. Continued stirring at -78 °C for 1.5 hours. The reaction was quenched with saturated aqueous sodium bicarbonate at -78 °C then warmed to room temperature. The mixture was diluted with water then extracted with ether. The organic layer was dried over sodium sulfate and concentrated under vacuum to afford 3-((tert-butyldimethylsilyloxy)methyl)-5-(trimethylstannyl)isothiazole (0.121 g, 95.1% yield) as a light yellow liquid.



6) bis(1,1-dimethylethyl) (6-(3-((((1,1-dimethylethyl)(dimethyl)silyl)oxy)methyl)-5-isothiazolyl)[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylimidodicarbonate. Bis(1,1-dimethylethyl) (6-chloro[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylimidodicarbonate (0.200 g, 0.521 mmol) was suspended in dioxane (3 mL) then added 3-((tert-butyldimethylsilyloxy)methyl)-5-(trimethylstannyl)isothiazole (0.429 g, 1.09 mmol), xantphos (0.0301 g, 0.0521 mmol), palladium (II) acetate (0.00585 g, 0.0261 mmol), and water (0.0188 ml, 1.04 mmol). The reaction mixture was heated at 100 °C for 3 hours. The reaction mixture was concentrated under vacuum. The sample was purified by flash chromatography eluting with 0-100% ethyl acetate to afford bis(1,1-dimethylethyl) (6-(3-((((1,1-dimethylethyl)(dimethyl)silyl)oxy)methyl)-5-isothiazolyl)[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylimidodicarbonate (0.170 g, 56.6% yield) as a yellow oil. MS (ESI pos. ion) m/z: 577.2 (MH^+).



7) (5-(3-(aminomethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)isothiazol-3-yl)methanol. Bis(1,1-dimethylethyl) (6-(3-((((1,1-dimethylethyl)(dimethyl)silyl)oxy)methyl)-5-isothiazolyl)[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylimidodicarbonate (0.170 g, 0.29 mmol) was dissolved in ethyl acetate (5 mL) then hydrochloric acid gas was bubbled through the mixture for approx. 5 minutes. A precipitate formed and stirring was continued at room temperature for 1.5 hours. The reaction was concentrated under vacuum then mostly redissolved in methanol (3.5 mL) and added ammonium hydroxide (0.052 ml, 1.3 mmol). The mixture was stirred at room temperature for 2 hours then concentrated under vacuum. The sample was purified by flash chromatography eluting with 50-100% 90:10:1 dichloromethane/methanol/NH4OH followed by 100% 90:10:1 dichloromethane/methanol/NH4OH to afford (5-(3-(aminomethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)isothiazol-3-yl)methanol (0.066 g, 85% yield) as a white solid. MS (ESI pos. ion) m/z: 263.0 (MH^+).



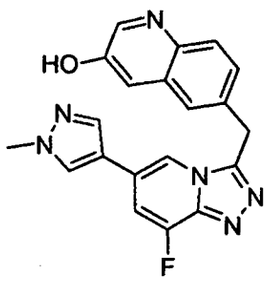
Example 437

6-((8-fluoro-6-phenyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)quinoline

1) 6-((6-chloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)quinoline. A mixture of 1-(5-chloro-3-fluoropyridin-2-yl)hydrazine (500 mg, 3095 μmol) and methyl 2-(quinolin-6-yl)acetate (600 mg, 2982 μmol) in HCl (conc., 600 μL, 7200 μmol) was heat at 100 °C for 20 min. The mixture was then heated in a microwave at 180 °C for 40 min. The mixture was quenched with NaOH (5 N, 1.5 mL) and the suspension was filtered and washed with H_2O. The resulting brown solid is mostly the desired product. The solid was then triturated with NaOH (5 N, 1 mL), filtered, and washed with H_2O. LCMS (ESI pos. ion): calc'd for $C_{16}H_{10}ClFN_4$: 312.0; found: 313.1 (M+1).

2) 6-((8-fluoro-6-phenyl-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)quinoline. A mixture of

$Pd(OAc)_2$ (6.46 mg, 28.8 μmol), potassium phosphate (367 mg, 1727 μmol), phenylboronic acid (211 mg, 1727 μmol), dicyclohexyl(2-(2,4,6-triisopropylcyclohexa-1,3-dienyl)phenyl)phosphine (27.6 mg, 57.6 μmol), and 6-((6-chloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)quinoline (180 mg, 576 μmol) in dioxane (6 mL)-H_2O (2 mL) was heated to 100 °C under nitrogen for 20 h. The mixture was cooled to rt and partitioned between H_2O and CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated. The residual was purified on silica using MeOH in DCM (0-5%) to give a pink solid. This solid was triturated with hexane-EtOAc-DCM (hot) to give a brown solid (105 mg). LCMS (ESI pos. ion): calc'd for $C_{22}H_{15}FN_4$: 354.1; found: 355.2 (M+1).

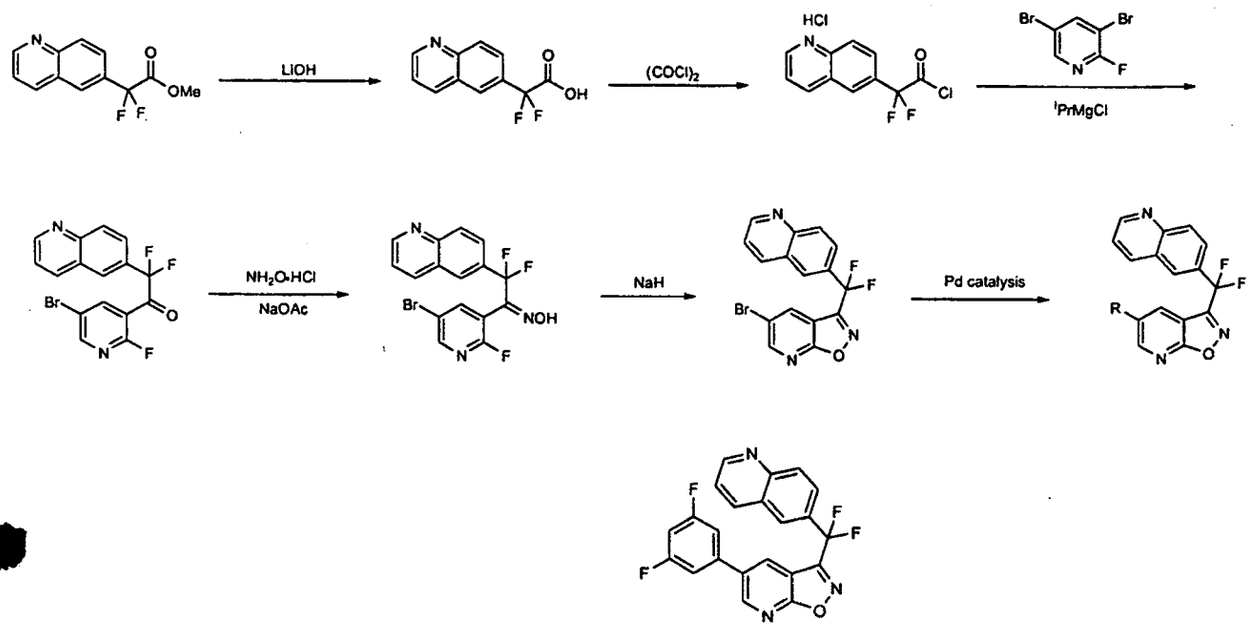


Example 438

6-((8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)quinolin-3-ol.

A mixture of crude 6-((6-chloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)-3-methoxyquinoline (200 mg, 584 μmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (600 mg, 2884 μmol), $PdCl_2(dppf)$-CH_2Cl_2 adduct (24 mg, 29 μmol), and Na_2CO_3 (500 mg, 4717 μmol) in DME (7 mL)-H_2O (5 mL) was heated at 100 °C under nitrogen. After overnight, the sludge was treated with DMSO (10 mL) and filtered. The DMSO solution was purified on HPLC (10-60%/10min). The product fraction was concentrated to dryness with toluene. The solid was then triturated with MeOH-hexane (1:2) to give a brown powder (60 mg). LCMS (ESI pos. ion): calc'd for $C_{20}H_{15}FN_6O$: 374.1; found 375.1 (M+1).

General Method F



Example 439

6-((5-(3,5-difluorophenyl)isoxazolo[5,4-b]pyridin-3-yl)difluoromethyl)quinoline

1) 2,2-difluoro-2-(quinolin-6-yl)acetic acid. To a solution of methyl 2,2-difluoro-2-(quinolin-6-yl)acetate (2.0g, 8.4 mmol) in dioxane (4 mL) and water (12 mL) was added lithium hydroxide monohydrate (0.53 g, 12 mmol). After stirring at 50 °C for thirty minutes, the solution was brought to pH 4 with 2.0 N HCl. The solution was concentrated and dried on a lyophilizer overnight to yield the product as an orange solid. MS m/z = 224.0 [M+1

2) 2,2-difluoro-2-(quinolin-6-yl)acetyl chloride hydrochloride. To a suspension of 2,2-difluoro-2-(quinolin-6-yl)acetic acid (1.9 g, 8.4 mmol) in dichloromethane (16 mL) was added oxalyl chloride (7.4 mL, 84 mmol). The mixture was stirred at 45 °C for one hour. The suspension was filtered and the resulting filtrate concentrated to yield the product as an orange oil (1.8 g, 73% step 1 and 2 combined).

3) 1-(5-bromo-2-fluoropyridin-3-yl)-2,2-difluoro-2-(quinolin-6-yl)ethanone. To a solution of 3,5-dibromo-2-fluoropyridine (3.1 g, 12 mmol) in anhydrous THF (12 mL) under argon was added isopropylmagnesium chloride (2.0 M in THF, 6.0 mL, 12 mmol). The solution was stirred at room temperature for ten minutes, then was added via cannula to a solution of 2,2-difluoro-2-(quinolin-6-yl)acetyl chloride hydrochloride (1.8 g, 6.1 mmol) in anhydrous THF (20 mL) at -78 °C. The solution was allowed to rise to -40 °C over one hour; then was stirred at 0 °C for one hour. The reaction was quenched with water and extracted with ethyl acetate; organic extracts were dried over magnesium sulfate and concentrated. Purification by MPLC

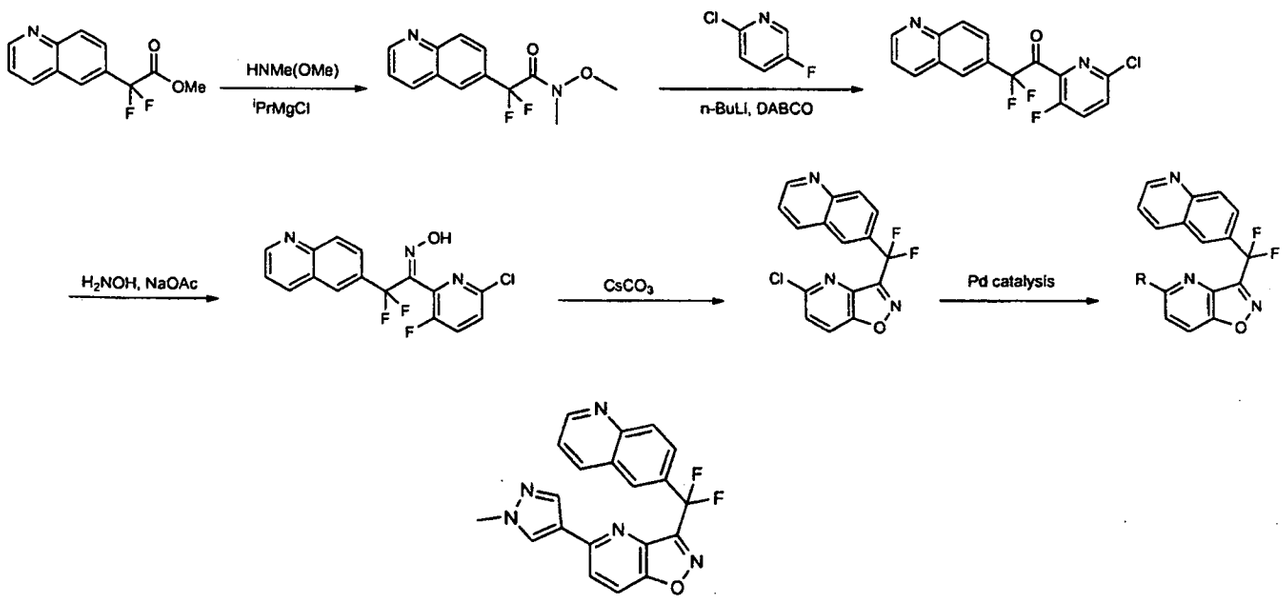
(eluted with a gradient of 20 to 80% ethyl acetate in hexanes) afforded the product as a tan solid (0.90 g, 38%).

4) 1-(5-bromo-2-fluoropyridin-3-yl)-2,2-difluoro-2-(quinolin-6-yl)ethanone oxime. To a pressure vessel was added hydroxylamine hydrochloride (1.6 g, 24 mmol), sodium acetate (2.9 g, 35 mmol) and 1-(5-bromo-2-fluoropyridin-3-yl)-2,2-difluoro-2-(quinolin-6-yl)ethanone (0.90 g, 2.4 mmol) in acetic acid (20 mL). The suspension was sealed and stirred at 100 °C for fifteen minutes, then was concentrated, triturated with water and filtered. Purification of the resulting solid by MPLC (eluted with a gradient of 0-10% methanol in dichloromethane) afforded the product as a beige solid (0.59 g, 63%). MS m/z = 396.0 $[M+1]^+$

5) 6-((5-bromoisoxazolo[5,4-b]pyridin-3-yl)difluoromethyl)quinoline. To a solution of 1-(5-bromo-2-fluoropyridin-3-yl)-2,2-difluoro-2-(quinolin-6-yl)ethanone oxime (0.59 g, 1.5 mmol) in anhydrous THF (10 mL) was added sodium hydride (0.090 g, 2.3 mmol) at 0 °C. After ten minutes, the solution was diluted with ethyl acetate and washed with water, organic extracts were dried over magnesium sulfate. Purification by MPLC (eluted with a gradient of 20-50% ethyl acetate in hexanes) afforded the product as a white solid (0.39g, 70%). MS m/z = 377.0 $[M+1]^+$ Calc'd for $C_{16}H_8BrF_2N_3O$: 376.2

6) 6-((5-(3,5-difluorophenyl)isoxazolo[5,4-b]pyridin-3-yl)difluoromethyl)quinoline. To a pressure vessel was added $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.0076 g, 0.0093 mmol), cesium carbonate (0.13 g, 0.40 mmol), 6-((5-bromoisoxazolo[5,4-b]pyridin-3-yl)difluoromethyl)quinoline (0.050 g, 0.13 mmol) and 3,5-difluorophenylboronic acid (0.031g, 0.020 mmol) in DMF (1.0 mL) water (0.25 mL). The vessel was purged with argon, sealed and stirred at 80 °C for two hours. The mixture was concentrated, triturated with water an filtered; purification of the resulting precipitate by MPLC (eluted with a gradient of 20 to 50 % ethyl acetate in hexanes afforded the product as a white solid (27 mg, 53%).

General Method G



Example 440

6-(difluoro(5-(1-methyl-1H-pyrazol-4-yl)isoxazolo[4,5-b]pyridin-3-yl)methyl)quinoline

1) 2,2-difluoro-N-methoxy-N-methyl-2-(quinolin-6-yl)acetamide. To a solution of N-methoxymethanamine hydrochloride (3.7 g, 38 mmol) and methyl 2,2-difluoro-2-(quinolin-6-yl)acetate (6.0 g, 25 mmol) in anhydrous THF (30 mL) was added isopropylmagnesium chloride (2.0 M, 38 mL, 76 mmol) at -20 °C. After thirty minutes the reaction was quenched with saturated ammonium chloride and extracted with diethyl ether; organic extracts were dried over magnesium sulfate. Purification by MPLC (eluted with a gradient of 10 to 70 % ethyl acetate in hexanes) afforded the product as an orange solid. MS m/z = 267.2 $[M+1]^+$.

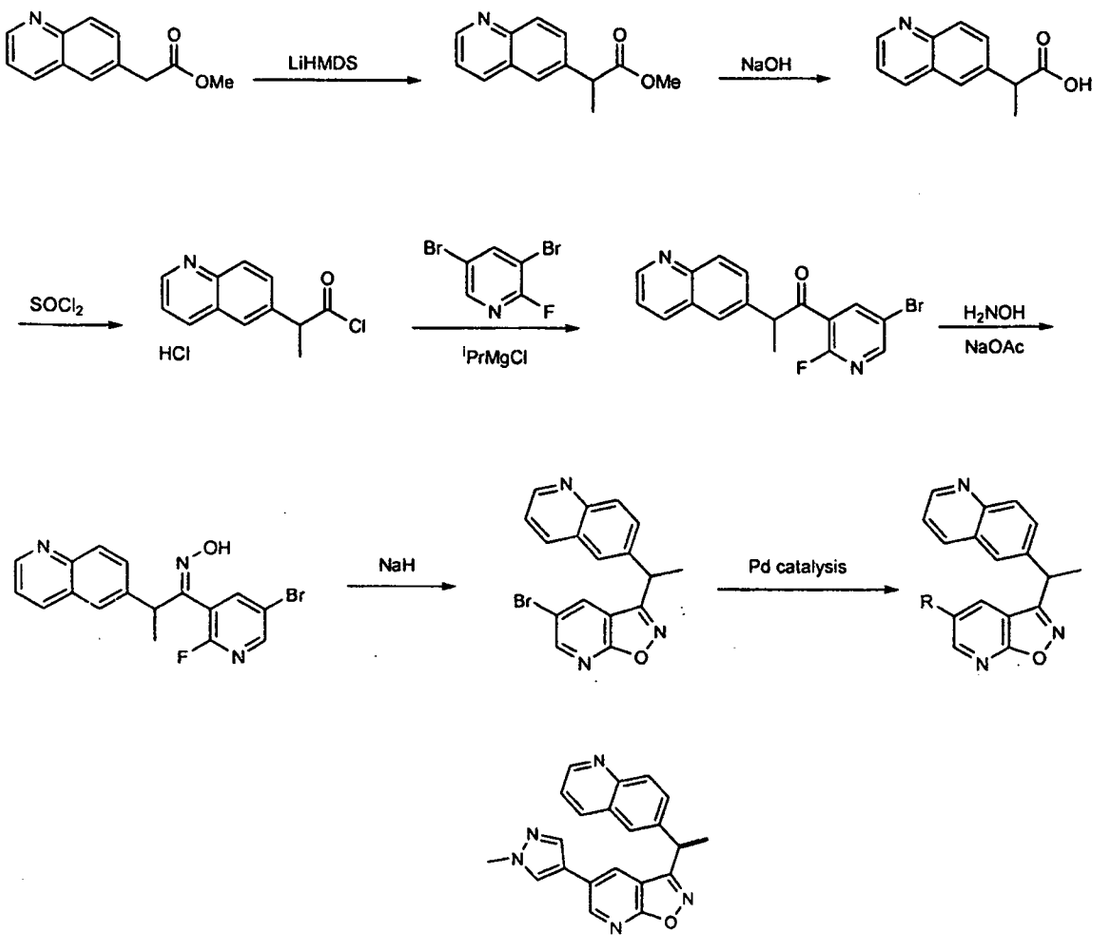
2) 1-(6-chloro-3-fluoropyridin-2-yl)-2,2-difluoro-2-(quinolin-6-yl)ethanone. n-Butyllithium (2.5M in hexanes, 3.70 ml, 9.25 mmol) was added to a stirred solution of DABCO (1.04 g, 9.25 mmol) in Et_2O (46 mL) at -78°C. The reaction mixture was stirred 1h at -20°C. and then cooled again at -78°C. 2-Chloro-5-fluoropyridine (0.939 ml, 9.25 mmol) in Et_2O (5 mL) was added. Stirring was continued at -78°C for 1h. 2,2-Difluoro-N-methoxy-N-methyl-2-(quinolin-6-yl)acetamide (2.24 g, 8.41 mmol) in Et_2O (20 mL) was added by cannula. The reaction mixture was stirred at -78°C for 70min. The cooling bath was replaced by an ice/water bath. After 10 min of stirring at 0°C , the reaction mixture was quenched with water. The water layer was extracted with EtOAc and DCM/MeOH(9/1). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by MPLC (hexanes/EtOAc: 100/0 to 40/60) afforded the title compound (2.27g, 80% yield).

3) 1-(6-chloro-3-fluoropyridin-2-yl)-2,2-difluoro-2-(quinolin-6-yl)ethanone oxime. To a pressure vessel was added 1-(6-chloro-3-fluoropyridin-2-yl)-2,2-difluoro-2-(quinolin-6-yl)ethanone (1.0 g, 3.0 mmol), sodium acetate (3.7 g, 45 mmol) and hydroxylamine hydrochloride (2.1 g, 30 mmol) in acetic acid (15 mL). The vessel was sealed and the suspension was stirred at 100 °C for twenty minutes. Following concentration and trituration with water, a white precipitate was collected via filtration. Purification of the solid by MPLC (eluted with 0-10% methanol in dichloromethane) afforded the product as a white solid (0.85 g, 82%) MS m/z = 352.0 $[M+1]^+$.

4) 6-((5-chloroisoxazolo[4,5-b]pyridin-3-yl)difluoromethyl)quinoline. To a pressure vessel was added 1-(6-chloro-3-fluoropyridin-2-yl)-2,2-difluoro-2-(quinolin-6-yl)ethanone oxime (0.050 g, 0.14 mmol) and cesium carbonate (0.14 g, 0.43 mmol) in anhydrous DMF (1 mL). After stirring at 80 °C for 30 minutes, the solution was diluted with ethyl acetate and washed with water. Organic extracts were dried over magnesium sulfate and purified by MPLC (eluted with a gradient of 10 to 50% ethyl acetate in hexanes) to yield the product as a white solid (35 mg, 74%) MS m/z = 332.2 $[M+1]^+$. Calc'd for C16H8ClF2N3O: 331.7.

5) 6-(difluoro(5-(1-methyl-1H-pyrazol-4-yl)isoxazolo[4,5-b]pyridin-3-yl)methyl)quinoline. To a pressure vessel was added 6-((5-chloroisoxazolo[4,5-b]pyridin-3-yl)difluoromethyl)quinoline) (0.10 g, 0.30 mmol), $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.012 g, 0.015 mmol), cesium carbonate (0.29 g, 0.90 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.094 g, 0.45 mmol) in DMF (2 mL) and water (0.5 mL). The vessel was purged with argon, sealed and stirred at 80 °C for forty minutes. The mixture was diluted with ethyl acetate and washed with water, organic extracts were dried over magnesium sulfate. Purification by MPLC (eluted with a gradient of 0 to 10% methanol in dichloromethane) afforded the product as a light yellow solid (45 mg, 40%). MS m/z = 378.2 $[M+1]^+$ Calc'd for $C_{20}H_{13}F_2N_5O$: 377.3.

General Method H



Example 441

6-((R)-1-(5-(1-methyl-1H-pyrazol-4-yl)isoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline

1) Methyl 2-(quinolin-6-yl)propanoate. To a solution of methyl 2-(quinoline-6-yl)acetate (7.0 g, 35 mmol) in anhydrous THF (70 mL) was added lithium bis(trimethylsilyl)amide (1.0 M in THF, 35 mL, 35 mmol) and solution of methyl iodide (2.2 mL, 35 mmol) in anhydrous THF (1mL) at -78 °C. The dry ice in acetone bath was removed and the mixture was stirred for 35 minutes, then was quenched with saturated ammonium chloride (30 mL), diluted with ethyl acetate and washed with saturated sodium bicarbonate. Organic extracts were dried over magnesium sulfate and purified via MPLC (eluted with a gradient of 10 to 30% ethyl acetate in hexanes) to yield the product as a light yellow oil (6.5 g, 87%).

2) 2-(quinolin-6-yl)propanoic acid. To a solution of methyl 2-(quinolin-6-yl)propanoate (1.4 g, 6.5 mmol) in methanol (7 mL) and water (1.5 mL) was added sodium hydroxide (6 N, 2.7 mL, 16 mmol) and the solution was stirred at 50 °C for one hour. The solution was concentrated, brought to pH 4 with 2.0 N HCl and the product was isolated via filtration as a white solid (0.94 g, 72%).

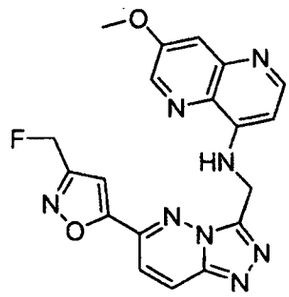
3) 2-(quinolin-6-yl)propanoyl chloride hydrochloride. To a suspension of 2-(quinolin-6-yl)propanoic acid (0.73 g, 3.6 mmol) in anhydrous dichloromethane (15 mL) was added thionyl chloride (1.3 mL, 18 mmol) and the solution was stirred at room temperature for ten minutes. The solution was concentrated to yield the product as an orange solid.

4) 1-(5-bromo-2-fluoropyridin-3-yl)-2-(quinolin-6-yl)propan-1-one. To a solution of 3,5-dibromo-2-fluoropyridine (2.4 g, 9.3 mmol) in anhydrous THF (10 mL) was added isopropylmagnesium chloride (2.0 M in THF, 4.7 mL, 9.3 mmol) and stirred at room temperature for ten minutes. The solution was added via cannula to a solution of 2-(quinolin-6-yl)propanoyl chloride hydrochloride (0.79 g, 3.1 mmol) in anhydrous THF (10 mL) at -78 °C and the combined reaction mixture was allowed to rise to -40 °C over one hour. The mixture was stirred at -40 °C for an additional 90 minutes, then was quenched with saturated sodium bicarbonate and extracted with ethyl acetate. Organic extracts were dried over magnesium sulfate and purified via MPLC (eluted with a gradient of 10-80% ethyl acetate in hexanes) to yield the product as a yellow oil (0.60 g, 54%).

5) 1-(5-bromo-2-fluoropyridin-3-yl)-2-(quinolin-6-yl)propan-1-one oxime. To a pressure vial was added sodium acetate (2.0 g, 24 mmol), hydroxylamine hydrochloride (1.1 g, 16 mmol) and 1-(5-bromo-2-fluoropyridin-3-yl)-2-(quinolin-6-yl)propan-1-one (0.58 g, 1.6 mmol) in acetic acid (10 mL). The vial was sealed and stirred at 100 °C for one hour, then was concentrated, diluted with ethyl acetate and washed with water. Organic extracts were concentrated and purified by MPLC (eluted with 0-10% methanol in dichloromethane) to yield the product as a tan oil (0.50 g, 83%).

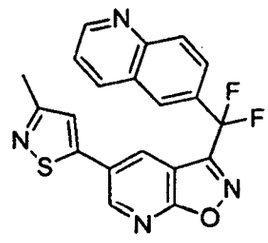
6) 6-(1-(5-bromoisoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline. To a solution of 1-(5-bromo-2-fluoropyridin-3-yl)-2-(quinolin-6-yl)propan-1-one oxime (0.58 g, 1.6 mmol) in THF (15 mL) was added sodium hydride (60% in mineral oil, 0.093, 2.3 mmol) at 0 °C. The solution was stirred at 0 °C for ten minutes, then was diluted with ethyl acetate and washed with water. Organic extracts were concentrated and purified by MPLC (eluted with a gradient of 10 to 50% ethyl acetate in hexanes) to yield the product as a colorless oil (0.10 g, 19%). MS m/z = 354.0 $[M+1]^+$. Calc'd for $C_{17}H_{12}BrN_3O$: 354.2

7) 6-((R)-1-(5-(1-methyl-1H-pyrazol-4-yl)isoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline. To a pressure vial was added 6-(1-(5-bromoisoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline (0.09 g, 0.25 mmol), $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.010 g, 0.013 mmol), cesium carbonate (0.25 g, 0.76 mmol) and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.079 g, 0.38 mmol) in DMF (2.5 mL) and water (0.5 mL). The vessel was flushed with argon, sealed and stirred at 90 °C for one hour. The mixture was concentrated, triturated in water and a brown solid was collected via filtration. Purification by MPLC (eluted with a gradient of 10 to 50% ethyl acetate) afforded a racemic mixture of the product. The desired enantiomer (>99% ee) was obtained via SFC. MS m/z = 356.2 $[M+1]^+$ Calc'd for $C_{21}H_{17}N_5O$: 355.4



Example 442

N-((6-(3-(fluoromethyl)isoxazol-5-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-methoxy-1,5-naphthyridin-4-amine: To a suspension of (5-(3-((7-methoxy-1,5-naphthyridin-4-ylamino)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)isoxazol-3-yl)methanol (0.080 g, 0.20 mmol) in anhydrous dichloromethane (3 mL) was added deoxofluor (0.10 mL, 0.060 mmol) under argon at 0 °C. The solution was brought to room temperature over one hour and stirred three additional hours. The reaction was quenched with saturated sodium bicarbonate and stirred for 15 minutes; a brown gum was collected by filtration. Purification via MPLC (eluted with a gradient of 0 to 10% methanol in dichloromethane) afforded the product as an off-white solid (9.0 mg, 11%). MS m/z = 407.2 $[M+1]^+$. Calc'd for $C_{19}H_{15}FN_8O_2$: 406.4

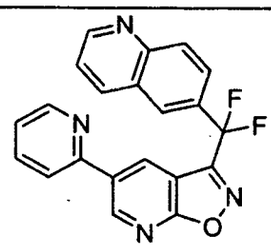
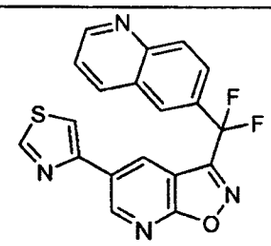
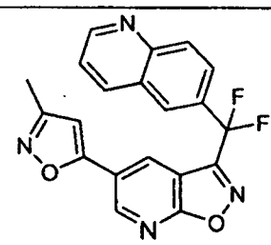
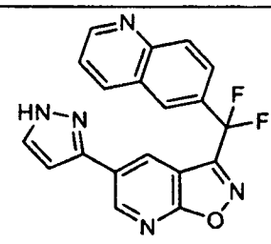


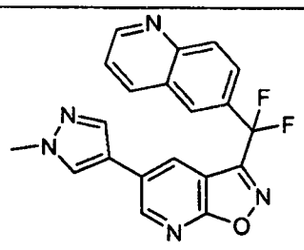
Example 443

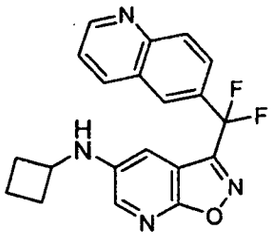
6-(difluoro(5-(3-methylisothiazol-5-yl)isoxazolo[5,4-b]pyridin-3-yl)methyl)quinoline

To a pressure vial was added 2-(dicyclohexylphosphino)biphenyl (9.3 mg, 0.013 mmol), 6-((5-bromoisoxazolo[5,4-b]pyridin-3-yl)difluoromethyl)quinoline (0.10 g, 0.27 mmol), 3-methyl-5-(trimethylstannyl)isothiazole (0.14g, 0.53 mmol) and $Pd_2(dba)_3$ (12 mg, 0.013 mmol) in anhydrous DMF (5 mL). The vessel was purged with argon, sealed and stirred at 80 °C for ninety minutes. The mixture was concentrated and purified by MPLC (eluted with a gradient of 10 to 50% ethyl acetate in hexanes) to yield the product as a light yellow solid. MS m/z = 395.0 $[M+1]^+$ Calc'd for $C_{20}H_{12}F_2N_4OS$: 394.4.

The following example compounds 444-448 were prepared using a method similar to 6-(difluoro(5-(3-methylisothiazol-5-yl)isoxazolo[5,4-b]pyridin-3-yl)methyl)quinoline:

Ex	Structure	MW	Mass Found
444		374	375
445		380	381
446		378	379
447		363	364

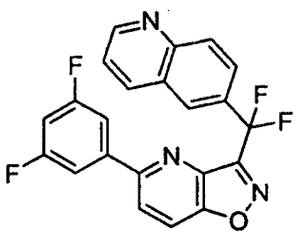
448		377	378



Example 449

N-cyclobutyl-3-(difluoro(quinolin-6-yl)methyl)isoxazolo[5,4-b]pyridin-5-amine

To a pressure vial was added sodium tert-butoxide (38 mg, 0.40 mmol), xantphos (0.12 g, 0.20 mmol), $Pd_2(dba)_3$ (61 mg, 0.066 mmol), 6-((5-bromoisoxazolo[5,4-b]pyridin-3-yl)difluoromethyl)quinoline (0.10 g, 0.27 mmol), and cyclobutanamine (0.025 mL, 0.29 mmol) in toluene (3 mL). The mixture was stirred at 80 °C for two hours then was diluted with dichloromethane and filtered through celite. Purification of the filtrate by MPLC (eluted with a gradient of 10 to 50% ethyl acetate in hexanes) afforded the product as a yellow oil (5.1 mg, 5%). MS m/z = 367.0 $[M+1]^+$ Calc'd for $C_{20}H_{16}F_2N_4O$: 366.4

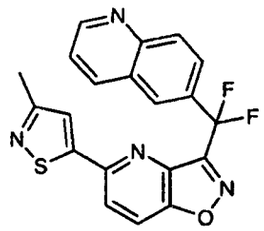


Example 450

6-((5-(3,5-difluorophenyl)isoxazolo[5,4-b]pyridin-3-yl)difluoromethyl)quinoline

To a pressure vessel was added cesium carbonate (0.61 g, 1.9 mmol), $PdCl_2(dppf)$-CH_2Cl_2 adduct (26 mg, 0.031 mmol), 1-(6-chloro-3-fluoropyridin-2-yl)-2,2-difluoro-2-(quinolin-6-yl)ethanone oxime (0.26 g, 0.63 mmol) and 3,5-difluorophenylboronic acid (0.15 g, 0.94 mmol) in anhydrous DMF (5 mL) and water (1mL). The mixture flushed with argon, sealed and stirred at 80 °C for one hour. The suspension was concentrated, triturated with water and filtered to afford a tan solid, purification by MPLC (eluted with a gradient of 20 to 50% ethyl

acetate in hexanes) afforded the product as a white solid (23 mg, 9%). MS m/z = 410.0 $[M+1]^+$ Calc'd for $C_{22}H_{11}F_4N_3O$: 409.3.



Example 451

6-(difluoro(5-(3-methylisothiazol-5-yl)isoxazolo[4,5-b]pyridin-3-yl)methyl)quinoline

To a solution of 5-bromo-3-methylisothiazole (0.19 g, 1.1 mmol) in anhydrous THF (3 mL) was added isopropylmagnesium lithium chloride (1.0 M in THF, 1.5 mL, 1.5 mmol) at -40 °C. The mixture was stirred at -40 °C for twenty minutes followed by the addition of zinc chloride (0.5 M in THF, 3.1 mL, 1.6 mmol). The mixture was brought to room temperature and stirred for thirty minutes followed by the addition of Q-Phos (0.12 g, 0.17 mmol), $Pd_2(dba)_3$ (0.097 g, 0.110 mmol), 6-((5-chloroisoxazolo[4,5-b]pyridin-3-yl)difluoromethyl)quinoline (0.10 g, 0.30 mmol), and anhydrous dimethylacetamide (3.5 mL). The mixture was stirred at 50 °C for ninety minutes then was diluted with ethyl acetate and washed with water. Organic extracts were dried over magnesium sulfate and purified by MPLC (eluted with a gradient of 10 to 50% ethyl acetate in hexanes), then purified by HPLC (eluted with a gradient of 15 to 90% acetonitrile in water) to afford the product as a white solid (4.2 mg, 3%). MS m/z = 395.2 $[M+1]^+$ Calc'd for $C_{23}H_{15}F_2N_3O$: 394.4.

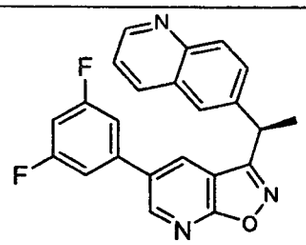
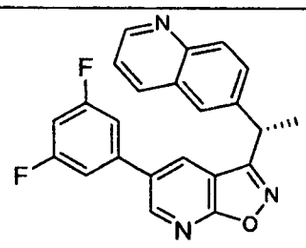


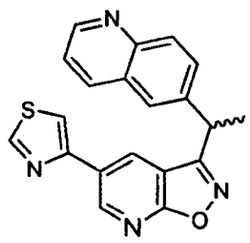
Example 452

3-(difluoro(quinolin-6-yl)methyl)-N,N-dimethylisoxazolo[4,5-b]pyridin-5-amine

To a microwave vial was added dimethylamine (2.0 M in THF, 0.75 mL, 1.5 mmol) and , 6-((5-chloroisoxazolo[4,5-b]pyridin-3-yl)difluoromethyl)quinoline (0.10 g, 0.30 mmol) in ethanol (3 mL). The mixture was stirred at 140 ° under microwave irradiation for two hours then was concentrated and purified by MPLC (eluted with a gradient of 10 to 50% ethyl acetate

in hexanes) to yield the product as a light yellow solid (87 mg, 85%). MS m/z = 341.2 $[M+1]^+$ Calc'd for $C_{18}H_{14}F_2N_4O$: 340.3.

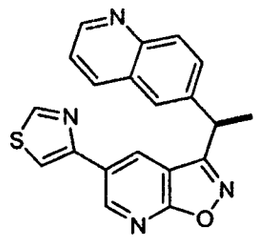
Ex	Structure	MW	Mass Found	Method
453		387	388	H
454		387	388	H



Example 455

6-(1-(5-(thiazol-4-yl)isoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline

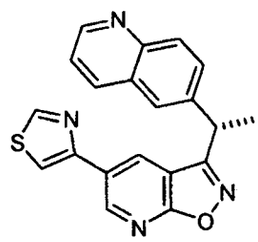
To a pressure vessel was added 2-(dicyclohexylphosphino)biphenyl (12 mg, 0.42 mmol), 6-(1-(5-bromoisoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline (0.10 g, 0.28 mmol), and 4-(tributylstannyl)thiazole (0.16 g, 0.42 mmol) in anhydrous DMF (3 mL). The vial was flushed with argon, sealed and stirred at 90 °C for two hours. The mixture was concentrated and purified by MPLC (eluted with a gradient of 0 to 10% methanol in dichloromethane) to afford the product as an off-white solid. MS m/z = 359.0 $[M+1]^+$ Calc'd for $C_{20}H_{14}N_4OS$: 358.4.



Example 456

6-((R)-1-(5-(thiazol-4-yl)isoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline

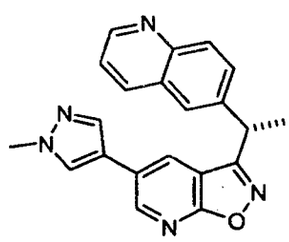
To a pressure vessel was added 2-(dicyclohexylphosphino)biphenyl (12 mg, 0.42 mmol), 6-(1-(5-bromoisoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline (0.10 g, 0.28 mmol), 4-(tributylstannyl)thiazole (0.16 g, 0.42 mmol) in anhydrous DMF (3 mL). The vial was flushed with argon, sealed and stirred at 90 °C for two hours. The mixture was concentrated and purified by MPLC (eluted with a gradient of 0 to 10% methanol in dichloromethane) to yield the racemic product as an off-white solid. The desired enantiomer (>99% ee) was obtained via SFC. MS m/z = 359.0 $[M+1]^+$ Calc'd for $C_{20}H_{14}N_4OS$: 358.4



Example 457

6-((S)-1-(5-(thiazol-4-yl)isoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline

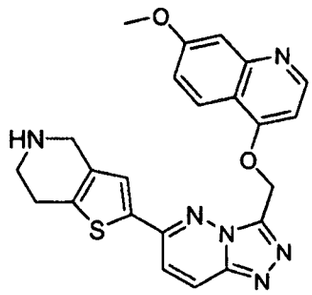
Prepared by a method similar to 6-((R)-1-(5-(thiazol-4-yl)isoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline. MS m/z = 359.0 $[M+1]^+$ Calc'd for $C_{20}H_{14}N_4OS$: 358.4.



Example 458

6-((S)-1-(5-(1-methyl-1H-pyrazol-4-yl)isoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline

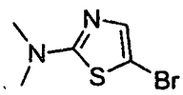
Prepared by a method similar to 6-((R)-1-(5-(1-methyl-1H-pyrazol-4-yl)isoxazolo[5,4-b]pyridin-3-yl)ethyl)quinoline. MS m/z = 356.2 $[M+1]^+$ Calc'd for $C_{21}H_{17}N_5O$: 355.4



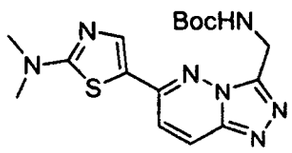
Example 459

7-methoxy-4-((6-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methoxy)quinoline

To a solution of tert-butyl 2-(3-((7-methoxyquinolin-4-yloxy)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-carboxylate (0.27 g, 0.50 mmol) (prepared according to general method A) was added trifluoroacetic acid (0.77 mL, 10 mmol). The mixture was stirred at room temperature for 90 minutes, then was concentrated, taken up in 2.0 M ammonia in methanol and purified by MPLC (eluted with a gradient of 0 to 10% methanol in dichloromethane) to yield the product as a pink solid. MS m/z = 445.0 $[M+1]^+$ Calc'd for $C_{23}H_{20}N_6O_2S$: 444.51.



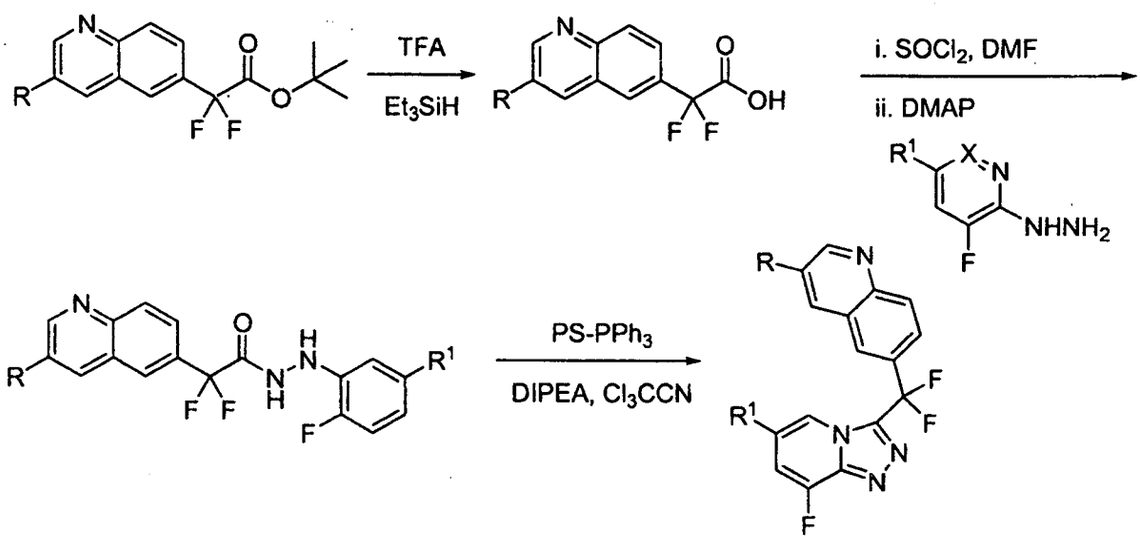
5-bromo-N,N-dimethylthiazol-2-amine: To a microwave vial was added N-ethyl-N-isopropylpropan-2-amine (0.72 mL, 4.1 mmol), 2,5-dibromothiazole (1.00 g, 4.1 mmol) and dimethylamine (40% in water, 0.52 mL, 4.1 mmol) in ethanol (10 mL). The vial was sealed and stirred at 140 °C under microwave irradiation for one hour, then was concentrated and purified by MPLC (eluted with a gradient of 0-50% ethyl acetate in hexanes) to yield the product as a white, crystalline solid (0.25 g, 29%).

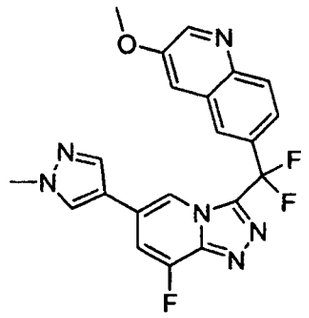


tert-butyl (6-(2-(dimethylamino)thiazol-5-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate: To a solution of 5-bromo-N,N-dimethylthiazol-2-amine (0.73 g, 3.53 mmol) in anhydrous THF (9 mL) was added isopropylmagnesium lithium chloride (1.0 M in THF, 4.8 mL, 4.8 mmol) at -40 °C. The solution was stirred for twenty minutes followed by

the dropwise addition of zinc chloride (0.5 M in THF, 10 mL, 5.2 mmol). The mixture was brought to room temperature and stirred for thirty minutes followed by the addition of dimethylacetamide (12 mL), $Pd_2(dba)_3$, (0.32 g, 0.35 mmol), Q-Phos (0.34 g, 0.56 mmol), and tert-butyl (6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (0.29 g, 1.0 mmol). The mixture was stirred at 50 ° for two hours then was quenched with saturated ammonium chloride and purified by MPLC chromatography (eluted with a gradient of 0 to 10% (1:10:90 NH_4OH:MeOH:DCM) in DCM) to yield the product as a light orange solid (0.27 g, 71%).

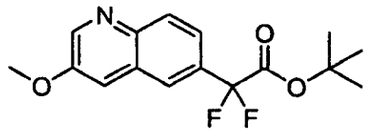
General Method I



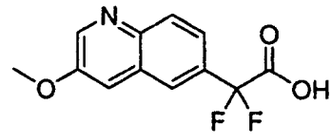


Example 460

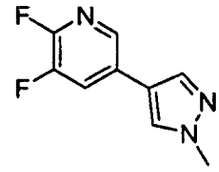
6-(difluoro(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)-3-methoxyquinoline



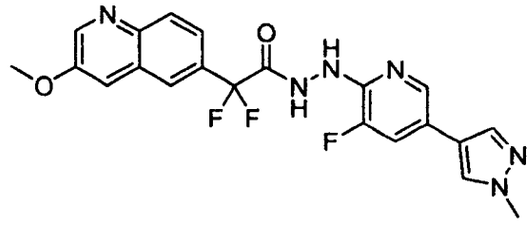
1) tert-butyl 2,2-difluoro-2-(3-methoxyquinolin-6-yl)acetate. The title compound was made from tert-butyl 2-(3-methoxyquinolin-6-yl)acetate in a similar fashion to the procedure reported for the synthesis of methyl 2,2-difluoro-2-(quinolin-6-yl)acetate.



2) 2,2-difluoro-2-(3-methoxyquinolin-6-yl)acetic acid. A 200 mL round bottom flask was charged with tert-butyl 2,2-difluoro-2-(3-methoxyquinolin-6-yl)acetate (5.06 g, 16 mmol) then CH_2Cl_2, then trifluoroacetic acid (16 ml, 213 mmol) followed by triethylsilane (6.5 ml, 41 mmol). The solution was maintained at rt for 24 h until LCMS showed disappearance of starting material. The solution was concentrated and was subjected to high vacuum for 40 h to give 4.1 g (99% yield) of 2,2-difluoro-2-(3-methoxyquinolin-6-yl)acetic acid as a brown solid. The material was of sufficient purity for use in subsequent steps.

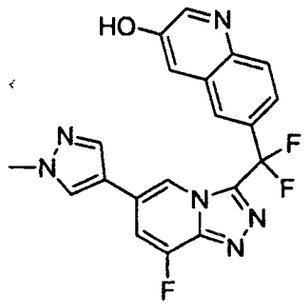


3) 2,3-difluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridine. A sealable flask was charged with 5-chloro-2,3-difluoropyridine (1.541 g, 10.3 mmol), palladium(ii) acetate (0.116 g, 0.515 mmol), potassium phosphate tribasic (6.56 g, 30.9 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.57 g, 12.4 mmol), and X-Phos (0.491 g, 1.03 mmol). The flask was sealed with a septum cap, then dioxane (20 mL) and H2O (2 mL) were added. The resulting mixture was sparged with N_2 for 10 min, and then heated at 100 °C for 2 h. The solution was cooled to rt and then concentrated and purified by flash chromatography using eluent 99:1 Hexanes : EtOAc to 60:40 Hexanes : EtOAc gradient to afford 2,3-difluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridine (1.78 g, 88.5% yield) as a colorless film. LRMS (ESI) *m/z* calcd for $C_9H_7F_2N_3$ (M+H) 197.1, found 197.4.



4) 2,2-difluoro-N'-(2-fluoro-5-(1-methyl-1H-pyrazol-4-yl)phenyl)-2-(3-methoxyquinolin-6-yl)acetohydrazide. A round bottom flask was charged with 2,2-difluoro-2-(3-methoxyquinolin-6-yl)acetic acid (389 mg, 1536 μmol) and DMF (8 mL). The solution was cooled to 0 C, thionyl chloride (224 μl, 3073 μmol), was added and the resulting solution was maintained 1 h at 0 °C. Then, triethylamine (641 μl, 4609 μmol)was added via syringe, followed by 1-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)hydrazine (382 mg, 1844 μmol) and 4-(dimethylamino)pyridine (18.8 mg, 154 μmol); both added as solids. The heterogeneous solution was stirred at 0 °C for 1 h, then allowed to warm to rt and stir for 18 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL) and the resulting mixture was extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were concentrated (heating to 50 °C) and the residue purified by SiO_2 chromatography solvent system: CH_2Cl_2:MeOH 99%:1% gradient 90:10 CH_2Cl_2 to yield 2,2-difluoro-N'-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-2-(3-methoxyquinolin-6-yl)acetohydrazide (225 mg, 33.1% yield) as a brown amorphous solid.

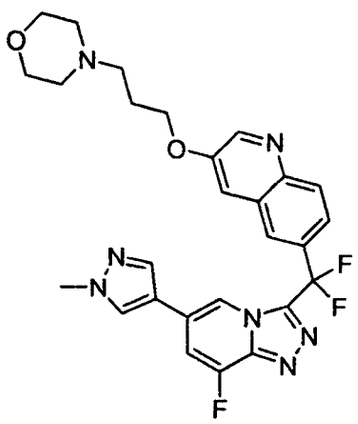
5) 6-(difluoro(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)-3-methoxyquinoline. A sealable microwave vial was charged with 2,2-difluoro-N'-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-2-(3-methoxyquinolin-6-yl)acetohydrazide (225 mg, 509 μmol) and polymer supported triphenylphosphine (2.3 mmol/g, 221 mg, 509 μmol). The flask was sealed and dichloroethane (4 mL) was added followed by diisopropylethylamine (89 μl, 509 μmol) and 2,2,2-trichloroacetonitrile (127 μl, 1271 μmol). The resulting mixture was irradiated in a microwave (Biotage Initiator) at 150 °C for 40 min. The reaction mixture was filtered and the filter cake was washed with CH_2Cl_2 (15 mL) and MeOH (10 mL). The filtrate was concentrated *in vacuo* and the resulting crude residue was purified by MPLC using 100% CH_2Cl_2 to 98:2 CH_2Cl_2 : MeOH to afford 6-(difluoro(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)-3-methoxyquinoline (94 mg, 44% yield) as a tan amorphous solid. LRMS (ESI) *m/z* calcd for $C_{21}H_{16}F_3N_6O$ (M+H) 425.1, found 425.4.



Example 461

6-(difluoro(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)quinolin-3-ol.

To a flask charged with 3-(benzyloxy)-6-(difluoro(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)quinoline (10 mg, 20 μmol) was added trifluoroacetic acid (1.5 mL, 20 mmol). The resulting solution was heated at 65 °C for 18 h. The solution was concentrated for purification by MPLC using 98:2 CH_2Cl_2 : MeOH to 90:10 CH_2Cl_2 : MeOH gradient to afford 6-(difluoro(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)quinolin-3-ol (3.6 mg, 44% yield) as a colorless solid. LRMS (ESI) *m/z* calcd for $C_{20}H_{14}F_3N_6O$ (M+H) 411.1, found 411.3.

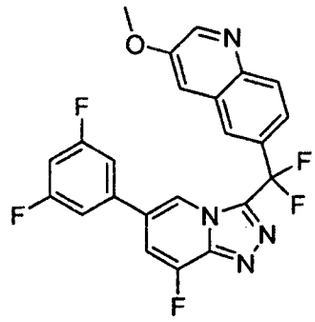


Example 462

6-(difluoro(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)-3-(3-morpholinopropoxy)quinoline.

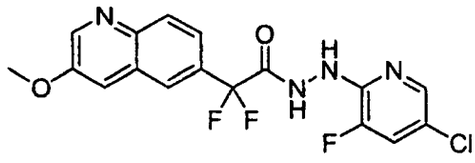
To a flask charged with 6-(difluoro(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)quinolin-3-ol (17.3 mg, 42 μmol), was added triphenylphosphine (55 mg, 211 μmol), THF (1 mL), and 4-(3-hydroxypropyl)-morpholine,95% (31 μl, 211 μmol). The mixture was placed under N_2 and cooled to 0 °C. Di-tert-butyl azodicarboxylate (49 mg, 211 μmol) was added as a solid in a single portion and the solution was allowed to warm to rt and was maintained for 48 h. The solution was concentrated for purification by MPLC (Teledine Isco combiFlash Companion). The crude residue was taken up in minimal CH_2Cl_2

and absorbed onto a 5 g loading cartridge and passed through a Redi-Sep® pre-packed silica gel column (40 g) using 99:1 CH_2Cl_2 : MeOH to 90:10 CH_2Cl_2 : MeOH gradient to afford 6-(difluoro(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)-3-(3-morpholinopropoxy)quinoline (7.5 mg, 33% yield) as a colorless solid.; . LRMS (ESI) *m/z* calcd for $C_{27}H_{27}F_3N_7O_2$ (M+H) 538.2, found 538.2.

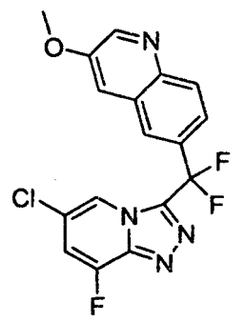


Example 463

6-((6-(3,5-difluorophenyl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)-3-methoxyquinoline

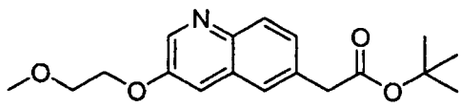


a) N'-(5-chloro-3-fluoropyridin-2-yl)-2,2-difluoro-2-(3-methoxyquinolin-6-yl)acetohydrazide. This compound was assembled from 2,2-difluoro-2-(3-methoxyquinolin-6-yl)acetic acid and 1-(5-chloro-3-fluoropyridin-2-yl)hydrazine according to General Method I. LRMS (ESI) *m/z* calcd for $C_{17}H_{13}ClF_3N_4O_2S$ (M+H) 397.1, found 397.2.



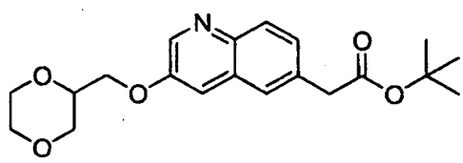
b) 6-((6-chloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)-3-methoxyquinoline. This compound was made from N'-(5-chloro-3-fluoropyridin-2-yl)-2,2-difluoro-2-(3-methoxyquinolin-6-yl)acetohydrazide according to General Method I. LRMS (ESI) *m/z* calcd for $C_{17}H_{11}ClF_3N_4O$ (M+H) 379.1, found 379.2.

c) 6-((6-(3,5-difluorophenyl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)-3-methoxyquinoline. A sealable microwave vial was charged with 6-((6-chloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)-3-methoxyquinoline (342.05mg, 903 μmol), palladium(II) acetate (30 mg, 135 μmol), potassium phosphate (575 mg, 2709 μmol), 3,5-difluorophenylboronic acid (285 mg, 1806 μmol), and X-Phos (129 mg, 271 μmol). The tube was sealed, and flushed with N_2. Dioxane (9 mL), then H_2O (1 mL) were added and the mixture was sparged with N_2 for 10 min, then heated at 100 °C for 24 h. The mixture was cooled to rt and concentrated absorbed onto a 5 g loading cartridge for MPLC purification using a 98:2 CH_2Cl_2 : MeOH to 90:10 CH_2Cl_2 : MeOH gradient to give 6-((6-(3,5-difluorophenyl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)-3-methoxyquinoline (72 mg, 17% yield). LRMS (ESI) *m/z* calcd for $C_{23}H_{14}F_5N_4O$ (M+H) 457.1, found 457.0.



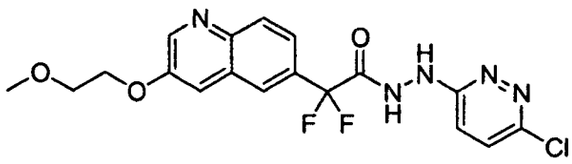
tert-butyl 2-(3-(2-methoxyethoxy)quinolin-6-yl)acetate.

A flask was charged with tert-butyl 2-(3-hydroxyquinolin-6-yl)acetate (581.04 mg, 2.241 mmol) and triphenylphosphine (1.175 g, 4.482 mmol) then sealed with a septum and an placed under N_2. Benzene (10 mL) was added, followed by 2-methoxyethanol (0.8838 ml, 11.20 mmol). The heterogeneous solution was cooled to 0 °C, and di-tert-butyl azodicarboxylate (1.032 g, 4.482 mmol) was added as a solid in a single portion. The solution was allowed to warm to rt and maintained 20 h. The solution was then partitioned between saturated aqueous. NH_4Cl, and the layers separated. The aqueous layer was extracted with EtOAc (2x50 mL), and the combined organic layers were washed with brine, dried (MgSO4), and concentrated *in vacuo*. The resulting residue was purified by MPLC (Teledine Isco combiFlash Companion), 80 g SiO_2, solvent system: 90:10 hexanes:EtOAc gradient to 50:50 hexanes:EtOAc to give tert-butyl 2-(3-(2-methoxyethoxy)quinolin-6-yl)acetate (585. 2 mg, 82% yield). LRMS (ESI) *m/z* calcd for $C_{18}H_{24}NO_4$ (M+H) 318.2, found 318.3.



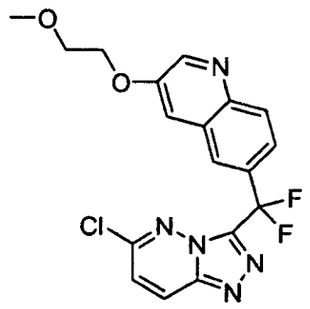
tert-butyl 2-(3-((1,4-dioxan-2-yl)methoxy)quinolin-6-yl)acetate (racemate).

The title compound was assembled from tert-butyl 2-(3-hydroxyquinolin-6-yl)acetate and (1,4-dioxan-2-yl)methanol according to the procedure described for tert-butyl 2-(3-(2-methoxyethoxy)quinolin-6-yl)acetate.



N'-(6-chloropyridazin-3-yl)-2,2-difluoro-2-(3-(2-methoxyethoxy)quinolin-6-yl)acetohydrazide.

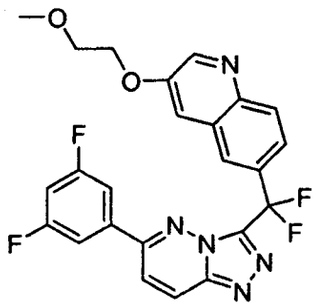
The title compound was assembled from 1-(6-chloropyridazin-3-yl)hydrazine and tert-butyl 2-(3-(2-methoxyethoxy)quinolin-6-yl)acetate as described in General Method I. LRMS (ESI) *m/z* calcd for $C_{18}H_{17}ClF_2N_5O_3$ (M+H) 424.1, found 424.2.



Example 464

6-((6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)difluoromethyl)-3-(2-methoxyethoxy)quinoline.

A sealable microwave vial was charged with N'-(6-chloropyridazin-3-yl)-2,2-difluoro-2-(3-(2-methoxyethoxy)quinolin-6-yl)acetohydrazide (46.98mg, 111 μmol), 1,2-dimethoxyethane (1.5 mL), and 1 drop of conc. HCl. The vial was sealed and heated at 130 °C for 40 min. The solution was concentrated and purified by MPLC (Teledine Isco combiFlash Companion). The residue was taken up in minimal CH_2Cl_2 and absorbed onto a 5 g loading cartridge and passed through a Redi-Sep® pre-packed silica gel column (12 g) using 98:2 CH_2Cl_2 : MeOH to 90:10 CH_2Cl_2 : MeOH to afford 6-((6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)difluoromethyl)-3-(2-methoxyethoxy)quinoline (25.3mg, 56.2% yield) as a colorless solid. LRMS (ESI) *m/z* calcd for $C_{18}H_{15}ClF_2N_5O_2$ (M+H) 406.1, found 406.2.

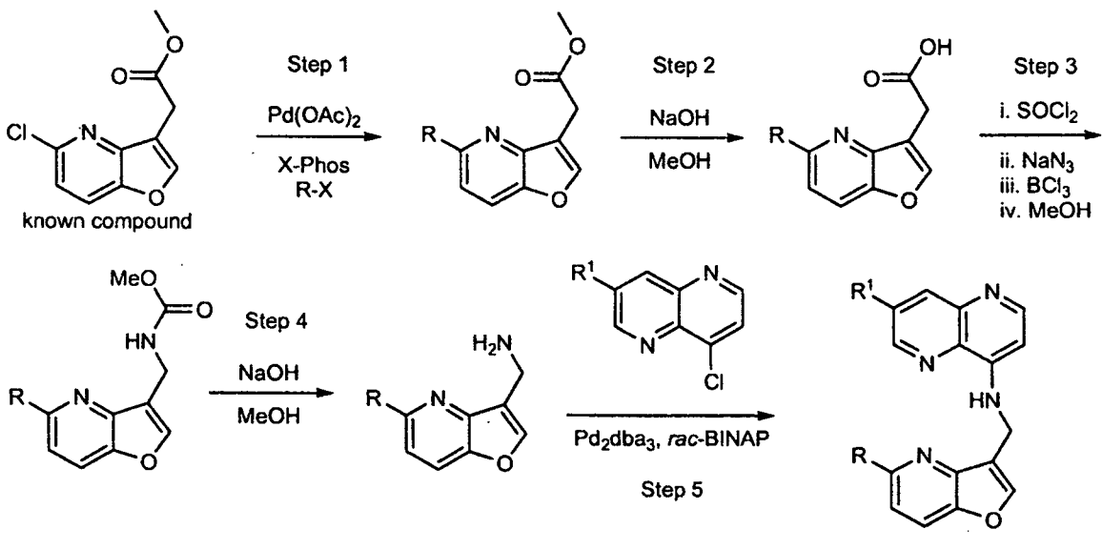


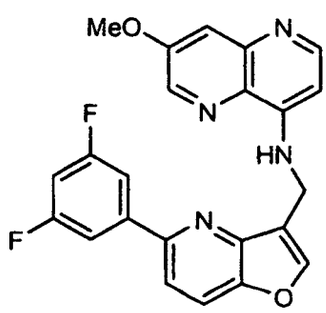
Example 465

6-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)difluoromethyl)-3-(2-methoxyethoxy)quinoline.

The title compound was synthesized from 6-((6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)difluoromethyl)-3-(2-methoxyethoxy)quinoline and 3,5-difluorophenylboronic acid in a similar manner as that described for 6-((6-(3,5-difluorophenyl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)difluoromethyl)-3-methoxyquinoline. LRMS (ESI) *m/z* calcd for $C_{24}H_{18}F_4N_5O_2$ (M+H) 484.1, found 484.2.

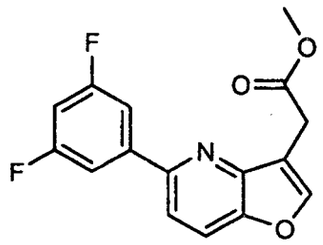
General Method J



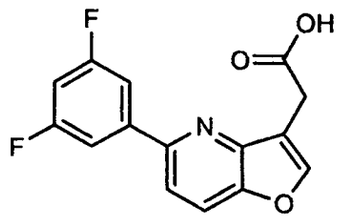


Example 466

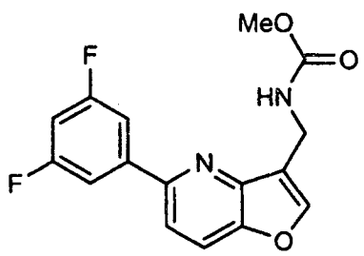
N-((5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methyl)-7-methoxy-1,5-naphthyridin-4-amine.



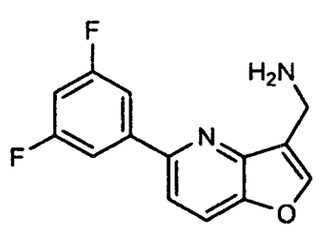
1) methyl 2-(5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)acetate. A sealable microwave vial was charged with methyl 2-(5-chlorofuro[3,2-b]pyridin-3-yl)acetate (1.30 g, 5.74 mmol), palladium(II) acetate (0.129 g, 0.574 mmol), potassium phosphate (3.66 g, 17.2 mmol), 3,5-difluorophenylboronic acid (1.81 g, 11.5 mmol), and X-Phos (0.548 g, 1.15 mmol). The vial was sealed, flushed with N_2, then dioxane (20 mL) and H_2O (2 mL) were added. The solution was sparged with N_2 for 10 min, then heated at 100 °C for 24 h. The mixture was then cooled to rt and concentrated for purification by MPLC (Teledine Isco combiFlash Companion). The crude residue was taken up in minimal CH_2Cl_2 and absorbed onto a 25 g loading cartridge and passed through a Redi-Sep® pre-packed silica gel column (120 g) using 98:2 Hexanes : EtOAc to 70:30 Hexanes : EtOAc gradient to afford methyl 2-(5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)acetate (1.46 g, 83.8% yield) as a colorless amorphous solid. LRMS (ESI) *m/z* calcd for $C_{16}H_{12}F_2NO_3$ (M+H) 304.1, found 304.2.



2) 2-(5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)acetic acid. To a flask charged with methyl 2-(5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)acetate (1.46g, 5 mmol) was added MeOH (1.5 mL), H_2O (0.5 mL), followed by NaOH (2 mL, 6 M, 12 mmol) to generate a yellow solution, which was capped and maintained at rt for 18 h. The solution was acidified with conc. HCl to pH=3 and poured into CH_2Cl_2. The layers were separated and the organic layer was extracted with CH_2Cl_2 (2x10 mL), followed by EtOAc (2x10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to produce a colorless solid, which was of sufficient purity for use in the next step.



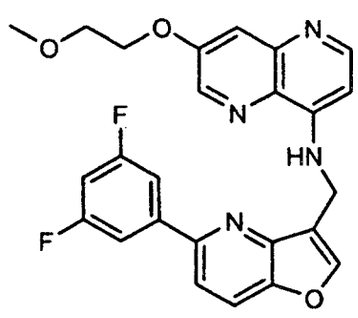
3) methyl (5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methylcarbamate. To a flask under N_2 charged with 2-(5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)acetic acid (1.033 g, 3.57 mmol) was added anhydrous CH_2Cl_2 (40 mL). The heterogeneous solution was cooled to 0 °C and oxalyl chloride (1.6 mL, 17.8 mmol) was added, followed by a catalytic amount of DMF. The solution was warmed to rt and maintained for 1 h. The solution was concentrated, then taken up in anhydrous acetone and added to a stirring aqueous solution of sodium azide (1.62 g, 25.0 mmol, in 10 mL H_2O) at 0 °C to generate a homogeneous orange solution. After 15 min at 0 °C, the mixture was diluted further with CH_2Cl_2 and stirred an additional 5 min to give a homogeneous solution. The solution was then partitioned between H_2O and CH_2Cl_2, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2x10 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was transferred to a dry flask, evacuated and flushed with N_2 (5x), and anhydrous CH_2Cl_2 (30 mL) was added. The solution was cooled to -78 °C, and boron trichloride (5.4 mL, 5.4 mmol, 1.0 M in CH_2Cl_2) was added dropwise. The cold bath was removed and the solution was allowed to warm to rt, and maintained 48 h. Anhydrous methanol (5 mL) was added and the solution maintained at rt for 3 h at which time it was concentrated for purification by MPLC (Teledine Isco combiFlash Companion). The residue was taken up in minimal CH_2Cl_2 and absorbed onto a 25 g loading cartridge and passed through a Redi-Sep® pre-packed silica gel column (80 g) using 99:1 CH_2Cl_2 : MeOH to 90:10:1 CH_2Cl_2 : MeOH : NH_4OH to afford methyl (5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methylcarbamate (680 mg, 60% yield) as a brown amorphous solid. LRMS (ESI) *m/z* calcd for $C_{16}H_{13}F_2N_2O_3$ (M+H) 319.1, found 319.2.



4) (5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methanamine. To a flask charged with methyl (5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methylcarbamate (680 mg, 2137 μmol)

was added MeOH (20 mL), then aqueous NaOH (18 mL, 6 N, 106 mmol). The solution was heated at reflux for 60 h. The solution was concentrated to remove MeOH, then partitioned between CH_2Cl_2 (30 mL) and $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (1x10 mL), then EtOAc (4x25 mL). The combined organic layers were concentrated to give a total of (5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methanamine (306.6 mg, 55% yield) as a brown foam. LRMS (ESI) *m/z* calcd for $C_{14}H_{11}F_2N_2O$ (M+H) 261.1, found 261.2.

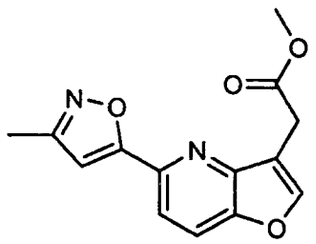
5) N-((5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methyl)-7-methoxy-1,5-naphthyridin-4-amine. A sealable microwave vial was charged with (5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methanamine (177.6 mg, 682 μmol), 8-chloro-3-methoxy-1,5-naphthyridine (146 mg, 751 μmol), and potassium phosphate (435 mg, 2047 μmol). A septum was attached and the vial was flushed with N_2, then toluene (5 mL) and H2O (1 mL) were added and the was solution sparged with N_2 for 5 min. The septum was then quickly removed and tris(dibenzylideneacetone)dipalladium (0) (15.6 mg, 17.1 μmol) and rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (42.5 mg, 68.2 μmol) were added together as solids. The vial was then sealed and the resulting purple solution was sparged again for 5 min. The mixture was then heated at 100 °C for 20 h. The mixture was concentrated *in vacuo* for purification by MPLC (Teledine Isco combiFlash Companion). The crude residue was taken up in minimal CH_2Cl_2 and absorbed onto a 25 g loading cartridge and passed through a Redi-Sep® pre-packed silica gel column (80 g) using 98:2 CH_2Cl_2 : MeOH to 90:10 CH_2Cl_2 : MeOH gradient to afford a tan amorphous solid. This solid was additionally triturated with CH_2Cl_2 (2x0.5 mL) to give N-((5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methyl)-7-methoxy-1,5-naphthyridin-4-amine (103 mg, 36.1% yield). LRMS (ESI) *m/z* calcd for $C_{23}H_{17}F_2N_4O_2$ (M+H) 419.1, found 419.2.



Example 467

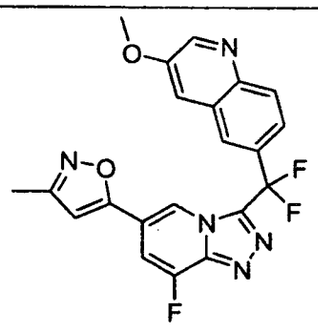
N-((5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methyl)-7-(2-methoxyethoxy)-1,5-naphthyridin-4-amine.

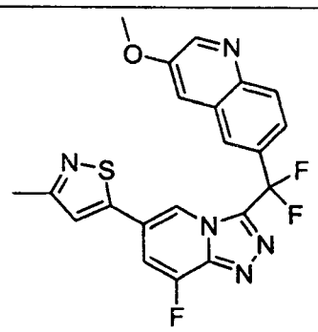
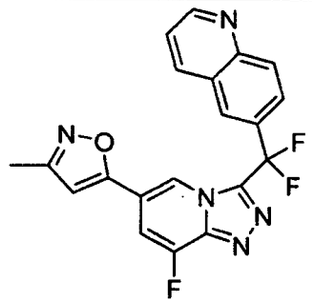
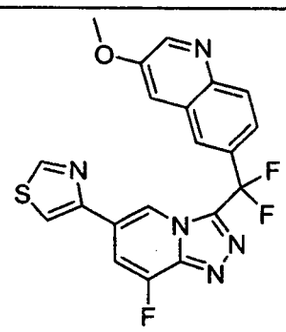
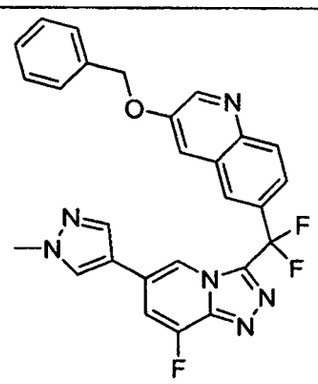
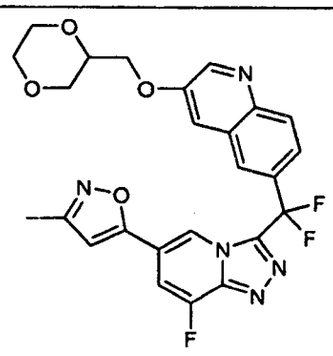
The title compound was assembled from (5-(3,5-difluorophenyl)furo[3,2-b]pyridin-3-yl)methanamine and 8-chloro-3-(2-methoxyethoxy)-1,5-naphthyridine in the manner described for 7-methoxy-N-((5-(3-methylisoxazol-5-yl)furo[3,2-b]pyridin-3-yl)methyl)-1,5-naphthyridin-4-amine. LRMS (ESI) *m/z* calcd for $C_{25}H_{21}F_2N_4O_3$ (M+H) 463.2, found 463.2.

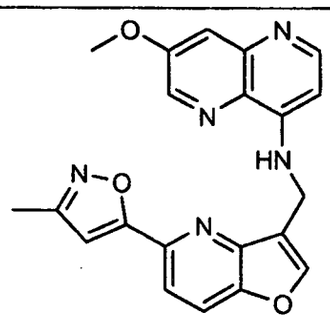


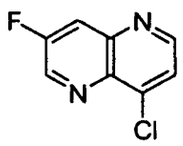
Methyl 2-(5-(3-methylisoxazol-5-yl)furo[3,2-b]pyridin-3-yl)acetate.

A sealable flask was charged with methyl 2-(5-chlorofuro[3,2-b]pyridin-3-yl)acetate, palladium (II) acetate (49.8 mg, 222 μmol), X-Phos (211 mg, 443 μmol), and 3-methyl-5-(tributylstannyl)isoxazole (1319 mg, 3546 μmol). The flask was sealed and dioxane (20 mL) was added. The mixture was sparged with N_2 for 10 min, then heated at 100 °C for 48 h. The mixture was cooled to rt and concentrated for purification by MPLC (Teledine Isco combiFlash Companion). The crude residue was taken up in minimal CH_2Cl_2 and absorbed onto a 25 g loading cartridge and passed through a Redi-Sep® pre-packed silica gel column (40 g) using 98:2 CH_2Cl_2 : MeOH to 90:10 CH_2Cl_2 : MeOH to afford methyl 2-(5-(3-methylisoxazol-5-yl)furo[3,2-b]pyridin-3-yl)acetate (581 mg, 96.3% yield). LRMS (ESI) *m/z* calcd for $C_{14}H_{13}N_2O_4$ (M+H) 273.1, found 273.3.

Ex	Structure	MW (M+H)	Mass Found	Method
468		426	426	I

469		442	442	I
470		396	396	I
471		428	428	I
472		501	501	I
473		512	512	I

474		388	388	J



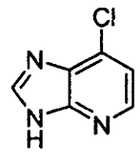
8-chloro-3-fluoro-1,5-naphthyridine

1) 5-((5-fluoropyridin-3-ylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione. A 150 mL sealed tube was charged with 2,2-dimethyl-1,3-dioxane-4,6-dione (6.0 g, 41.6 mmol) and trimethyl orthoformate (41.6 mL, 41.6 mmol). This was heated to 100 °C, and stirred at this temperature for 2 hours. Reaction then cooled to 30°C and 5-fluoropyridin-3-amine (4.7 g, 41.6 mmol) added portion-wise. Reaction vessel resealed and mixture stirred at 100 °C for 3 hours. LC/MS shows completion. Reaction mixture was cooled to room temperature, diluted with hexane, filtered, and air dried to yield 5-((5-fluoropyridin-3-ylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (9.1 g, 82% yield) as a bright yellow solid. MS [M+H]= 267.2. Calc'd for $C_{12}H_{11}FN_2O_4$=266.2.

2) 7-fluoro-1,5-naphthyridin-4(1H)-one. A 500 mL round bottom flask equipped with a reflux condenser was charged with 5-((5-fluoropyridin-3-ylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (8.0 g, 30.0 mmol) and diphenyl ether (83.5 mL). This was heated to 250 °C in heating mantle and allowed to stay at this temperature for five minutes. Cooled to room temperature, diluted with hot hexanes, and filtered to afford 7-fluoro-1,5-naphthyridin-4(1H)-one (2.2 g, 45% yield) as a crude brown solid. The title compound was used without further purification. MS [M+H]=165.2, Calc'd for $C_8H_5FN_2O$=164.14.

3) 8-chloro-3-fluoro-1,5-naphthyridine. A pressure resistant vial was charged with 7-fluoro-1,5-naphthyridin-4(1H)-one (600 mg, 3.66 mmol) and POCl3 (6.8 mL, 73.1 mmol). Vessel sealed and stirred at 110°C for 16hrs. Reaction mixture was cooled to room temperature and poured onto ice while stirring vigorously. While keeping reaction mixture at 0°C, it was basified to pH~8 with 6N NaOH. Product extracted with dichloromethane. Organic layer

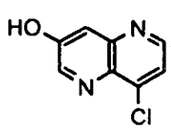
collected, dried over sodium sulfate and concentrated to afford desired material. This was passed through a silica plug in 1-5% (90:10:1 DCM/MeOH/NH_4OH)/DCM to afford 8-chloro-3-fluoro-1,5-naphthyridine (430mg, 64% yield) as a tan solid. MS [M+H]=182.9. Calc'd for $C_8H_4ClFN_2$=182.58



7-chloro-3H-imidazo[4,5-b]pyridine

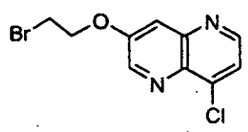
1) 4-azabenzimidazole N-oxide . Hydrogen peroxide (30wt% solution in water, 38.0 ml, 372 mmol) was added to a suspension of 3H-imidazo[4,5-b]pyridine (4.93 g, 41.4 mmol) in AcOH (40 mL) at room temperature. The reasulting reaction mixture was stirred at 80°C for 3h, cooled to RT and concentrated in vacuo to a volume ~50 mL. Concentration to dryness was done using a stream of N_2. The resulting residue was suspended in water (~10mL). Filtration afforded the title compound (4.61g, 82.4% yield).

2) 7-chloro-3H-imidazo[4,5-b]pyridine. A 50mL round bottom flask set up with a reflux condenser under nitrogen atmosphere was charged 4-azabenzimidazole N-oxide (1.2 g, 8.88 mmol) and 11 mL of DMF. This was heated to 50^{0}C and methanesulfonyl chloride (1.86 ml, 23.98 mmol) was added dropwise via syringe. The resulting mixture was heated to 80^{0}C and stirred at this temperature for 16 hours. This was cooled to room temperature and quenched with water (approximately 10 mL) and reaction mixture brought to pH 7 by adding 6N NaOH aqueous solution. The reaction was extracted four times with dichloromethane (50mL). Some product was present in aqueous layer; this was concentrated and residue set aside. The combined organic layers were dried with sodium sulfate, filtered, and concentrated. The material was purified via column chromatography (RediSep 40g column, gradient elution 0-10% MeOH:DCM) to afford 7-chloro-3H-imidazo[4,5-b]pyridine (450mg, 33.0% yield). MS [M+H]=154.2. Calc'd $C_6H_4ClN_3$ = 153.56.



8-chloro-1,5-naphthyridin-3-ol

A pressure-resistant vial was charged with 8-chloro-3-methoxy-1,5-naphthyridine (2.5 g, 12.8 mmol), boron tribromide (13.4 mL, 141.3 mmol) and dichloroethane (0.6M, 21.4mL). Vessel sealed and mixture stirred at 60^{0}C for 16hrs. Next day the reaction mixture was chilled in ice bath and diluted with dichloromethane (200mL). This was allowed to sit under nitrogen system until all fuming ceased. The resulting yellow solid material was then filtered and dried under high vacuum. This was suspended in 40% (90:10:1 DCM/MeOH/NH4OH)/DCM and purified in this system by ISCO silica gel chromatography (80g) afford 8-chloro-1,5-naphthyridin-3-ol (1.3g, 56% yield). MS [M+H]=181.2. Calc'd for $C_8H_5ClN_2O$=180.59.

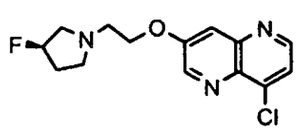


3-(2-bromoethoxy)-8-chloro-1,5-naphthyridine.

A resealable pressure bottle was charged with 8-chloro-1,5-naphthyridin-3-ol (400mg, 2.2 mmol), 2-dibromoethane (3.2 mL, 37.7 mmol), and DMF (0.15M, 14.8 mL). Vessel sealed and placed in a pre-heated at 65^{0}C oil bath. Reaction allowed to stir at this temperature for 4hrs. Reaction cooled to room temperature and passed through a pad of celite. Filtrate concentrated and purified by ISCO silica gel chromatography (20-40%EtOAc/Hexanes) to afford 3-(2-bromoethoxy)-8-chloro-1,5-naphthyridine (460mg, 72% yield). MS [M+H]=289.0 Calc'd for $C_{10}H_8BrClN_2O$=287.54

The following compound was prepared using the procedure for 3-(2-bromoethoxy)-8-chloro-1,5-naphthyridine:

8-chloro-3-((tetrahydrofuran-2-yl)methoxy)-1,5-naphthyridine;
8-chloro-3-((tetrahydrothiophen-1,1-dioxide-3-yl)methoxy)-1,5-naphthyridine (starting with the alkyl chloride).



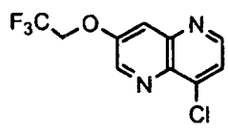
(R)-8-chloro-3-(2-(3-fluoropyrrolidin-1-yl)ethoxy)-1,5-naphthyridine.

A 25mL round bottom flask at rt was charged with (R)-3-fluoropyrrolidine hydrochloride (124 mg, 0.99 mmol). To this was added potassium carbonate (365 mg, 2.64 mmol), 3-(2-bromoethoxy)-8-chloro-1,5-naphthyridine (190mg, 0.66 mmol), sodium iodide (149 mg, 0.99

mmol) and DMF (2mL). Reaction mixture placed in oil bath preheated to 60^{0}C and allowed to stir for 16hrs. Reaction mixture passed through celite cake, rinsed with 10%MeOH/DCM and filtrate concentrated to afford yellow oil. This was purified by ISCO silica gel chromatography (20-40% EtOAC/Hexanes) to afford (R)-8-chloro-3-(2-(3-fluoropyrrolidin-1-yl)ethoxy)-1,5-naphthyridine (105mg, 54% yield). MS [M+H]=296.2. Calc'd for $C_{14}H_{15}ClFN_3O$=295.7.

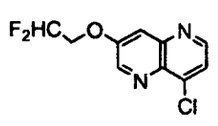
The following compounds were prepared in a similar fashion as 8-chloro-3-(2-(3-fluoropyrrolidin-1-yl)ethoxy)-1,5-naphthyridine:

8-chloro-3-(2-(3-fluoropyrrolidin-1-yl)ethoxy)-1,5-naphthyridine;
8-chloro-3-(2-(3,3-difluoropyrrolidin-1-yl)ethoxy)-1,5-naphthyridine;
1-(2-(8-chloro-1,5-naphthyridin-3-yloxy)ethyl)pyrrolidin-3-ol;
3-(2-(1H-1,2,4-triazol-1-yl)ethoxy)-8-chloro-1,5-naphthyridine (using NaH as the base);
3-(2-(1H-pyrazol-1-yl)ethoxy)-8-chloro-1,5-naphthyridine;
3-(2-(1H-1,2,3-triazol-1-yl)ethoxy)-8-chloro-1,5-naphthyridine.



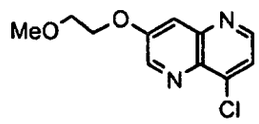
8-chloro-3-(2,2,2-trifluoroethoxy)-1,5-naphthyridine.

A resealable pressure bottle was charged with 8-chloro-1,5-naphthyridin-3-ol (80mg, 0.44 mmol), cesium carbonate (433 mg, 1.3 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (360 mg, 1.55 mmol), and DMF (0.9 ml). Vessel sealed and placed in a pre-heated at 50^{0}C oil bath. Reaction allowed tostir at this temperature for 45 minutes. LC/MS shows complete conversion. Quench with water, dilute with aqueous sodium bicarbonate solution and dichloromethane. Layers separated, organic layer collected and dried over sodium sulfate. This was concentrated to afford yellow oil; which was purified by ISCO silica gel chromatography (20-40%EtOAc/Hexanes) to afford 8-chloro-3-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (65mg, 56% yield). MS [M+H]=263.0@1.89minutes. Calc'd for $C_{10}H_6ClF_3N_2O$=262.6.



8-chloro-3-(2,2-difluoroethoxy)-1,5-naphthyridine.

The title compound was prepared using the method described for 8-chloro-3-(2,2,2-trifluoroethoxy)-1,5-naphthyridine.

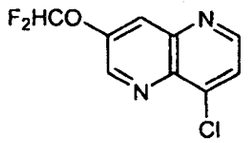


8-chloro-3-(2-methoxyethoxy)-1,5-naphthyridine.

A round bottom flask under nitrogen environment was charged with 8-chloro-1,5-naphthyridin-3-ol (1.05 g, 5.8 mmol), 22.8 g of PS-Triphenylphosphine (loading: 2.2mmol/g), 2-methoxyethanol (2.2 mL, 27.9 mmol), and THF (29.1 ml, 5814 μmol)/ DCM (58.1 mL). Mixture cooled to 0^0C and to this was added DEAD (1.84 mL) dropwise via syringe. Reaction mixture allowed to stir at room temperature for 16 hours. Diluted with 50mL of 10%MeOH/dichloromethane and resin bound reagent filtered. Filtrate concentrated under reduced pressure and purified by ISCO silica gel chromatography (10-30% EtOAc/Hexanes) to afford 8-chloro-3-(2-methoxyethoxy)-1,5-naphthyridine (770mg, 55% yield) as white solid. MS [M+H]=238.9. Calc'd for $C_{11}H_{11}ClN_2O_2$=238.67.

The following compounds were prepared in a similar fashion as 8-chloro-3-(2-methoxyethoxy)-1,5-naphthyridine:

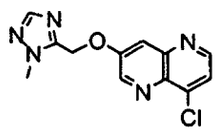
8-chloro-3-(2-(pyrrolidin-1-yl)ethoxy)-1,5-naphthyridine;
8-chloro-3-(3-morpholinopropoxy)-1,5-naphthyridine;
3-((1,4-dioxan-2-yl)methoxy)-8-chloro-1,5-naphthyridine;
8-chloro-3-(pyrrolidin-2-ylmethoxy)-1,5-naphthyridine.



8-chloro-3-(difluoromethoxy)-1,5-naphthyridine.

A round bottom flask under nitrogen atmosphere was charged with sodium 2-chloro-2,2-difluoroacetate (0.49 g, 3.2 mmol), 8-chloro-1,5-naphthyridin-3-ol (0.25 g, 1.4 mmol), cesium carbonate (1.4 g, 4.2 mmol), and DMF (2.8 mL, 0.5M). This was then placed in a 100^0C preheated oil bath and stirred at this temperature for 3 hours. Reaction mixture diluted with 10%Methanol/Dichloromethane and filtered over celite. Filtrate concentrated and purified by ISCO silica gel chromatography (40g) in 1%MeOH/DCM to afford pure 8-chloro-3-

(difluoromethoxy)-1,5-naphthyridine (0.18 g, 56% yield) as white solid. MS [M+H]=231.2. Calc'd for $C_9H_5ClF_2N_2O$=230.60.

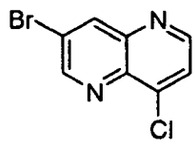


8-chloro-3-((2-methyl-2H-1,2,4-triazol-3-yl)methoxy)-1,5-naphthyridine

1) 2-methyl-2H-1,2,4-triazole-3-carbaldehyde. A dry round bottom flask under nitrogen atmosphere was charged with 1-methyl-1H-1,2,4-triazole (1.0 g, 12.04 mmol) and THF (6.0 ml, 2M). This was cooled to 0^0C followed by addition of 2M solution of isopropylmagnesium chloride in THF (6.6 mL, 13.24 mmol) via syringe. Ice bath removed and reaction allowed to stir at room temperature for 1.5 hours. Reaction mixture cooled back to 0^0C and N,N-dimethylformamide (1.39 ml, 18.05 mmol) added dropwise via syringe. Reaction mixture allowed to warm up to room temperature over 1 hour and stirred at this temperature for 16 hours. Next day reaction mixture was quenched with 2N HCl and mixture diluted with dichloromethane. Layers separated, and aqueous layer neutralized with aq. sodium bicarbonate solution and extracted with dichloromethane. All organic layers combined, dried over sodium sulfate and concentrated at room temperature (most THF remains) to afford clear material. This was purified by ISCO silica gel chromatography (10-40%EtOAc/Hex) to afford 2-methyl-2H-1,2,4-triazole-3-carbaldehyde (1.0 g, 75% yield). Yield was estimated based on H'NMR. Product was isolated as a solution in EtOAc (did not remove all EtOAc due to volatility of aldehyde, b.p.~60^0C). MS [M+H] = 112.2; MS [M+H+H_2O] = 130.2@0.23minutes . Calc'd for $C_4H_5N_3O$ = 111.10.

2) (2-methyl-2H-1,2,4-triazol-3-yl)methanol. 2-methyl-2H-1,2,4-triazole-3-carbaldehyde (0.50 g, 4.50 mmol) in MeOH (10 mL)was treated with sodium borohydride (0.17 g, 4.50 mmol) at room temperature and allowed to stir for 2 hours. Reaction mixture was quenched with aqueous sodium bicarbonate solution, diluted with 10%MeOH/DCM, and organic layer collected. Aqueous layer was saturated with sodium sulfate and extracted with 50 mL of dichloromethane (3 times). Organic portions combined, dried over sodium sulfate and concentrated to 1/4 volume at room temp. This was then diluted with ether, causing a precipitate to form. This was concentrated yielding 2-methyl-2H-1,2,4-triazol-3-yl)methanol as a foamy white solid (0.44 g, 86.4% yield). This was used 'as is' for next step. MS [M+H]= 114.2. Calc'd for $C_4H_7N_3O$=113.1.

3) 8-chloro-3-((2-methyl-2H-1,2,4-triazol-3-yl)methoxy)-1,5-naphthyridine. The title compound was prepared in a similar fashion as 8-chloro-3-(2-methoxyethoxy)-1,5-naphthyridine.



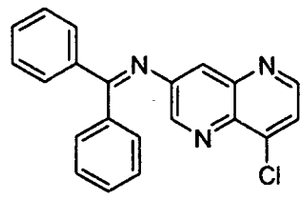
3-bromo-8-chloro-1,5-naphthyridine

1) 5-((5-bromopyridin-3-ylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione. A 350mL sealed tube was charged with 2,2-dimethyl-1,3-dioxane-4,6-dione (21.6 g, 150.0 mmol) and triethyl orthoformate (150 mL, 150.0 mmol). This was heated to 100 °C, and stirred at this temperature for 2 hours. Reaction then cooled to 30°C and 55-bromopyridin-3-amine (25.95 g, 150.0 mmol) added portion-wise. Reaction vessel resealed and mixture stirred at 100 °C for 3 hours. LC/MS shows completion. Reaction mixture was cooled to room temperature, diluted with hexane, filtered, and air dried to yield 5-((5-bromopyridin-3-ylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (41.5 g, 85% yield) as a yellow solid. MS [M+H]= 327.0. Calc'd for $C_{12}H_{11}BrN_2O_4$=327.1.

2) 7-bromo-1,5-naphthyridin-4(1H)-one. A 500 mL round bottom flask equipped with a reflux condenser was charged with 5-((5-bromopyridin-3-ylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (10.5 g, 32.1 mmol) and diphenyl ether (84.5 mL, 32.1 mmol). This was heated to 250 °C in heating mantle and allowed to stay at this temperature for 1 hour. Reaction mixture was cooled to room temperature and diluted with 300mL of Hexanes. This was heated to 60°C and triturated in this system for 3 hrs to afford 7-bromo-1,5-naphthyridin-4(1H)-one (6.05 g, 84% yield) as a crude brown solid. This was used without further purification. MS[M+H]=227.0. Calc'd for $C_8H_5BrN_2O$=225.0.

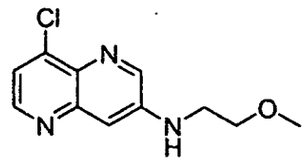
3) 3-bromo-8-chloro-1,5-naphthyridine. 7-bromo-1,5-naphthyridin-4(1H)-one (23.8 g, 105.8 mmol), acetonitriel (192 mL, 105.8 mmol), and DMF (2.05 mL, 26.5 mmol) were placed in a 3-necked round bottom flask set up with a reflux condenser. Argon bubbled through. Reaction mixture brought to reflux (~95°C). Oxalyl chloride (28.7 ml, 328.1mmol) was added dropwise via addition funnel over 40 minutes and reaction allowed to stir at this temperature for 16 hrs. Reaction mixture cooled to 0°C and basified to pH ~8 with aqueous sodium bicarbonate solution. Product extracted with DCM (500mL) three times. Organic layers combined, dried

over sodium sulfate and concentrated to afford brown solid. This was purified by ISCO silica gel chromatography to afford 3-bromo-8-chloro-1,5-naphthyridine (3.6 g, 14% yield) as fluffy tan solid. MS[M+H]=245.0@. Calc'd for $C_8H_4BrClN_2$=243.5.

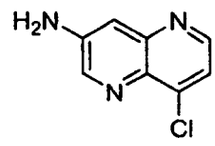


8-chloro-N-(diphenylmethylene)-1,5-naphthyridin-3-amine

A 25ml round bottom flask set up under nitrogen was charged with $Pd_2(dba)_3$ (301mg, 0.33mmol), BINAP (614 mg, 0.99 mmol) and sodium tert-butoxide (237mg, 2.46 mmol). System was purged with Argon and 3-bromo-8-chloro-1,5-naphthyridine (400mg, 1.64 mmol), diphenylmethanimine (0.28 mL, 1.64 mmol), and toluene (1M, 1.64 mL) were added. This was placed in a preheated oil bath at 80°C and stirred at this temperature for 16 hours. Reaction cooled to room temperature, diluted with dichloromethane, and passed over a celite cake. Filtrate collected was concentrated to afford brown oil. This was purifed by ISCO silica gel chromatography (40g, 1%MeOH/DCM over 50mins) to afford clean 8-chloro-N-(diphenylmethylene)-1,5-naphthyridin-3-amine (280mg, 50% yield). MS[M+H]=344.0. Calc'd for $C_{21}H_{14}ClN_3$ =343.8.

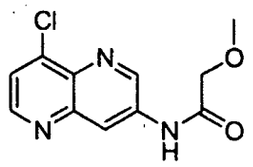


8-chloro-N-(2-methoxyethyl)-1,5-naphthyridin-3-amine.



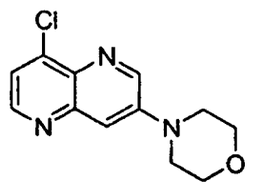
1) 8-chloro-1,5-naphthyridin-3-amine. A round bottom flask under nitrogen was charged with 8-chloro-N-(diphenylmethylene)-1,5-naphthyridin-3-amine (315mg, 0.92 mmol), 2M aqueous HCl (1.42 mL, 2.84 mmol), and tetrahydrofuran (0.25M, 3.67mL). This was stirred at RT for 30 minutes. Reaction basified with aq. sodium bicarbonate solution and product extracted with dichloromethane. This was dried over sodium sulfate and concentrated to afford orange solid; which was purified via ISCO silica gel chromatography, 40g column, 30% (90/10/1 DCM:MeOH:NH4OH)/DCM over 40 minutes to afford 7-amino-1,5-naphthyridin-4-ol (140mg, 95% yield) as yellow solid. MS[M+H]=180.2. Calc'd for $C_8H_6ClN_3$=179.6.

2) 8-chloro-N-(2-methoxyethyl)-1,5-naphthyridin-3-amine. A round bottom flask under nitrogen atmosphere was charged with 8-chloro-1,5-naphthyridin-3-amine (160mg, 0.89 mmol), DMF (2.2 mL, 0.89 mmol). This was cooled to 0°C and SODIUM HYDRIDE (60% dispersion in oil) (107 mg, 4.45 mmol) added portionwise. This was quickly followed by addition of 1-bromo-2-methoxyethane (0.12 mL, 1.25 mmol) dropwise via syringe. Ice bath removed and reaction mixture heated to 85°C and stirred at this temperature for 16 hours. Reaction diluted with 5mL of 5%MeOH/Dichloromethane, loaded onto silica gel column and eluted with 2%MeOH/DCM to afford 8-chloro-N-(2-methoxyethyl)-1,5-naphthyridin-3-amine (70mg, 33% yield) as a light yellow solid. MS[M+H]=238.2. Calc'd for $C_{11}H_{12}ClN_3O$=237.7.



N-(8-chloro-1,5-naphthyridin-3-yl)-2-methoxyacetamide

A round bottom flask under nitrogen was charged with 8-chloro-1,5-naphthyridin-3-amine (41mg, 0.23 mmol), triethylamine (64 µl, 0.46 mmol), and dichloromethane (1mL). To this was added 2-methoxyacetyl chloride (42 µl, 0.46 mmol) dropwise via syringe and reaction allowed to stir overnight at room temperature. Next day reaction mixture was diluted with dichloromethane and washed with aqueous sodium bicarbonate solution. Layers separated and organic layer dried over sodium sulfate to afford yellow oil. This was purified by ISCO silica gel chromatography (2-5%MeOH/DCM) to afford N-(8-chloro-1,5-naphthyridin-3-yl)-2-methoxyacetamide (43mg, 75% yield) as light yellow solid. MS[M+H]=251.9. Calc'd for $C_{11}H_{10}ClN_3O_2$=251.7.



8-chloro-3-morpholino-1,5-naphthyridine

A round bottom flask under nitrogen atmosphere was charged with $Pd_2(dba)_3$ (578 mg, 0.63 mmol), Xantphos (1.1 g, 1.89 mmol) , and sodium tert-butoxide (364 mg, 3.79 mmol). This was purged with Argon followed by addition of 3-bromo-8-chloro-1,5-naphthyridine (615 mg, 2.53 mmol), morpholine (0.22 mL, 2.53 mmol), and toluene (1M, 2.53 mL). This was then placed in a preheated oil bath at 80°C. After 2.5 hours, reaction was stopped, cooled to room

temp and diluted with Dichloromethane. This was passed over a celite cake and filtrate concentrated to afford brown oil; which was purifed by ISCO silica gel chromatography (40g, 1%MeOH/DCM over 50mins) to afford 8-chloro-3-morpholino-1,5-naphthyridine (200mg, 32% yield). MS[M+H]=250.2. Calc'd for $C_{12}H_{12}ClN_3O$=249.7.

4-bromo-1-phenyl-1H-pyrazole.

A sealable tube was charged with 4-bromopyrazole (4.000 g, 27.2 mmol), 1-iodobenzene (3.64 ml, 32.7 mmol), (+/-)-trans-1,2-diaminocyclohexane (0.654 ml, 5.44 mmol), Copper iodide (I) (0.518 g, 2.72 mmol), potassium carbonate (8.28 g, 59.9 mmol) and 13 mL dioxane added. The mixture was blanketed with N2, the vessel sealed and heated to 100 C for 16 h. The mixture was allowed to cool to rt, diluted with EtOAc, washed with water, and an emullsion formed. The organic layer separated and the aqueous emulsion mixture was filter through a pad of celite and rinsed with EtOAc, and sat. $NaHCO_3$. The combined organig layers were dried over Na_2SO_4, filtered and evaporate. The mixture was purified via flash chromatography using a 0 % to 100 % CH_2Cl_2 in hexanes gradient. The title compound was collected as a yellow solid (3.18 g)

1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole.

The title compound was prepared in the same manner as 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole starting with 4-bromo-1-phenyl-1H-pyrazole.

4-bromo-1-(tetrahydrofuran-3-yl)-1H-pyrazole

The title compound was prepared in the same manner as 4-bromo-1-(cyclobutyl)-1H-pyrazole, but using tetrahydrofuran-3-yl methanesulfonate (prepared according to procedures known in the art).

1-(tetrahydrofuran-3-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole.

The title compound was prepared in the same manner as 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole starting with 4-bromo-1-(tetrahydrofuran-3-yl)-1H-pyrazole.

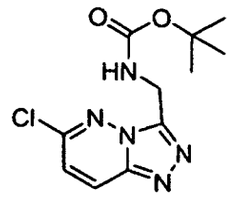
4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) -1-cyclopropyl-1H-pyrazole

a) 1-cyclopropyl-1H-pyrazole . In a 1000 mL 3-neck flask, to a mixture of potassium hydroxide (104 g, 1857 mmol) in water (200 mL) was added cyclopropylamine (131 ml, 1857

mmol) and the mixture stirred at 50 C. A solution of hydroxylamine-O-sulfonic acid (HOS)(30.00 g, 265 mmol) in 100 mL water was added dropwise resulting in the formation of a white precipitate after the first few drops. The stirring stopped during the first half of the addition and some cyclopropylamine condensed on top of the HOS soln. Additional amine (10 mL) was added to the reaction and addition of HOS solution continuted. Mixture bubbles during the addition. The flask was remove from heat and cool in ice bath to 25 C. HCl (conc) was added slowly, 150-200 mL, to achieve PH 3. The mixture was filtered to remove the white solid and the filtrate heated with 1,1,3,3-tetramethoxypropane (43.7 ml, 265 mmol). The mixture took 1.5 h to reach 90 C, maintained the temperature at 90 for 1 h, then allowed the mixture to cool to 40 C with stirring for an additional 17 h. The mixture was allowed to cool to ~35 C and extracted with Et_2O (400 mL then 2 x100 mL), the combined organic layers were with water, 6N NaOH, 2N NaOH, then sat NaHCO3, and the organic layer dried over Na_2SO_4, filtered and evaporate gently. Upon evaporation, when volume is reduced from ~600 mL to ~100 mL, the white solid that has precipitated was filtered. The title compound was obtained as a golden liquid (~ 2g).

b) 4-bromo-1-cyclopropyl-1H-pyrazole. To a golden solution of 1-cyclopropyl-1H-pyrazole (2.360 g, 22 mmol) in 100 mL chloroform, was added bromine (1.2 ml, 24 mmol) as a soln in 100 mL $CHCl_3$ dropwise over 1.5 h. the mixture was heated in oil bath to 60 C for 2 h. The mixture was allowed to cool to RT, washed with sat $NaHCO_3$, dried over Na_2SO_4, filtered and evaporated to afford the title compound as a tan liquid (3.64 g).

c) 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) -1-cyclopropyl-1H-pyrazole. The title compound was prepared in the same manner as 1-ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole starting with 4-bromo-1-cyclopropyl-1H-pyrazole.

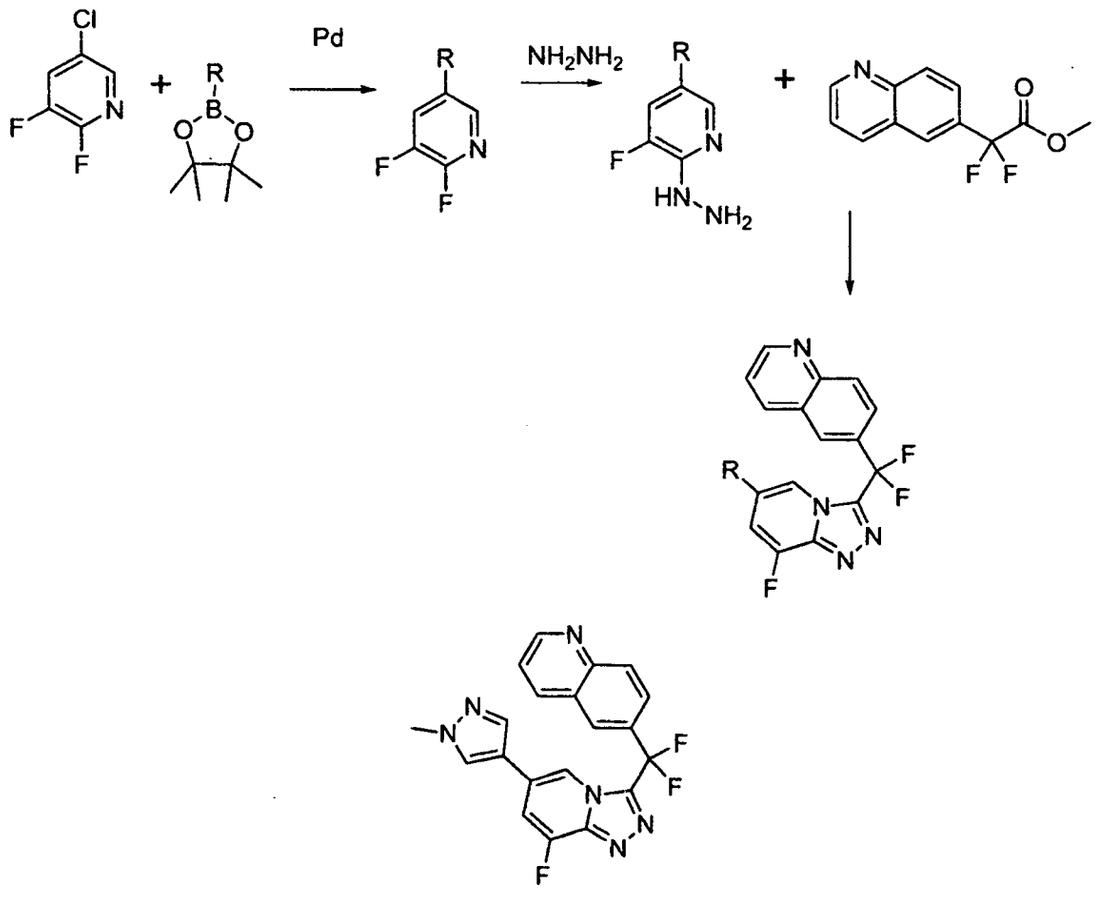


tert-butyl (6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate .

A 2-L round bottom flask flask equipped with a magnetic stirbar was charged with di(1H-imidazol-1-yl)methanone (121 g, 749 mmol) and acetonitrile (500 mL). The stirred slurry was cooled by immersing the flask in an ice bath. A solution of N-Boc glycine (125 g, 714 mmol)

in acetonitrile (500 mL) was added via a 500-mL addition funnel over the course of 30-45 min. The mixture was aged for 1 h while a 5-L, 3-neck, round bottom flask equipped with a mechanical overhead stirrer and a thermocouple w/adapter was charged with 1-(6-chloropyridazin-3-yl)hydrazine (108 g, 749 mmol) and acetonitrile (900 mL) and cooled to <5 deg C in an ice bath. The cold solution of the acylimidazole was then transferred via a polyethylene cannula into the thick suspension of the hydrazine over a period of 30-45 min). The ice bath was removed, and the mixture was allowed to warm. After 2.5 h of stirring, 4-methylbenzenesulfonic acid hydrate (143 g, 749 mmol) was added. The flask was then equipped with a heating mantle and a reflux condenser and was heated to reflux (82 deg C) for 13 h, then cooled back to about 60 deg C. At this point, the warm solution was vacuum filtered through paper. The brown filtrate was then concentrated by rotary evaporation. The resulting thick yellow-brown slurry was stirred in an ice bath and diluted with ACN (about 100 mL). After stirring for 1 h, the solids were isolated by vacuum filtration, washed with ice-cold 1:1 ACN/H_2O (2x150 mL) and air-dried on the filter until a freely flowing solid was obtained (159 g, 78.5% yield).

General Method K

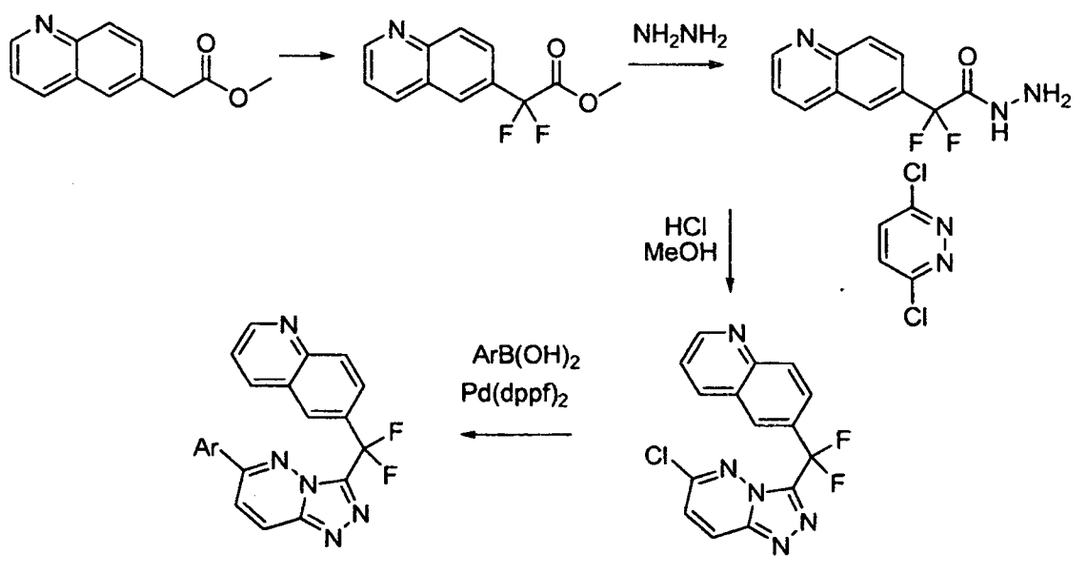


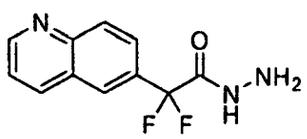
Example 475

6-(Difluoro(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)quinoline.

To a stirring suspension of 1-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)hydrazine (190 mg, 917 μmol), methyl 2,2-difluoro-2-(quinolin-6-yl)acetate (218 mg, 917 μmol), triphenylphosphine polymer supported (241 mg, 917 μmol), DIEA (200 μl, 1146 μmol) in DCM (4mL) was added 2,2,2-trichloroacetonitrile (92 μl, 917 μmol). The reaction vessel was then appropriately sealed and heated to 150 °C with microwaves for 15 min. The reaction was then concentrated onto dry silica under reduced pressure and product purified on silica (40 g) eluting with 1-4% of 2 M NH_3 in MeOH/DCM. The product was then further purified by RP-HPLC eluting with water/ACN (0.1% TFA). Collected fractions concentrated under reduced pressure, dissolved in MeOH/DCM (5mL) and stirred with Si-Carbonated (300 mg; 0.2 mmol) for 30 min at 23 °C. Solids were then removed by filtration, and washed with MeOH (3x1mL). The filtrate was then concentrated under reduced pressure, and product isolated as an off white solid. MS (ESI pos. ion) m/z: 395 (MH+). Calc'd exact mass for $C_{20}H_{13}F_3N_6$: 394.

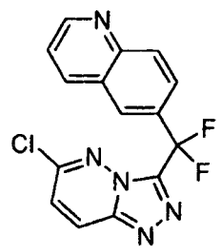
General Method L





2,2-Difluoro-2-(quinolin-6-yl)acetohydrazide

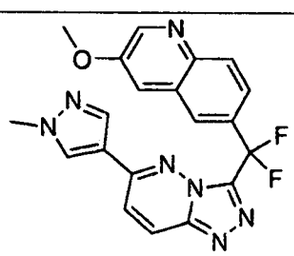
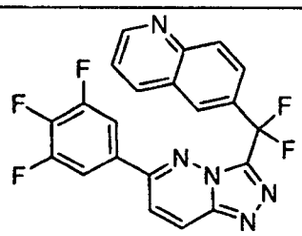
A solution methyl 2,2-difluoro-2-(quinolin-6-yl)acetate (400 mg, 1686 µmol) and anhydrous hydrazine (2153 µl, 67453 µmol) in MeOH (4 mL) was stirred for 1 h at 23 °C. The solvents were then removed under reduced pressure to provide product as a white solid. MS (ESI pos. ion) m/z: 238 (MH+). Calc'd exact mass for $C_{11}H_9F_2N_3O$: 237.

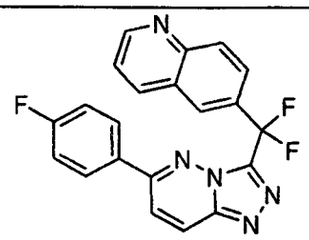
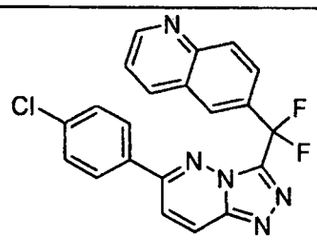
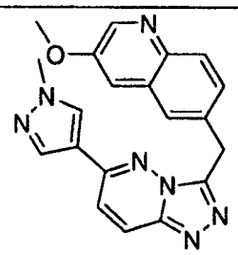
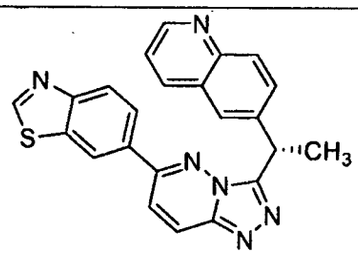
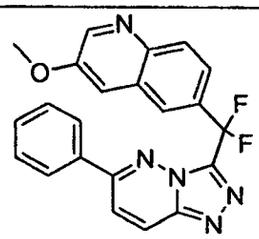


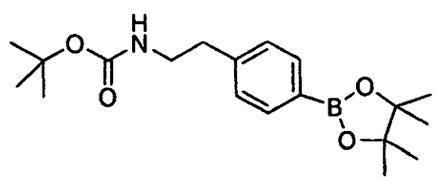
Example 476

6-((6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)difluoromethyl)quinoline

A suspension of 2,2-difluoro-2-(quinolin-6-yl)acetohydrazide (2000 mg, 8432 µmol) and 3,6-dichloropyridazine (3768 mg, 25295 µmol) in 1.25 M HCl in MeOH (20 mL) was heated to 90 °C with microwaves for 50 min. The solvents were then removed under reduced pressure and residue partitioned between 9:1 $CHCl_3$/IPA (60 mL) and 1 M NaOH (20 mL). The organic phase then dried over $MgSO_4$, concnetrated, then purified on silica (120 g) eluting with 1>2.5% of 2 M NH_3 in MeOH/DCM to provide product isolated as a dark tan soild. MS (ESI pos. ion) m/z: 332 (MH+). Calc'd exact mass for $C_{15}H_8ClF_2N_5$: 331.

Ex	Structure	MW	Mass Found	Method
477		407	408	L
478		427	428	L

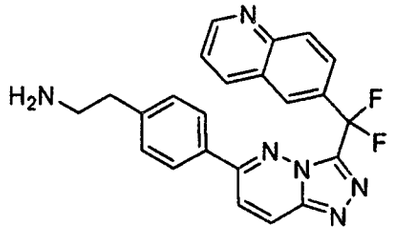
479		391	392	L
480		407	408	L
481		371	372	M
482		408	409	M
483		403	404	M



<u>*tert*-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethylcarbamate</u>

A suspension of tert-butyl 4-bromophenethylcarbamate (2700 mg, 8994 μmol), bis(pinacolato)diboron (2284 mg, 8994 μmol), bis(pinacolato)diboron (2284 mg, 8994 μmol), potassium acetate (1765 mg, 17989 μmol) in dioxane (12mL) was sparged with argon for 5 min then heated to 120 °C in an appropriately sealed vessel for 1 h. The reaction was then

partitioned between ether (50 mL) and 5% $NaHCO_3$ (25 mL). The organic phase was then dried over $MgSO_4$, concentrated, then purified on silica (120 g) eluting with 10>30% EtOAc/Hexanes. The product tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethylcarbamate (2200 mg, 70% yield) was isolated as a white solid. MS (ESI pos. ion) m/z: 292 (MH+1-56). Calc'd exact mass for $C_{19}H_{30}BNO_4$: 347.



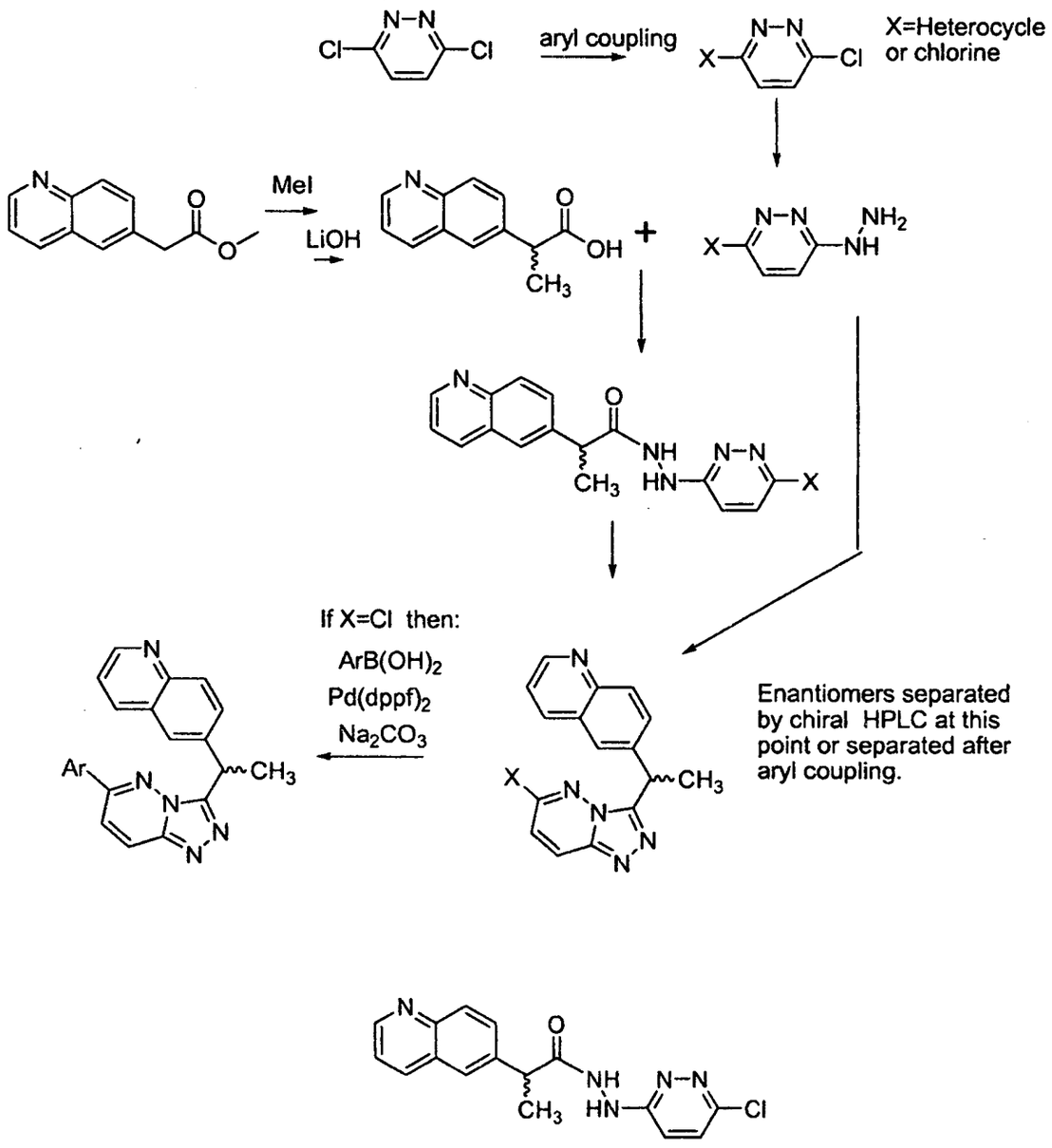
Example 484

2-(4-(3-(Difluoro(quinolin-6-yl)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)phenyl)ethanamine

a) *tert*-Butyl 2-(4-(3-(difluoro(quinolin-6-yl)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)phenyl)ethylcarbamate. A suspension of 6-((6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)difluoromethyl)quinoline (350 mg, 1055 μmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenethylcarbamate (733 mg, 2110 μmol), 1,1'-bis (diphenylphosphino)ferrocene-palladium(ii)dichloride dichloromethane complex (77 mg, 106 μmol), Na2CO3 (447 mg, 4221 μmol) in DME (4mL) and water (2mL) was sparged with argon for 5 min then heated to 85 °C in an appropriately sealed vessel for 4 h. The reaction was then partitioned between DCM (30 mL) and 1 M NaOH (10 mL). The organic phase was then dried over $MgSO_4$, concentrated, then purified on silica (40 g) eluting with 1>4% of 2 M NH_3 in MeOH/DCM. The product was isolated as an off white solid.

b) 2-(4-(3-(Difluoro(quinolin-6-yl)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)phenyl)ethanamine. A solution of tert-butyl 2-(4-(3-(difluoro(quinolin-6-yl)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)phenyl)ethylcarbamate (70 mg, 136 μmol) in DCM (1 mL) and TFA (1 mL) was stirred for 30 min at 23 °C. The solvents were then removed under reduced pressure and crude product purified by RP-HPLC eluting with water/ACN (0.1% TFA). The desired collected fractions were then concentrated under reduced pressure and the resulting residue dissolved in MeOH/DCM (5 mL). Solution was then stirred as a suspension with Si-Carbonated (300 mg; 0.2 mmol) for 30 min at 23 °C. The solids were then removed by filtration, washed with MeOH (3x1mL), and filtrate concentrated under reduced pressure. The product was isolated as a white fluffy solid. MS (ESI pos. ion) m/z: 417 (MH+). Calc'd exact mass for $C_{23}H_{18}F_2N_6$: 416.

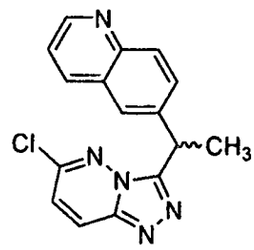
General Method M



N'-(6-chloropyridazin-3-yl)-2-(quinolin-6-yl)propanehydrazide

To a stirring solution of 2-(quinolin-6-yl)propanoic acid (3260 mg, 16201 μmol) and DIEA (2830 μl, 16201 μmol) in DMF (25 mL) was added o-(7-azabenzotriazol-1-yl)-n,n,n',n-tetramethyl uronium hexafluorophosphate (6160 mg, 16201 μmol) whole at 23 °C under nitrogen. The solution was stirred for 60 min, cooled to 0°C, then added 1-(6-chloropyridazin-3-yl)hydrazine (2342 mg, 16201 μmol). After 20 h stirring at 23 °C, the reaction was then partitioned between 9:1 $CHCl_3$/IPA (100 mL) and 5% $NaHCO_3$ (50 mL). The organic phase

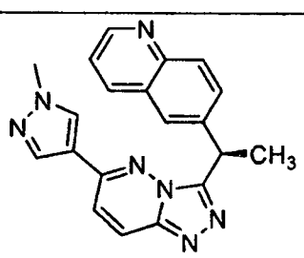
was then dried over $MgSO_4$, concentrated to an oil, then purifed on silica (120 g) eluting with 0>10% of 2 M NH_3 in MeOH/DCM. The product was isolated as an off white solid. MS (ESI pos. ion) m/z: 328 (MH+). Calc'd exact mass for $C_{16}H_{14}ClN_5O$: 327.

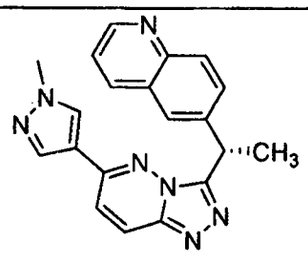
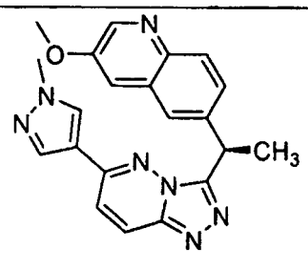
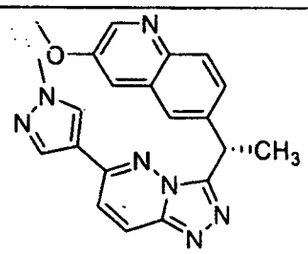
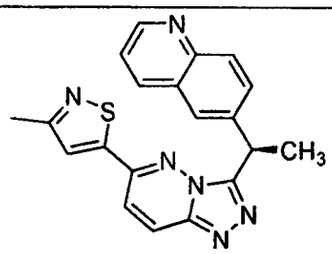
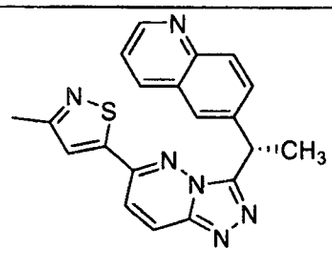


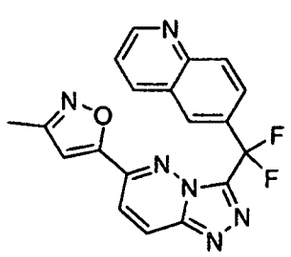
6-(1-(6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)ethyl)quinoline.

A solution of N'-(6-chloropyridazin-3-yl)-2-(quinolin-6-yl)propanehydrazide (2700 mg, 8238 μmol) in TFA (20 mL) was heated to 120 °C with microwaves (2 bar; 10 watts) for 40 min. The solution was concentrated under reduced pressure then partitioned between 9:1 CHCl3/IPA (75 mL) and 1 M NaOH (100 mL). The aqueous layer was further extracted with 9:1 $CHCl_3$/IPA (2x20 mL). The combined organics were dried over $MgSO_4$ then concentrated to an amber oil under reduced pressure. The product was isolated as off white crystaline solid from ACN. MS (ESI pos. ion) m/z: 310 (MH+). Calc'd exact mass for $C_{16}H_{12}ClN_5$: 309. Enantiomer resolved with: Chiralpak AD-H (3x25cm) column using 45% ethanol (0.1% DEA)/CO2

The following compounds were prepared using same method as *tert*-Butyl 2-(4-(3-(difluoro(quinolin-6-yl)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)phenyl)ethylcarbamate and resolved from racemic mixtures:

Ex	Structure	MW	Mass Found	Peak #
485		355	356	1

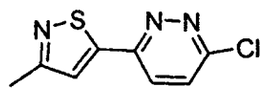
486		355	356	2
487		385	386	1
488		385	386	2
489		372	373	1
490		372	373	2



Example 491

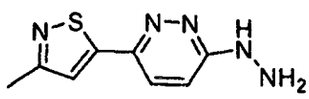
6-(difluoro(6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)quinoline

A suspension of 1-(6-(3-methylisoxazol-5-yl)pyridazin-3-yl)hydrazine hydrochloride (200 mg, 879 μmol) and methyl 2,2-difluoro-2-(quinolin-6-yl)acetate (208 mg, 879 μmol) in 5 M HCl (1 mL) was appropriately sealed and heated to 150 °C with microwaves for 4 h. The reaction was then quenched by a dropwise into cold 5 M NaOH (2 mL) and aqueous extracted with $CHCl_3$/IPA (25 mL). The organic phase was then dried over $MgSO_4$, concentrated, and purified with silica (40 g) eluting with 1>5% 2 M NH_3 in MeOH/DCM. The product was then further purified on RP-HPLC eluting with water/ACN (0.1% TFA). Combined fractions concentrated, dissolved in DCM (5 mL) and MeOH (5 mL), then stirred with Si-Carbonate (0.5 g; 35 mmol) for 1 h. Si-Carbonate removed by filtration and filtrated concentrated with <0.5 mL remaining with product isolated by trituration. MS (ESI pos. ion) m/z: 379 (MH+). Calc'd exact mass for $C_{19}H_{12}F_2N_6O$: 378.



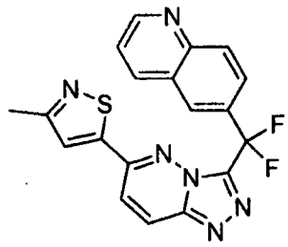
3-chloro-6-(3-methylisothiazol-5-yl)pyridazine

To a solution of 5-bromo-3-methylisothiazole (2.42 g, 14 mmol) in 20 mL of THF at -45 °C was added isopropylmagnesium chloride (19 ml, 19 mmol) in THF (1 M). After 20 minutes, zinc(II) chloride (41 ml, 20 mmol) in THF (0.5 M) was added and the solution was warmed up to rt. 3,6-dichloropyridazine (2.4 g, 16 mmol), 3,6-dichloropyridazine (2.4 g, 16 mmol) and Q-Phos (2.5 g) were added and the reaction was heated to 50 °C for 16 hours. The reaction was then cooled to 23 °C and quenched with 60 mL of satd. NH_4Cl aq. solution. The mixture was mixed with celite and 100 mL of EtOAc. The insoluble material was removed by filtration. The filtrate was diluted with 40 mL of EtOAc and 30 mL of water. The organic phase was separated and washed with 60 mL of brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (10% to 80% hex/EtOAc) to afford red solid as desired product. MS (ESI pos. ion) m/z: 212 (MH+). Calc'd exact mass for $C_8H_6ClN_3S$: 211.



1-(6-(3-methylisothiazol-5-yl)pyridazin-3-yl)hydrazine

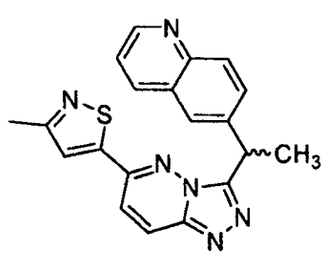
A mixture of 3-chloro-6-(3-methylisothiazol-5-yl)pyridazine (0.85 g, 4.0 mmol) and anhydrous hydrazine (3.8 ml, 120 mmol) in 30 mL of sec-BuOH was heated at 130 °C for 3 hours. The mixture was cooled to 23 °C and diluted with 5 mL of water. The solid was collected by filtration and was washed by 2 mL of water to produce a yellow solid. MS (ESI pos. ion) m/z: 208 (MH+). Calc'd exact mass for $C_8H_6ClN_3S$: 207.



Example 492

6-(difluoro(6-(3-methylisothiazol-5-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)quinoline

A mixture of methyl 2,2-difluoro-2-(quinolin-6-yl)acetate (0.50 g, 2.1 mmol), 1-(6-(3-methylisothiazol-5-yl)pyridazin-3-yl)hydrazine (0.25 g, 1.2 mmol) and p-toluenesulfonic acid monohydrate (0.40 g, 2.1 mmol) in 5 mL of dioxane was heated at 150 °C for 1 hour in a microwave. The mixture was then diluted with 70 mL of EtOAc and 40 mL of satd. $NaHCO_3$ solution. The organic phase was separated and washed with 40 mL of brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by a silica gel column chromatography (EtOAc to 10% MeOH/EtOAc) to give yellow glass. The product was further purified by a prep-HPLC to give yellow glass. MS (ESI pos. ion) m/z: 395 (MH+). Calc'd exact mass for $C_{19}H_{12}F_2N_6S$: 394.

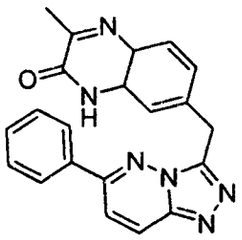


Example 493

6-(1-(6-(3-methylisothiazol-5-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)ethyl)quinoline

To a solution of 5-bromo-3-methylisothiazole (1.00 g, 5.6 mmol) in 10 mL of THF at -45 °C (CH_3CN/dry ice) was added isopropylmagnesium chloride LiCl complex (7.9 ml, 7.9 mmol) (LiCl complex, 1 M in THF). The mixture was stirred at -45 °C for 20 minutes and to this was added zinc chloride, 0.5 M in THF (17 ml, 8.4 mmol) slowly via a syringe. The mixture was

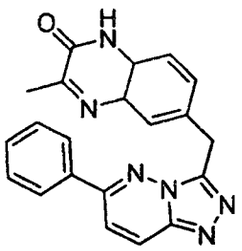
then warmed up to rt and continued to stir for additional 30 minutes. 6-(1-(6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)ethyl)quinoline (0.5787 g, 1.9 mmol), tris(dibenzylideneacetone)dipalladium (0) (0.51 g, 0.56 mmol) and Q-Phos (0.65 g) in 15 mL of N,N-dimethyl acetamide was added to the reaction mixture. The reaction was warmed up to 50 °C for 6 hours and was quenched with 50 mL of satd. NH_4Cl aq. solution. The mixture was extracted with 150 mL of EtOAc and the organic phase was washed with 60 mL of brine. The aqueous phases were further extracted with 100 mL EtOAc. The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (EtOAc to 15% MeOH in EtOAc) to give afford a red solid. MS (ESI pos. ion) m/z: 373 (MH+). Calc'd exact mass for $C_{20}H_{16}N_6S$: 372.



Example 494

3-methyl-6-((6-phenyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)quinoxalin-2(1H)-one

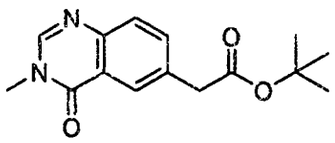
(See Example 495)



Example 495

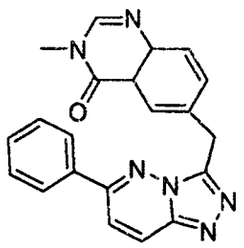
3-methyl-7-((6-phenyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)quinoxalin-2(1H)-one.

A mixture of tert-butyl 2-(2-methyl-3-oxo-3,4-dihydroquinoxalin-6-yl)acetate (0.10 g, 0.36 mmol), tert-butyl 2-(3-methyl-2-oxo-1,2-dihydroquinoxalin-6-yl)acetate (0.10 g, 0.36 mmol), 1-(6-phenylpyridazin-3-yl)hydrazine (0.081 g, 0.44 mmol) and p-toluenesulfonic acid monohydrate (0.069 g, 0.36 mmol) in 3 mL of dioxane was heated with microwave at 150 °C for 1 hour. The mixture was diluted with 70 mL of EtOAc and 40 mL of satd. $NaHCO_3$ solution. The organic phase was separated and was washed with 40 mL of brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by prep-HPLC to resolve the regiostereomers as example compounds 494 and 495. For each regiosteroemer MS (ESI pos. ion) m/z: 369 (MH+). Calc'd exact mass for $C_{21}H_{16}N_6O$: 368.



tert-butyl 2-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)acetate

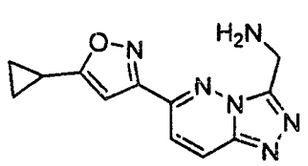
To a solution of 6-bromo-3-methylquinazolin-4(3H)-one (0.485 g, 2.0 mmol), tris(dibenzylideneacetone)dipalladium (0) (0.19 g, 0.20 mmol) and Q-phos (0.20 g) in 40 mL of THF was added 2-tert-butoxy-2-oxoethylzinc chloride 0.5 M in diethyl ether (8.1 ml, 4.1 mmol). The reaction was heated at 50 °C for 16 hours and was quenched with 40 mL of satd. NH_4Cl. The mixture was diluted with 60 mL of EtOAc. The organic phase was separated, washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give red solid. The residue was purified by a silica gel column chromatography (5% EtOAc/Hex to EtOAC) to provide a red solid. MS (ESI pos. ion) m/z: 275 (MH+). Calc'd exact mass for $C_{15}H_{18}N_2O_3$: 274.



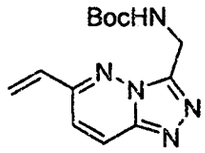
Example 496

3-Methyl-6-((6-phenyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)quinazolin-4(3H)-one:

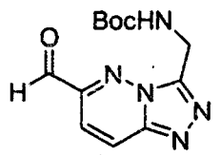
The title compound was prepared using the method for 3-methyl-6-((6-phenyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)quinoxalin-2(1H)-one. MS (ESI pos. ion) m/z: 369 (MH+). Calc'd exact mass for $C_{21}H_{16}N_6O$: 368.



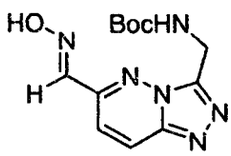
(6-(5-cyclopropylisoxazol-3-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methanamine



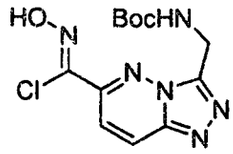
1) tert-butyl (6-vinyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate. To an argon purged flask were added 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (7.65 ml, 45.1 mmol), tert-butyl (6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (3.20 g, 11.3 mmol), cesium carbonate (11.0 g, 33.8 mmol), and $PdCl_2(dppf)$-CH_2Cl_2 (0.461 g, 0.564 mmol). The mixture was dissolved in 38 mL of dioxane and 4 mL of water (0.25M 10:1) and was heated to 80 °C for 12 h. The mixture was cooled to room temperature, concentrated, and purified directly via MPLC (DCM/MeOH+1%NH_4OH)to afford the title compound (3.0 g, 95% yield).



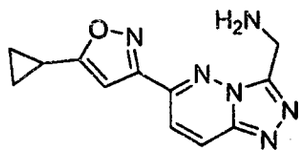
2) tert-butyl (6-formyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate. Tert-butyl (6-vinyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (485 mg, 1.76 mmol) was dissolved in 5 mL of THF and 5 mL of water then osmium tetroxide (0.687 mL (4% water solution), 0.0176 mmol) was added and stirred for 5 min. Sodium periodate was added (141, 3.53 mmol) and the reaction was stirred for 2 h. The reaction was then extracted with dichloromethane (3 x 10 mL), dried over Na_2SO_4 and concentrated. Purification via MPLC (DCM/MeOH+1%NH_4OH) afforded title compound as a tan solid (350 mg, 72% yield).



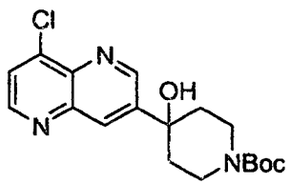
3) (E)-tert-butyl (6-((hydroxyimino)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate. Tert-butyl (6-formyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (400 mg, 1.44 mmol) and hydroxylamine hydrochloride (200 mg, 2.86 mmol) were combined in a flask with 25 mL of THF and 25 mL of 1 N NaOH solution. Stirred at rt for 1 h. Then added dichloromethane (50 mL) and extracted the aqueous layer 3 times with DCM (50 mL), dried over Na_2SO_4 and concentrated. Purified the oxime via MPLC (DCM/MeOH+1%NH_4OH) to give title compound (200 mg, 47% yield) as a tan solid.



4) (Z)-tert-butyl (6-(chloro(hydroxyimino)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate. Dissolved (E)-tert-butyl (6-((hydroxyimino)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (200 mg, 0.684 mmol) in 25 mL of DMF and added 1-chloropyrrolidine-2,5-dione (95.9 mg, 0.718 mmol). Let stir at rt for 2 h. Poured reaction mixture onto water (20 mL) and extracted with ether (3 x 20 mL). Washed organics with water (2 x 20 mL), brine (1 x 20 ml), dried over sodium sulfate, filtered and concentrated. Title compound used without further purification (220 mg, 97% yield).

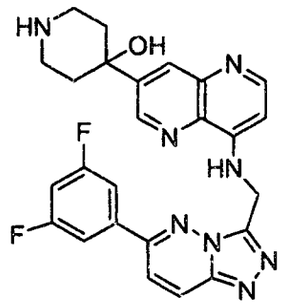


5) (6-(5-cyclopropylisoxazol-3-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methanamine. Dissolved (Z)-tert-butyl (6-(chloro(hydroxyimino)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (110 mg, 337 μmol), ethynylcyclopropane (28 μl, 337 μmol), and potassium hydrogencarbonate (67.4 mg, 673 μmol) in 0.3 mL of EtOAc and heated to 60 °C for 12 h to afford the protected intermediate. The solvent was removed by rotary evaporation and the residue was redissolved in dicholoromethane (5 mL) and TFA (2 mL) and stirred for 30 min at room temperature. The solvent was then removed and the residue was redissolved in MeOH. Solid K_2CO_3 was added and the mixture was stirred for 1 h to free base the title compound. Purified the amine via MPLC (DCM/MeOH+1%NH_4OH) to afford the title compound(20 mg, 23% yield).



tert-butyl 4-(8-chloro-1,5-naphthyridin-3-yl)-4-hydroxypiperidine-1-carboxylate. Dissolved 3-bromo-8-chloro-1,5-naphthyridine (210 mg, 862 μmol) in 8 mL of THF and cooled to -78 °C. Then added butyllithium (517 μl, 1294 μmol) and stirred for 15 min. Added tert-butyl 4-oxopiperidine-1-carboxylate (258 mg, 1294 μmol) and let warm to room temperature over 1 h. The reaction was quenched with saturated NH_4Cl and extracted with dichloromethane (3 X 20 mL), dried over $NaSO_4$ and concentrated. Intermediate was purified

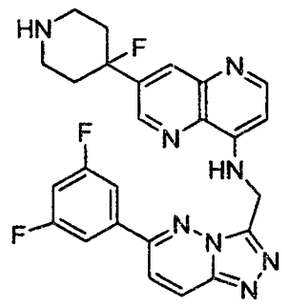
via MPLC (DCM/MeOH/NHOH) to yield tert-butyl 4-(8-chloro-1,5-naphthyridin-3-yl)-4-hydroxypiperidine-1-carboxylate (120 mg, 38% yield.



Example 497

4-(8-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylamino)-1,5-naphthyridin-3-yl)piperidin-4-ol.

Deprotection of tert-butyl 4-(8-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylamino)-1,5-naphthyridin-3-yl)-4-hydroxypiperidine-1-carboxylate using the method described for (6-(3-methylisothiazol-5-yl)-[1,2,4]triazolo[4,3-*b*]pyridazin-3-yl)methanamine. M/Z = 489.2 [M+H], calc 488.19 for $C_{25}H_{22}F_2N_8O$.

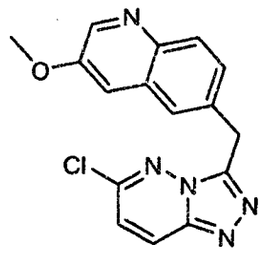


Example 498

N-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-(4-fluoropiperidin-4-yl)-1,5-naphthyridin-4-amine.

A solution of tert-butyl 4-(8-((6-(3,5-difluorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylamino)-1,5-naphthyridin-3-yl)-4-hydroxypiperidine-1-carboxylate (30 mg, 51 µmol) in 0.5 mL of DCM was cooled to -78 C. Then added DAST (13 µl, 102 µmol) and let stir to room temperature over 30 min. TFA was then added to the reaction mixture and stirred for 30 min. The solvent was then removed by rotary evaporation and the residue was redissolved in MeOH and free based through a cation exchange column. Purification via MPLC

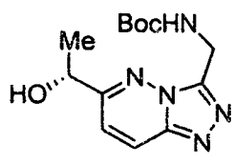
(DCM/MeOH+1%NH_4OH) yielded the title compound (15 mg, 60% yield). M/Z = 491.2 [M+H], calc 490.18 for $C_{25}H_{21}F_3N_8$.

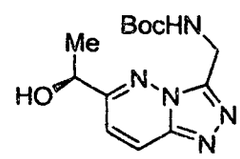


Example 499

6-((6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-3-methoxyquinoline

To a 5 ml CEM microwave tube was added tert-butyl 2-(3-methoxyquinolin-6-yl)acetate (0.05 g, 0.2 mmol) , 1-(6-chloropyridazin-3-yl)hydrazine (0.04 g, 0.3 mmol), water (0.5 mL) and hydrochloric acid (0.05 ml, 0.5 mmol). The vial was sealed and first heated at 90 °C for 30 min then placed into CEM microwave for 10 min. at 100 °C, with 100 Watts of power via Powermax. The reaction mixture was adjusted the pH to 7 by adding 5 N NaOH - brown ppt. was generated. The brown ppt. was dissolved in DCM. The organic was washed with water, dried over $MgSO_4$, and removed solvent *in vacuo*. The crude product was purified using SiO_2 chromatography (Teledyne Isco RediSep®, P/N 68-2203-026, 12 g SiO_2, DCM:EtOAc:MeOH=75%:20%:5%, Flow = 30 mL/min). A peak at 25 min was collected. The solvent was removed *in vacuo* to afford the desired product as light yellowish solid. Wt: 20.0 mg. MS (ESI pos. ion) m/z: 326.53. Calc'd exact mass for $C_{16}H_{12}ClN_5O$: 325.75.

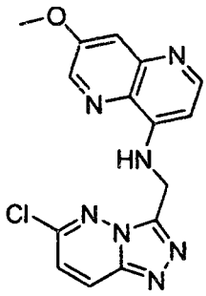




(*R/S*)-tert-butyl (6-(1-hydroxyethyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate

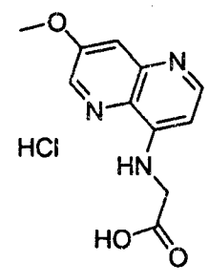
In a 10 mL round bottom flask under N_2 was dissolved *tert*-butyl (6-formyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (200 mg, 721 µmol) in 3 mL of THF then cooled at -78 °C and treated with methylmagnesium bromide (721 µl, 2164 µmol). After 30 minutes, the reaction mixture was warmed to 0 °C over 1h. After 1h the reaction mixture based on LC-MS was neutralized with NH_4Cl (sat.). The aqueous phase was extracted 3X with DCM then the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The

crude tert-butyl (6-(1-hydroxyethyl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (202 mg, 95.5% yield) was used without further purification in the next step. MS *m/z* = 294.4 $[M+1]^+$. Calc'd for $C_{13}H_{19}N_5O_3$: 293.3.



Example 500

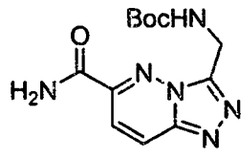
N-((6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-methoxyquinolin-4-amine.



a) 2-(7-methoxy-1,5-naphthyridin-4-ylamino)acetic acid hydrochloride. In a 100 mL round bottom flask were dissolved 8-chloro-3-methoxy-1,5-naphthyridine (5.00 g, 25.7 mmol) and glycine tert-butyl ester hydrochloride (17.2 g, 103 mmol) in 50 mL of 2-BuOH then stirred and heated at 100 °C. After 5h the solvent based on LC-MS was removed by reduced pressure and then the solid was dissolved in 200 mL of HCl 1N and stirred at 60 °C overnight. After 10h the reaction mixture based on LC-MS was cooled down to rt then 0°C and the desired acid precipitate. Filtered the solid (3.97 g) then evaporated the aqueous solution and triturated in 75 mL of H_2O at 0 °C then filter again and washed with 25 mL of H_2O at 0 °C (1.58 g) to afforded total 2-(7-methoxy-1,5-naphthyridin-4-ylamino)acetic acid hydrochloride (5.55 g, 80.1% yield) as a tan solid. MS *m/z* = 234.1 $[M+1]^+$. Calc'd for $C_{11}H_{11}N_3O_3$: 233.1.

b) N-((6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-methoxy-1,5-naphthyridin-4-amine . In a 250 mL round bottom flask under N_2 were dissolved HATU (1762 mg, 4635 µmol), 1-(6-chloropyridazin-3-yl)hydrazine (536 mg, 3708 µmol), 2-(7-methoxy-1,5-naphthyridin-4-ylamino)acetic acid hydrochloride (1.00 g, 3708 µmol) in 25 mL of MeCN then stirred and cooled down at -40 °C then treated with TRIETHYLAMINE (2584 µl, 18540 µmol) and warmed to rt. After 30 min the reaction mixture based on LC-MS was evaporated

under reduced pressure and dry under high vacuum. The crude solid was dissolved in 100 mL of i-PrOH then treated with Ts-OH (2821 mg, 14832 μmol) and heated at 80 °C. After 3h the reaction mixture based on LC-MS was diluted with DCM then neutralized with NaOH (1N). The aqueous phase was extracted 3X with DCM with 10% MeOH then the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was triturated with hot i-PrOH then cooled down and filtered (662 mg) and the mother liquor was evaporated under reduced pressure and purified by MPLC (ISCO) (210 mg) with DCM:MeOH 100:0 to 90:10 to afforded in combined yields N-((6-chloro-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-7-methoxy-1,5-naphthyridin-4-amine (872 mg, 69% yield) as a off-white solid. MS *m/z* = 342.1 $[M+1]^+$. Calc'd for $C_{15}H_{12}ClN_7O$: 341.7.



tert-Butyl (6-carbamoyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate

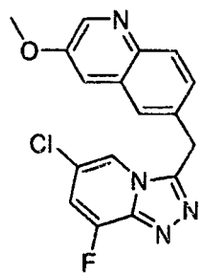
a) 3-((tert-butoxycarbonyl)methyl)-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxylic acid. In a 25 mL round bottom flask were dissolved 2-methyl-2-butene (21639 μl, 43278 μmol), potassium dihydrogen phosphate (2356 mg, 17311 μmol) and tert-butyl (6-formyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate (600 mg, 2164 μmol) in 5 mL of *t*-BuOH and 5 mL of water then was added at 0 °C sodium chlorite (783 mg, 8656 μmol) and the reaction mixture was warmed to rt. After 10h the reaction mixture based on LC-MS was concentrated under reduced pressure and the crude acid was extract from the solid salts mixture with MeOH, filtered and the solvent was concentrated under reduced pressure. The crude 3-((tert-butoxycarbonyl)methyl)-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxylic acid (635 mg, 100% yield) was used without further purification in the next step. MS *m/z* = 294.2 $[M+1]^+$. Calc'd for $C_{12}H_{15}N_5O_4$: 293.1

b) tert-butyl (6-carbamoyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate. In a 10 mL round bottom flask under N_2 were dissolved 3-((tert-butoxycarbonyl)methyl)-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxylic acid (250 mg, 852 μmol), HATU (389 mg, 1023 μmol), triethylamine (356 μl, 2557 μmol) in 1.5 mL of DMF then was treated with a (92 μl, 4262 μmol) and stirred at rt. After 2h the reaction mixture based on LC-MS was concentrated under reduced pressure and then purified by MPLC (ISCO) with DCM:MeOH+NH_4OH (1%) 100:0 to 90:10 to afforded tert-butyl (6-carbamoyl-[1,2,4]triazolo[4,3-b]pyridazin-3-

yl)methylcarbamate (129 mg, 52% yield). MS *m/z* = 293.2 $[M+1]^+$. Calc'd for $C_{12}H_{16}N_6O_3$: 292.3.

3-(aminomethyl)-N-methyl-[1,2,4]triazolo[4,3-b]pyridazine-6-carboxamide.

The title compound was made using the same conditions as tert-butyl (6-carbamoyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methylcarbamate.

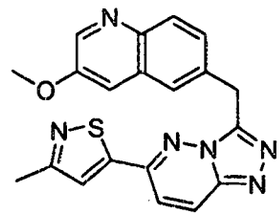


Example 501

6-((6-chloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)-3-methoxyquinoline

a) 1-(5-chloro-3-fluoropyridin-2-yl)hydrazine. A mixture of 5-chloro-2,3-difluoropyridine (10.0 g, 66.9 mmol) and hydrazine (10.0 ml, 319 mmol) in ^{i}PrOH (50 mL) was heated to 65 - 70 °C for 6 hours. The mixture was cooled to 23 °C, filtered, and washed with Na_2CO_3 (satd), and H_2O. Product isolated as a white solid. MS (ESI pos. ion) m/z: 162 (MH+). Calc'd exact mass for $C_5H_5ClFN_3$: 161.

b) 6-((6-chloro-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)-3-methoxyquinolin. To a mixture of 2-(3-methoxyquinolin-6-yl)acetic acid (0.22 g, 1.0 mmol), 1-(5-chloro-3-fluoropyridin-2-yl)hydrazine (0.11 g, 0.68 mmol) and triphenylphosphine (0.97 g, 2.0 mmol) (on solid support) in DCM (5 mL) was added DIEA (0.24 ml, 1.4 mmol) followed by 2,2,2-trichloroacetonitrile (0.14 ml, 1.4 mmol) via a syringe. The mixture was then heated to 150 °C for 15 minutes in an appropriately sealed vial. The mixture was filtered and the filtrate was diluted with 50 mL of EtOAc. The solution was washed with 30 mL of satd. $NaHCO_3$ followed by 30 mL of brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by a silica gel column chromatography (EtOAc to 10% MeOH/EtOAc) to give light yellow solid as desired product. MS (ESI pos. ion) m/z: 343 (MH+). Calc'd exact mass for $C_{17}H_{12}ClFN_4O$: 342.

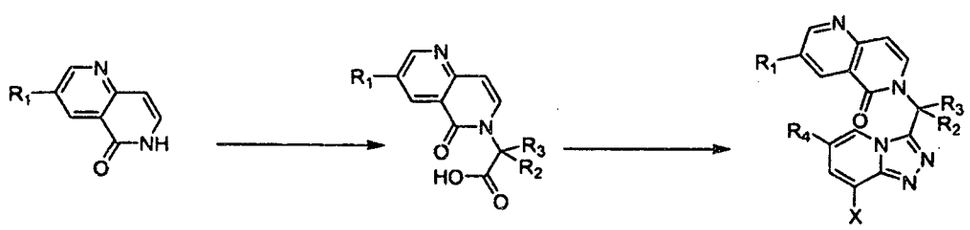


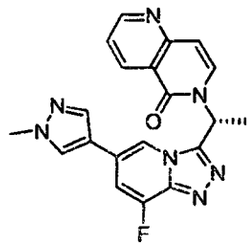
Example 502

3-Methoxy-6-((6-(3-methylisothiazol-5-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)quinoline

A flask charged with 5-bromo-3-methylisothiazole (0.049 g, 0.28 mmol) and 0.3 mL dry THF was cooled to 0 °C, and isopropylmagnesium chloride (0.30 ml, 0.30 mmol) added dropwise over 5 minutes and the mixture stirred an additional 5 minutes before allowing to warm to rt. The mixture was stirred at rt 10 minutes and the mixture cannulated to a solution of zinc(II) chloride (0.30 ml, 0.30 mmol) [1M] and the slurry stirred 10 minutes. The zincate was treated with 6-((6-iodo-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)-3-methoxyquinoline (0.0890 g, 0.21 mmol), 1 mL dry THF, and a preformed solution of 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (0.012 g, 0.021 mmol) and Pd(OAc)2 (0.0024 g, 0.011 mmol) dissolved in 1 mL dry THF. The flask was fitted with a reflux condenser and heated with a 90 °C oil bath for 24 h. The zincate portion of this procedure was repeated, added to the reaction mixture, and the mixture heated at 90 °C for 1 h. The mixture was allowed to cool to rt and loaded onto 10 g of SiO_2 wet-packed with THF, and eluted with 200 mL THF. The eluents were concentrated *in vacuo*, and taken up in 5 mL EtOH. To the solution was added Si-sulfonic acid (1.5 g, 1.1 mmol) and the mixture stirred at room temperature for 24 h, and the solid collected. The solid was washed with EtOH (discarded), and then 2M NH_3 in EtOH (5 x 5 mL). The ammoniacal eluents were concentrated and the residue purified by HPLC to afford 3-methoxy-6-((6-(3-methylisothiazol-5-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)quinoline (0.0013 g, 1.6% yield).

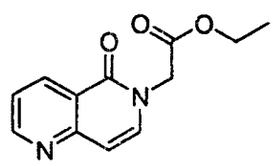
General Method N.





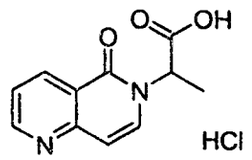
Example 503

(R)-6-(1-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one



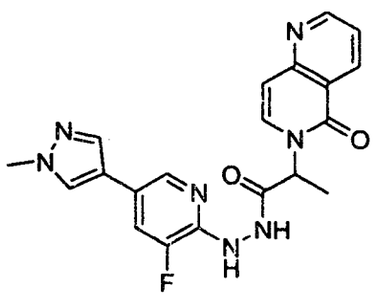
1. **ethyl 2-(5-oxo-1,6-naphthyridin-6(5H)-yl)acetate.**

1,6-naphthyridin-5-ol (1.00 g, 6.8 mmol), ethyl iodoacetate (1.6 ml, 14 mmol) and cesium carbonate (4.5 g, 14 mmol) were dissolved in 25 mL of THF then stirred and heated at 100 °C for 2h until the reaction was complete. The reaction was concentrated and purified via MPLC using a gradient to 90% DCM : 10% MeOH to afford ethyl 2-(5-oxo-1,6-naphthyridin-6(5H)-yl)acetate (1.5 g, 94% yield).



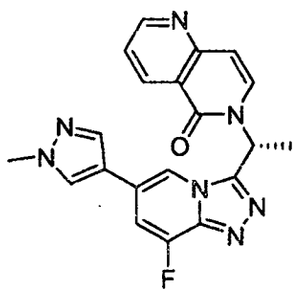
2. **2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride.**

2-(5-oxo-1,6-naphthyridin-6(5H)-yl)acetate (32.0 g) was dissolved in 450 mL of a 6 N HCl solution, then stirred and heated at 100 °C for 1 hr until the reaction was complete. The reaction mixture was concentrated under reduced pressure, and azeotroped 3 times with benzene (200 mL) to remove the water. The crude 2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride (30.56 g, 92.3% yield) was used without further purification.



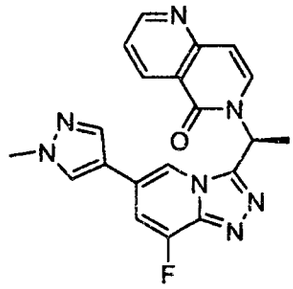
3. **N'-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanehydrazide.**

HATU (1053 mg, 2.7 mmol), 2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride (470 mg, 1.8 mmol) and 1-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)hydrazine (421 mg, 2 mmol) (step 1 of General Method K) were taken up in 6 mL of acetonitrile. DIPEA (967 µl, 5.5 mmol) was added and the reaction was stirred for 30 minutes, until reaction was complete. The crude material was concentrated and then purified via MPLC with a gradient 100% DCM to 90% DCM / 10% MeOH / 1% NH_4OH) to yield N'-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanehydrazide (500 mg, 67% yield).



4. **(R)-6-(1-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one.**

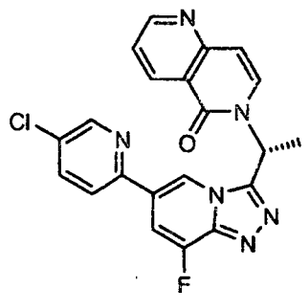
N'-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanehydrazide (400 mg, 982 µmol) and triphenylphosphine (386 mg, 1.4 mmol) were taken up in THF (9.8 mL). TMS-azide (195 µl, 1.4 mmol) was added, followed by slow addition of DEAD (233 µl, 1.4 mmol) and the reaction was stirred at room temperature for 1 hr until complete. The reaction was concentrated and purified via MPLC with a gradient 100 % DCM to 90% DCM / 10% MeOH / 1% NH_4OH to yield racemic 6-(1-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one (220 mg, 57% yield) as a tan solid. Separated by preperative SFC (ChiralPak® OJ-H, (20 x 150 mm, 5 □m), 20% MeOH, 80% CO_2, 0.2% DEA; 100 bar system pressure; 70 mL/min; t_r : 3.5 min) to yield (R)-6-(1-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one (60 mg, 15% yield). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. MS *m/z* = 390.2 [M+H], calc 389.14 for $C_{20}H_{16}FN_7O$. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) □ ppm 2.16 (d, *J*=5.18 Hz, 3 H) 3.97 (s, 3 H) 6.82 (d, *J*=6.55 Hz, 1 H) 7.01 - 7.13 (m, 2 H) 7.41 - 7.49 (m, 1 H) 7.54 (d, *J*=6.26 Hz, 1 H) 7.61 (s, 1 H) 7.71 (s, 1 H) 8.33 (s, 1 H) 8.78 (d, *J*=7.73 Hz, 1 H) 8.93 (s, 1 H).



Example 504

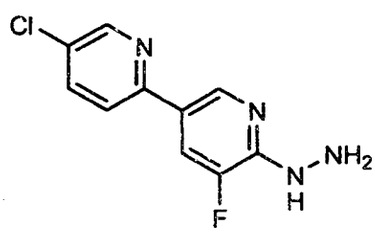
(S)-6-(1-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

The title compound was synthesized in the same general manner as that previously described for example 503. Seperated by preperative SFC (ChiralPak® OJ-H, (20 x 150 mm, 5 □m), 20% MeOH, 80% CO_2, 0.2% DEA; 100 bar system pressure; 70 mL/min; t_r : 4.3 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. MS *m*/z = 390.2 [M+H], calc 389.14 for $C_{20}H_{16}FN_7O$.

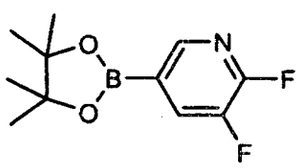


Example 505

(*R*)-6-(1-(6-(5-chloropyridin-2-yl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

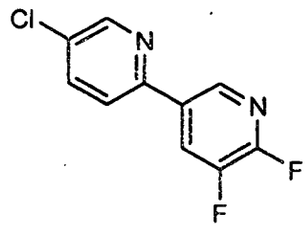


1. **1-(5-(5-chloropyridin-2-yl)-3-fluoropyridin-2-yl)hydrazine**



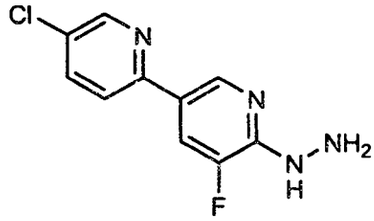
a. **2,3-difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine.**

A 350 mL resealable pressure vial was charged with 5-chloro-2,3-difluoropyridine (5.0 g, 33 mmol), pinacol diborane (13 g, 50 mmol), x-phos (1.9 g, 4.0 mmol), Pd_2dba_3 (1.8 g, 2.0 mmol), , and 1,4-dioxane (215 ml, 0.16 M), flushed with argon, sealed, then heated at 100°C for 16 hours. The mixture was concentrated and diluted with DCM (200 mL), then washed with water (50 mL). The organic layer was dried with $MgSO_4$, filtered, then concentrated to give a brown oil. The oil was purified by MPLC, eluting with 10-60% EtOAc/Hexanes. 2,3-difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (5.6 g, 69% yield) was isolated as a light orange oil which solidified upon standing. LC/MS shows the product as the boronic acid. However, the structure of the product is as drawn above. MS m/z = 160.2 $[M+1]^+$. Calc'd for $C_{11}H_{14}BF_2NO_2$: 241.0



b. **5-(5-chloropyridin-2-yl)-2,3-difluoropyridine.**

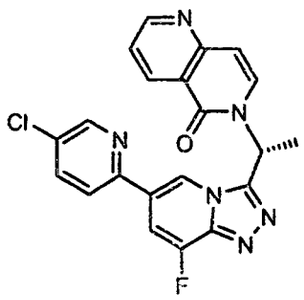
To a pressure vessel was added 2-bromo-5-chloropyridine (3.0 g, 16 mmol), cesium carbonate (15 g, 47 mmol), 1,1'-bis (diphenylphosphino)ferrocene-palladium(ii) dichloride dichloromethane complex (2.5 g, 3.1 mmol), and 2,3-difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (4.5 g, 19 mmol) in 1,4-dioxane (120 mL) and water (22 mL). The mixture was flushed with argon, sealed and stirred at 90°C for three hours. The mixture was concentrated, diluted with dichloromethane and washed with water. Organic extracts were concentrated and purified by MPLC (eluted with 0-10% methanol in dichloromethane) to yield 5-(5-chloropyridin-2-yl)-2,3-difluoropyridine as a yellow solid (2.4 g, 68%). MS m/z = 227.2 $[M+1]^+$. Calc'd for $C_{10}H_5ClF_2N_2$: 226.6.



c. **1-(5-(5-chloropyridin-2-yl)-3-fluoropyridin-2-yl)hydrazine.**

To a solution of 5-(5-chloropyridin-2-yl)-2,3-difluoropyridine (2.4 g, 11 mmol) in IPA (35 mL, 0.3 M) at room temperature was added hydrazine (4 mL, 127 mmol). The reaction mixture was stirred at 60°C for 2 h, at which point the reaction was cooled to room temperature and concentrated in vacuo. The concentrated material was suspended in saturated $NaHCO_3$ and

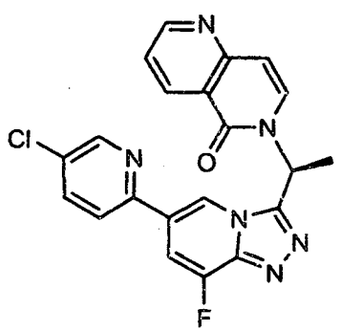
filtered to obtain product as a white, fluffy solid. The material was re-suspended in water (30 mL), and filtered to obtain 1-(5-(5-chloropyridin-2-yl)-3-fluoropyridin-2-yl)hydrazine (2.1 g, 83% yield). MS m/z = 239.2 $[M+1]^+$. Calc'd for $C_{10}H_8ClFN_4$: 238.6.



2. **(R)-6-(1-(6-(5-chloropyridin-2-yl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one**

Prepared according to General Method N. Chiral separation by preparative SFC (ChiralCel® OD-H (20 x 150 mm 5m), 30% MeOH 0.2% DEA, 70 mL/min and 100bar system backpressure (t_r: 4.0mins). On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer.

MS m/z = 420.8 $[M+1]^+$. Calc'd for $C_{21}H_{14}ClFN_6O$: 420.8. 1H NMR (400 MHz, DMSO-d_6) □ ppm 2.01 (d, *J*=7.04 Hz, 3 H) 6.78 (d, *J*=7.82 Hz, 1 H) 7.03 (d, *J*=6.94 Hz, 1 H) 7.54 (dd, *J*=8.07, 4.55 Hz, 1 H) 7.78 (d, *J*=7.82 Hz, 1 H) 7.97 - 8.09 (m, 2 H) 8.16 (dd, *J*=8.56, 2.49 Hz, 1 H) 8.61 (dd, *J*=7.97, 1.71 Hz, 1 H) 8.70 - 8.78 (m, 1 H) 8.92 (dd, *J*=4.55, 1.81 Hz, 1 H) 9.03 (d, 1 H).

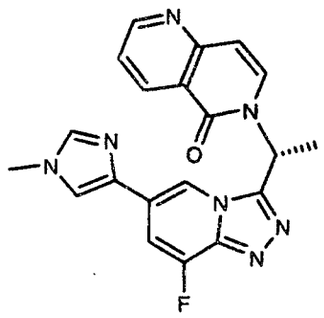


Example 506

(S)-6-(1-(6-(5-chloropyridin-2-yl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

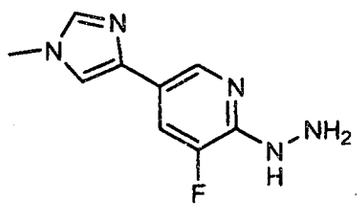
Prepared in the same general manner as that previously described for example 505 using General Method N. Chiral separation by preparative SFC (ChiralCel® OD-H (20 x 150 mm 5m), 30% MeOH 0.2% DEA, 70 mL/min and 100bar system backpressure (t_r: 5.8 mins). On the basis of previous crystallographic data and potency recorded for related compounds in the

same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. MS m/z = 420.8 $[M+1]^+$. Calc'd for $C_{21}H_{14}ClFN_6O$: 420.8.



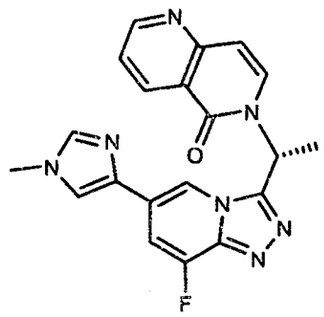
Example 507

***(R)*-6-(1-(8-fluoro-6-(1-methyl-1H-imidazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one**



1. **1-(3-fluoro-5-(1-methyl-1H-imidazol-4-yl)pyridin-2-yl)hydrazine**

Prepared in the same general manner as that previously described for 1-(5-(5-chloropyridin-2-yl)-3-fluoropyridin-2-yl)hydrazine

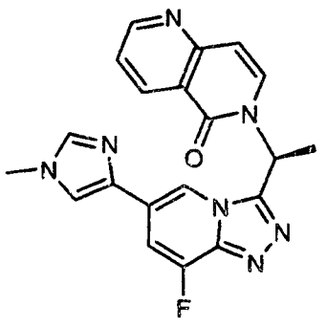


2. ***(R)*-6-(1-(8-fluoro-6-(1-methyl-1H-imidazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one.**

Prepared according to General Method N. Chiral separation by preparative SFC (ChiralPak® AD-H (20 x 250 mm 5m), 40% MeOH 0.2% DEA, 70 mL/min and 100bar system backpressure (t_r 4.1mins).

On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. MS m/z = 389.8 $[M+1]^+$. Calc'd for $C_{20}H_{16}FN_7O$: 389.4. 1H NMR (400 MHz, DMSO-d_6) □ ppm 1.97 (d, *J*=6.94 Hz, 3 H) 3.68 (s, 3 H) 6.75 (d, *J*=7.73 Hz, 1 H) 6.94 (d, *J*=6.85 Hz, 1 H) 7.52 -

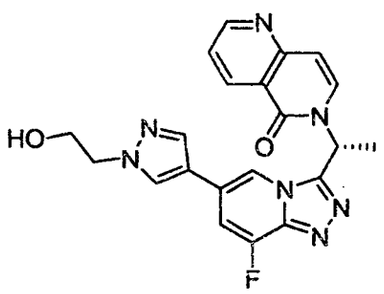
7.59 (m, 1 H) 7.64 (dd, *J*=7.78, 0.54 Hz, 1 H) 7.69 - 7.75 (m, 3 H) 8.46 (s, 1 H) 8.63 (dt, *J*=8.12, 0.88 Hz, 1 H) 8.90 - 8.94 (m, 1 H)



Example 508

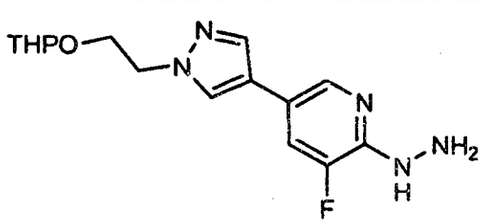
(*S*)-6-(1-(8-fluoro-6-(1-methyl-1H-imidazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

Prepared in the same general manner as that previously described for example 507 using General Method N. Chiral separation by preparative SFC (ChiralPak® AD-H (20 x 250 mm 5m), 40% MeOH 0.2% DEA, 70 mL/min and 100bar system backpressure (t_r: 5.9 mins). On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. MS m/z = 389.8 $[M+1]^+$. Calc'd for $C_{20}H_{16}FN_7O$: 389.4 .

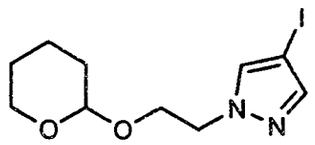


Example 509

(R)-6-(1-(8-fluoro-6-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

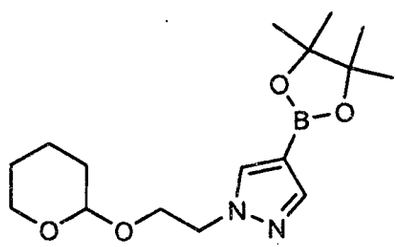


1. **1-(3-fluoro-5-(1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)hydrazine**



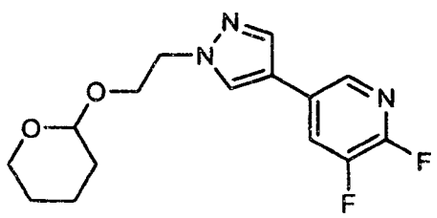
a. **4-iodo-1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazole.**

A mixture of cesium carbonate (20.7 g, 63.4 mmol) and 4-iodopyrazole (10.00 g, 51.6 mmol) in DMF (100 mL) was allowed to stir for 10 min. To the mixture was added 2-(2-bromoethoxy)tetrahydro-2h-pyran (9.98 ml, 63.4 mmol) and heated at 80°C overnight. The mixture was diluted with water and extracted with EtOAc (3 x 50 mL), and subsequently washed with water (2 x 50 mL) and brine, dried over sodium sulfate, and filtered. The crude mixture was evaporated onto silica gel and purified via MPLC (0% to 50%; EtOAc in hexanes). Isolated 4-iodo-1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazole (15.3 g, 92%) as a clear oil. MS m/z = 323.0 $[M+1]^+$. Calc'd for $C_{10}H_{15}IN_2$: 322.1.



b. **1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole.**

To a solution of 4-iodo-1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazole (8.7 g, 27.1 mmol) in THF (75 mL) at 0°C under argon was added isopropylmagnesium chloride as a 2 M solution in THF (27.1 mL, 54.3 mmol). The reaction was stirred for 1h at 0°C. To it was added 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.7 mL, 40.7 mmol) and the mixture was stirred for an additional 1 h while allowing to warm to room temperature. It was then treated with saturated ammonium chloride (100 mL) solution and the product was extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine, dried over sodium sulfate, and filtered. Crude material was concentrated under reduced pressure to afford 7.1 g (81%) of 1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole as a clear yellow oil. The material was taken on crude to the next step. MS m/z = 323.2 $[M+1]^+$. Calc'd for $C_{16}H_{27}BN_2O_4$: 322.2



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División de Nuevas Creaciones

SOLICITUD
PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 10-98383

54. **TÍTULO** _____ 2/3

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51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** _____

DOMICILIO _____

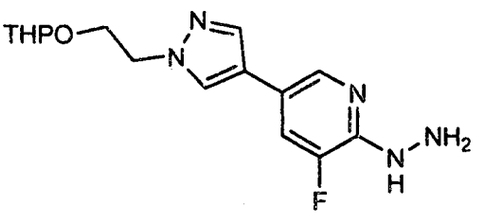
74. **APODERADO** _____

22. **BOGOTÁ, D.C.,** _____

(FORMA P-10)

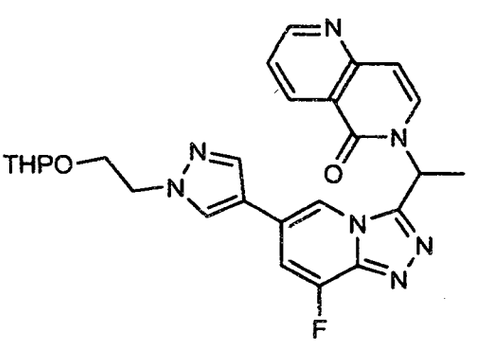
c. **2,3-difluoro-5-(1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)pyridine.**

A 48 mL tube was charged with 1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (6.4 g, 19.9 mmol), 5-chloro-2,3-difluoropyridine (1.7 mL, 16.6 mmol), X-Phos (1.6 g, 3.3 mmol), Potassium phosphate (3.5 g, 16.6 mmol), $PdOAc_2$ (0.4 g, 1.7 mmol), 1,4-dioxane (50 mL), and water (5.0 mL), flushed with argon, sealed, then heated at 100°C for 3 hours. The mixture was concentrated and purified by MPLC, eluting with 2.5% MeOH/DCM over 40 minutes to afford 2,3-difluoro-5-(1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)pyridine as a clear oil which solidified upon standing at room temperature (3.1 g, 60.5% yield). LC/MS shows the product as the free alcohol. However, the structure of the product is as drawn above. MS m/z = 226.2 $[M+1]^+$. Calc'd for $C_{15}H_{17}F_2N_3O_2$: 309.3



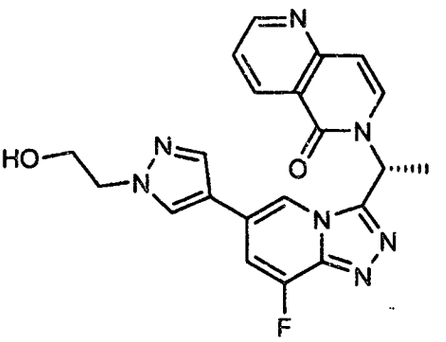
d. **1-(3-fluoro-5-(1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)hydrazine.**

To a solution of 2,3-difluoro-5-(1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)pyridine (3.0 g, 9.5 mmol) in IPA (47.7 mL, 0.2 M) at room temperature was added hydrazine (3.6 mL, 114.4 mmol). The reaction mixture was stirred at 60 °C for 2 h, at which point the reaction was cooled to room temperature and concentrated in vacuo. The concentrated material was suspended in saturated $NaHCO_3$ solution and filtered to obtain product as a white, fluffy solid. The material was re-suspended in water (30 mL), filtered, and driend under high vacuum to obtain 1-(3-fluoro-5-(1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)hydrazine (2.2 g, 72% yield) as an orange solid. MS m/z = 322.2 $[M+1]^+$. Calc'd for $C_{15}H_{20}FN_5O_2$: 321.4.



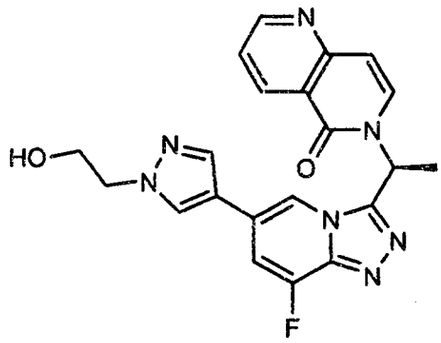
2. **6-(1-(8-fluoro-6-(1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one.**

The THP-protected compound was synthesized according to the General Method N.



3. **(R)-6-(1-(8-fluoro-6-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one.**

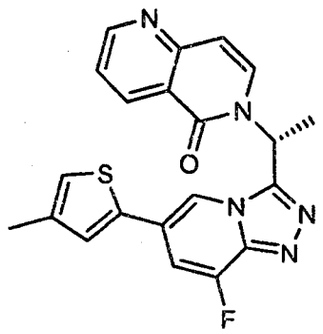
6-(1-(8-fluoro-6-(1-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one (0.5 g, 1.0 mmol) was dissolved in EtOH (12 mL) and to the solution was added hydrochloric acid (2.0 mL, 4.0 mmol). The reaction was stirred at rt for 3 hours at which time it was diluted with 5 mL of water and 10 mL of aq. saturated sodium bicarbonate solution. The product was extracted with DCM (30mL) three times. The organic layers were combined, dried over sodium sulfate and concentrated to dryness to afford 6-(1-(8-fluoro-6-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one (0.4 g, 96%). Chiral separation by preparative SFC (Chiralpak® AD-H (20 x 150 m, 5□m), 35% EtOH, 65% CO2, 0.2 DEA; 100 bar system pressure, 50 mL/min; t_r :4.4 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. M/Z = 420.2 [M+H], calc 419.15 for $C_{21}H_{18}FN_7O_2$. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) □ ppm 2.17 (d, *J*=7.14 Hz, 3 H) 4.00 - 4.09 (m, 2 H) 4.29 - 4.33 (m, 2 H) 6.91 (d, *J*=7.92 Hz, 1 H) 7.04 (dd, 1 H) 7.10 (dd, *J*=10.56, 1.17 Hz, 1 H) 7.51 (dd, *J*=8.17, 4.74 Hz, 1 H) 7.59 (d, *J*=7.82 Hz, 1 H) 7.72 (d, *J*=0.68 Hz, 1 H) 7.76 (d, *J*=0.78 Hz, 1 H) 8.34 (d, *J*=1.17 Hz, 1 H) 8.84 (dd, *J*=8.07, 1.22 Hz, 1 H) 8.92 (dd, *J*=4.74, 1.81 Hz, 1 H)



Example 510

(S)-6-(1-(8-fluoro-6-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

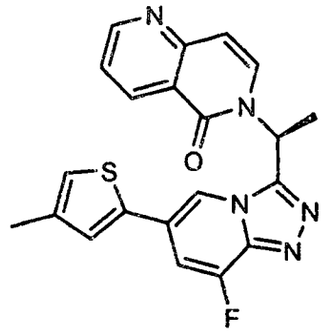
Prepared in the same general manner as that previously described for example 509 using General Method N. Chiral separation by preparative SFC (Chiralpak® AD-H (20 x 150 m, 5□m), 35% EtOH, 65% CO2, 0.2 DEA; 100 bar system pressure, 50 mL/min; t_r :6.0 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. M/Z = 420.2 [M+H], calc 419.15 for $C_{21}H_{18}FN_7O_2$.



Example 511

(R)-6-(1-(8-fluoro-6-(4-methylthiophen-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

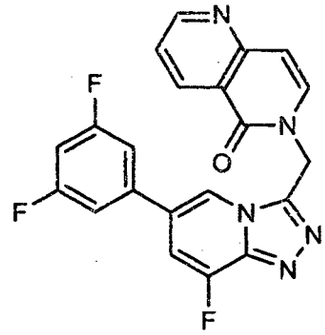
The compound was prepared according to General Method N. The hydrazine was prepared in an analogous fashion to 1-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)hydrazine. Chiral separation by preparative SFC (Chiralpak® AD-H (20 x 250 mm 5m), 40% MeOH 0.2% DEA, 80 mL/min and 100bar system backpressure, retention time = 5.1 minutes. On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the R enantiomer. MS m/z = 406.0 $[M+1]^+$. Calc'd for $C_{21}H_{16}FN_5OS$: 405.5.



Example 512

(S)-6-(1-(8-fluoro-6-(4-methylthiophen-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

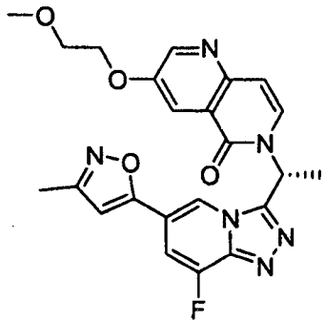
The compound was prepared according to General Method N. The hydrazine was prepared in an analogous fashion to 1-(3-fluoro-5-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)hydrazine. Chiral separation by preparative SFC (Chiralpak® AD-H (20 x 250 mm 5m), 40% MeOH 0.2% DEA, 80 mL/min and 100bar system backpressure, retention time = 6.1 minutes. On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the S enantiomer. MS m/z = 406.0 $[M+1]^+$. Calc'd for $C_{21}H_{16}FN_5OS$: 405.5.



Example 513

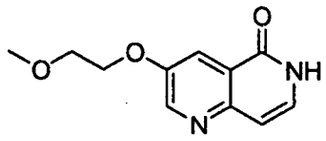
6-((6-(3,5-difluorophenyl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methyl)-1,6-naphthyridin-5(6H)-one

The title compound was synthesized in the same general manner as that previously described for example 503 using 1-(5-(3,5-difluorophenyl)-3-fluoropyridin-2-yl)hydrazine. MS *m/z* = 408.2 [M+H], calc 407.4for $C_{21}H_{12}F3N_5O$.

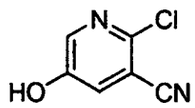


Example 514

(R)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-((2-methoxyethoxy)methyl)-1,6-naphthyridin-5(6H)-one

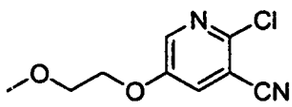


1. **3-(2-methoxyethoxy)-1,6-naphthyridin-5(6H)-one**



a. **2-chloro-5-hydroxynicotinonitrile.**

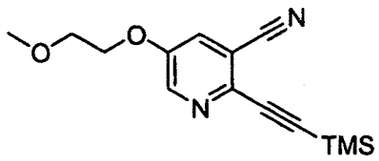
In a 300 mL sealed tube under N_2 were dissolved potassium acetate (20 g, 207 mmol), 5-bromo-2-chloronicotinonitrile (15 g, 69 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (21 g, 83 mmol) and $PdCl_2(dppf)$-CH_2Cl_2 Adduct (1.7 g, 2.1 mmol) in 150 mL of p-dioxane then stirred and heated at 85 °C for 2 hrs. After completion, the reaction was cooled to 0 °C and treated with hydrogen peroxide (31.5%) (22 ml, 207 mmol) then stirred at rt for 1 hr. The reaction mixture was diluted with DCM (100 mL) then water was added (200 mL). The aqueous phase was extracted 3 times with DCM (100 mL), then the organic layer was washed with saturated sodium thiosulfate solution (300 mL). The organics were then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude 2-chloro-5-hydroxynicotinonitrile (7.5 g, 70% yield) was carried through crude to the next step.



b. **2-chloro-5-(2-methoxyethoxy)nicotinonitrile.**

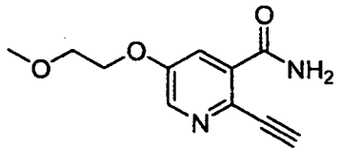
In a 100 mL round bottom flask under N_2 were dissolved triphenylphosphine (19 g, 73 mmol),

2-chloro-5-hydroxynicotinonitrile (7.5 g, 49 mmol), and 2-methoxyethanol (5.7 ml, 73 mmol) in THF (130 mL) followed by a slow addition of DEAD (27 ml, 68 mmol), and then stirred at room temperature. After 2h the reaction showed full conversion to the desired compound. The crude mixture was purified by MPLC eluting with 100% DCM to 90% DCM:10% MeOH to afford 2-chloro-5-(2-methoxyethoxy)nicotinonitrile (6.46 g, 63% yield) as a tan solid.



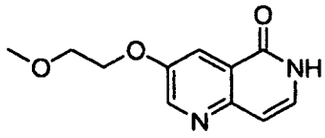
c. **5-(2-methoxyethoxy)-2-(2-(trimethylsilyl)ethynyl)nicotinonitrile.**

In a sealed tube, dichlorobis(triphenyl-phosphine)palladium (ii) (0.17 g, 0.24 mmol), trimethylacetylene (2.0 ml, 14 mmol), 2-chloro-5-(2-methoxyethoxy)nicotinonitrile (2.50 g, 12 mmol), and copper(I) iodide (0.11 g, 0.59 mmol) were dissolved in acetonitrile (0.5 M, 24 mL) and to the reaction was added triethylamine (3.3 ml, 24 mmol). The reaction mixture was heated to 85 °C for 12 hrs. The reaction was concentrated and purified directly via MPLC, eluting with 0-100% EtOAc in hexanes to yield 5-(2-methoxyethoxy)-2-(2-(trimethylsilyl)ethynyl)nicotinonitrile (1.9 g, 59% yield).



d. **2-ethynyl-5-(2-methoxyethoxy)nicotinamide.**

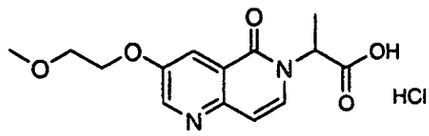
5-(2-methoxyethoxy)-2-(2-(trimethylsilyl)ethynyl)nicotinonitrile (4.23 g, 15 mmol) was dissolved in acetone (60 mL). To the solution was added 3 M sodium carbonate (62 ml, 185 mmol) and hydrogen peroxide (31 ml, 308 mmol) dropwise, and it was stirred at room temperature for 4 h. After completion, the reaction was cooled to 0 °C and to it was slowly added sodium thiosulfate (200 mL) with stirring. The aqueous layer was extracted with DCM (x3, 200 mL), and the combined organics were concentrated and purified via MPLC eluting with 100% DCM to 90% DCM:10% MeOH:1% NH_4OH to yield 2-ethynyl-5-(2-methoxyethoxy)nicotinamide (2.0 g, 59% yield).



e. **3-(2-methoxyethoxy)-1,6-naphthyridin-5(6H)-one.**

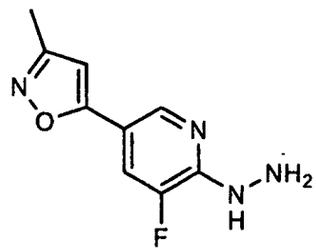
2-ethynyl-5-(2-methoxyethoxy)nicotinamide (2.04 g, 9 mmol) was dissolved in 1M dimethylamine (in methanol or ethanol) (46 ml, 93 mmol). The reaction was heated to 85 °C

for 12 hrs. The reaction was concentrated and purified via MPLC eluting with 100% DCM to 90% DCM:10% MeOH:1% NH_4OH to yield 3-(2-methoxyethoxy)-1,6-naphthyridin-5(6H)-one (0.900 g, 44% yield).

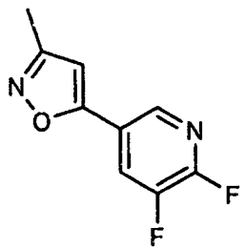


2. **2-(3-(2-methoxyethoxy)-5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride.**

The compound was synthesized from 3-(2-methoxyethoxy)-1,6-naphthyridin-5(6H)-one similar to the synthesis of 2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride in Method N (Example 503).

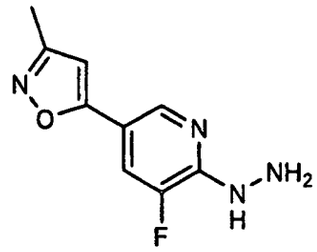


3. **1-(3-fluoro-5-(3-methylisoxazol-5-yl)pyridin-2-yl)hydrazine**



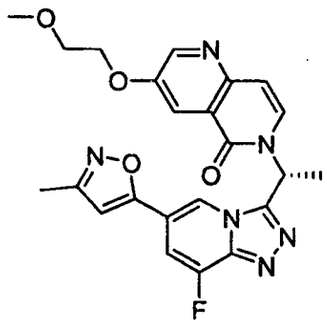
a. **2,3-difluoro-5-(3-methylisoxazol-5-yl)pyridine.**

A 330 mL pressure vessel was charged with 5-chloro-2,3-difluoropyridine (5.00 g, 33.4 mmol), 3-methyl-5-(tributylstannyl)isoxazole (14.9 g, 40.1 mmol), XPhos (2.23 g, 4.68 mmol), $PdOAc_2$ (0.526 g, 2.34 mmol), and 1,4-dioxane (167 ml, 33.4 mmol), flushed with argon, sealed, then heated at 100°C for 16 hours. The mixture was concentrated; the black oil was absorbed onto silica gel and purified by MPLC, eluting with 20% EtOAc in hexanes isocratic to yield an orange solid; this was triturated with hexanes to give 2,3-difluoro-5-(3-methylisoxazol-5-yl)pyridine (3.6278 g, 55.3% yield) as a yellow solid.



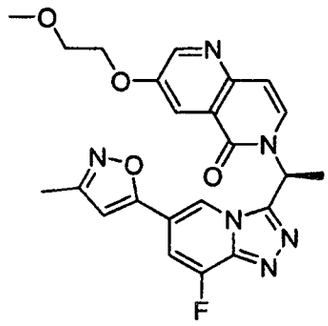
b. 1-(3-fluoro-5-(3-methylisoxazol-5-yl)pyridin-2-yl)hydrazine.

A 330 mL pressure vessel was charged with 4,5-difluoro-2-(3-methylisoxazol-5-yl)pyridine (3.6695 g, 18.7 mmol), hydrazine (3.53 ml, 112 mmol), and IPA (93.5 ml, 18.7 mmol), sealed, then heated at 65°C for 3 hours. The mixture was filtered; the solid was triturated with sat. aqueous $NaHCO_3$ solution and washed with water (2 x 20 mL). 1-(4-fluoro-6-(3-methylisoxazol-5-yl)pyridin-3-yl)hydrazine (3.5668 g, 91.6% yield) was isolated as a white powder.



4. (R)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-((2-methoxyethoxy)methyl)-1,6-naphthyridin-5(6H)-one.

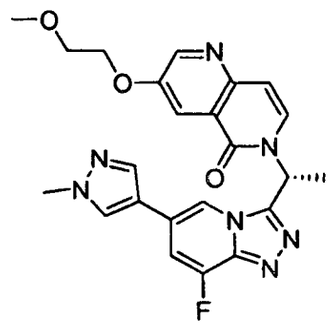
Using 3-(2-methoxyethoxy)-1,6-naphthyridin-5(6H)-one and 1-(3-fluoro-5-(3-methylisoxazol-5-yl)pyridin-2-yl)hydrazine, the title compound was synthesized using General Method N to yield (R)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-((2-methoxyethoxy)methyl)-1,6-naphthyridin-5(6H)-one. Chiral separation by preparative SFC (Chiralpak® AD-H (20 x 150 mm, 5□m), 25% MeOH, 75% CO_2, 0.2% DEA; 100 bar system pressure; 75 mL/min; t_r 5.78 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. M/Z = 465.2 [M+H], calc 464.16 for $C_{23}H_{21}FN_6O_4$. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) □ ppm 2.17 (d, *J*=7.14 Hz, 3 H) 2.39 (s, 3 H) 3.49 (s, 3 H) 3.78 - 3.94 (m, 2 H) 4.23 - 4.43 (m, 2 H) 6.43 (s, 1 H) 6.85 (d, *J*=7.82 Hz, 1 H) 7.08 (q, *J*=7.11 Hz, 1 H) 7.29 (dd, *J*=10.07, 1.17 Hz, 1 H) 7.43 (d, *J*=7.82 Hz, 1 H) 8.17 (d, *J*=2.93 Hz, 1 H) 8.58 - 8.81 (m, 2 H).



Example 515

(S)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-((2-methoxyethoxy)methyl)-1,6-naphthyridin-5(6H)-one

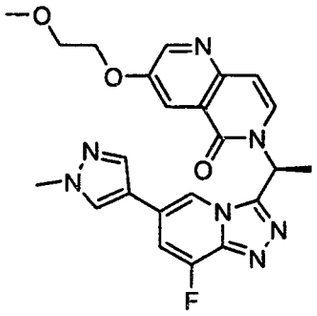
Synthesized in the same general manner as that previously described for example 509 using General Method N. Chiral separation by preparative SFC (Chiralpak® AD-H (20 x 150 mm, 5□m), 25% MeOH, 75% CO_2, 0.2% DEA; 100 bar system pressure; 75 mL/min; t_r 4.75min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. M/Z = 465.2 [M+H], calc 464.16 for $C_{23}H_{21}FN_6O_4$



Example 516

(*R*)-6-(1-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-(2-methoxyethoxy)-1,6-naphthyridin-5(6H)-one

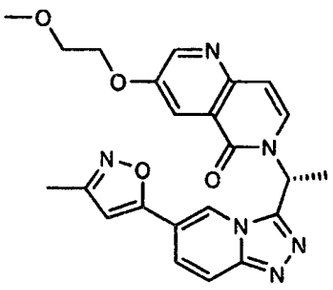
The title compound was synthesized using General Method N. Chiral separation by preparative SFC (Chiralpak® AS-H (20 x 150 mm, 5 □m), 20% iPrOH, 80% CO_2; 100 bar system pressure, 50 mL/min; t_r 1.67 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. M/Z = 464.2 [M+H], calc 463.18 for $C_{23}H_{22}FN_7O_3$. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) □ ppm 2.15 (d, *J*=7.14 Hz, 3 H) 3.49 (s, 3 H) 3.80 - 3.90 (m, 2 H) 3.97 (s, 3 H) 4.27 - 4.39 (m, 2 H) 6.83 (d, *J*=7.73 Hz, 1 H) 7.00 - 7.13 (m, 2 H) 7.42 (d, *J*=7.82 Hz, 1 H) 7.61 (s, 1 H) 7.72 (s, 1 H) 8.15 (d, *J*=2.84 Hz, 1 H) 8.31 (s, 1 H) 8.72 (d, *J*=3.03 Hz, 1 H).



Example 517

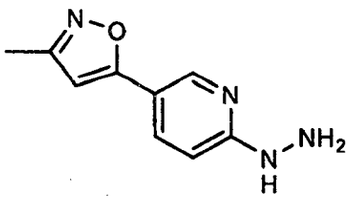
(*S*)-6-(1-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-(2-methoxyethoxy)-1,6-naphthyridin-5(6H)-one

The compound was synthesized in the same general manner as that previously described for example 516 according to General Method N. Chiral separation by preparative SFC (Chiralpak® AS-H (20 x 150 mm, 5 □m), 20% iPrOH, 80% CO_2; 100 bar system pressure, 50 mL/min; t_r : 2.02 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. M/Z = 464.2 [M+H], calc 463.18 for $C_{23}H_{22}FN_7O_3$.

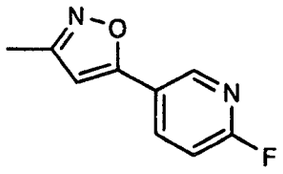


Example 518

(R)-3-(2-methoxyethoxy)-6-(1-(6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

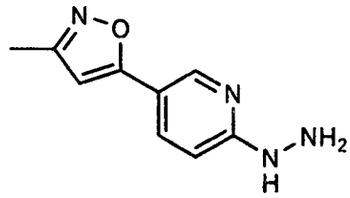


1. 1-(5-(3-methylisoxazol-5-yl)pyridin-2-yl)hydrazine



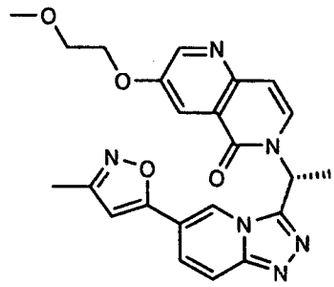
a. 2-fluoro-5-(3-methylisoxazol-5-yl)pyridine.

A 48 mL tube tube was charged with 5-bromo-2-fluoropyridine (1.17 ml, 11.4 mmol), 3-methyl-5-(tributylstannyl)isoxazole (5.29 g, 14.2 mmol), cyclohexyl JohnPhos (0.398 g, 1.14 mmol), Pd_2dba_3 (0.312 g, 0.341 mmol), and DMF (12.4 ml, 159 mmol), flushed with argon, sealed, then heated at 90°C for 16 hours. Additional 3-methyl-5-(tributylstannyl)isoxazole (5.29 g, 14.2 mmol) (2 g), Pd_2dba_3 (0.312 g, 0.341 mmol), and cyclohexyl JohnPhos (0.398 g, 1.14 mmol) were added and the mixture was stirred at 90°C for 10 more hours. This was concentrated and the brown residue was purified by MPLC, eluting with 15% ethyl acetate in hexanes isocratic. 2-fluoro-5-(3-methylisoxazol-5-yl)pyridine (1.1029 g, 54.5% yield) isolated as a light yellow solid.



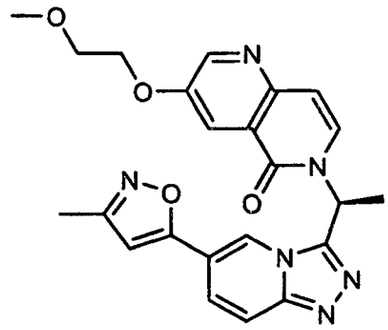
b. <u>1-(5-(3-methylisoxazol-5-yl)pyridin-2-yl)hydrazine.</u>

The hydrazine was synthesized similar to 1-(3-fluoro-5-(3-methylisoxazol-5-yl)pyridin-2-yl)hydrazine (except heated to 60°C) (84.2% yield).



2. <u>(R)-3-(2-methoxyethoxy)-6-(1-(6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one.</u>

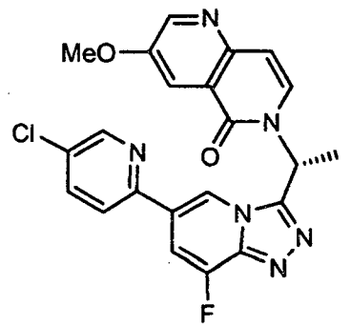
The title compound was synthesized according to General Method N. Chiral separation by preparative SFC (Chiralcel OH-H (2 cm ID x 25 cm length, 5 μ), 35 – 65% MeOH 0.2% DEA in CO_2, 80 mL/min; t_r = 4.95 min). On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. MS m/z = 447.2 $[M+1]^+$. Calc'd for $C_{23}H_{22}N_6O_4$: 446.5. 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.89 (t, 1 H), 8.68 (d, *J*=3.03 Hz, 1 H), 8.01 - 8.02 (m, 1 H), 7.96 (dd, *J*=9.59, 1.08 Hz, 1 H), 7.79 (dd, *J*=9.54, 1.61 Hz, 1 H), 7.60 (d, *J*=7.82 Hz, 1 H), 7.01 - 7.05 (m, 1 H), 6.99 (s, 1 H), 6.75 (d, *J*=7.63 Hz, 1 H), 4.29 - 4.32 (m, 2 H), 3.70 - 3.73 (m, 2 H), 3.32 (s, 3 H), 2.31 (s, 3 H), 1.99 (d, *J*=7.04 Hz, 3 H).



Example 519

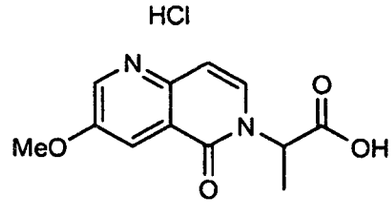
(S)-3-(2-methoxyethoxy)-6-(1-(6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

Compound was synthesized in the same general manner as that previously described for example 518 according to General Method N. Chiral separation by preparative SFC (Chiralcel OH-H (2 cm ID x 25 cm length, 5 μ), 35 – 65% MeOH 0.2% DEA in CO_2, 80 mL/min; t_r = 7.05 min). On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. MS m/z = 447.2 $[M+1]^+$. Calc'd for $C_{23}H_{22}N_6O_4$: 446.5.



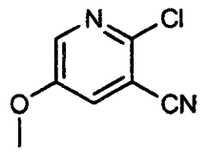
Example 520

***(R)*-6-(1-(6-(5-chloropyridin-2-yl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-methoxy-1,6-naphthyridin-5(6H)-one**



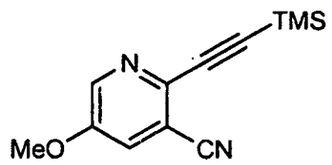
1. 2-(3-methoxy-5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride

All steps for the synthesis of this acid are the same as for 2-(3-(2-methoxyethoxy)-5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride (Example 514). with the following exceptions:



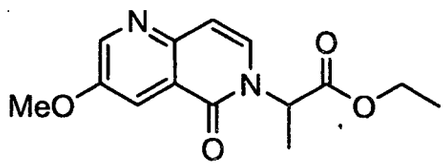
a. 2-chloro-5-methoxynicotinonitrile.

2-chloro-5-hydroxynicotinonitrile (18.0 g, 116 mmol) was placed in a resealable pressure-resistant tube and suspended in DMF (146 ml, 116 mmol). To this was added cesium carbonate (76 g, 233 mmol) and methyl iodide (36 mL, 582 mmol). The vessel was sealed and the mixture stirred at 65 ^{0}C for 17 h. The reaction mixture was diluted with water (250 mL) and the product was extracted with DCM (3 X400mL). The organic layers were combined, dried over sodium sulfate and concentrated to afford 40g of brown thick oil. This was passed through a plug of silica to afford 13g of 85% pure material. This was triturated in 10%DCM/Hexanes (hot ~ 40^{0}C) and solids filtered, rinsed with hexanes and dried to afford 2-chloro-5-methoxynicotinonitrile as brown solid (10.0 g, 51%). MS m/z = 169[M+1]$^+$. Calc'd for $C_7H_5ClN_2O$: 168.6.



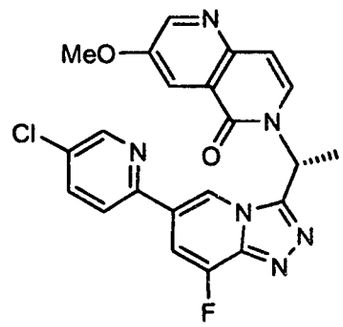
b. 5-methoxy-2-(2-(trimethylsilyl)ethynyl)nicotinonitrile.

This step was run at 65°C instead of 85°C.



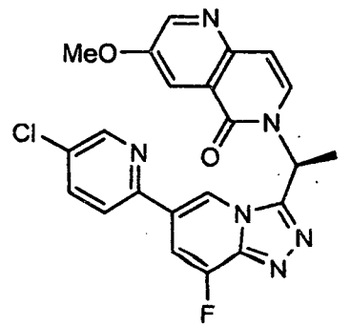
c. ethyl 2-(3-methoxy-5-oxo-1,6-naphthyridin-6(5H)-yl)propanoate.

Ethyl 2-bromopropanoate was used instead of the iodide and the reaction temperature was also lower (60^{0}C).



2. **(R)-6-(1-(6-(5-chloropyridin-2-yl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-methoxy-1,6-naphthyridin-5(6H)-one.**

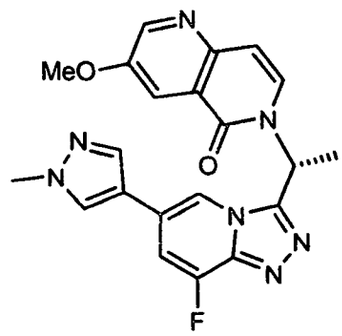
The title compound was synthesized according to General Method N. Chiral separation by preparative SFC (ChiralCel® OD-H (20 x 250 mm 5m), 35% MeOH 0.2% DEA, 70 mL/min and 100bar system backpressure (t_r: 6.3 mins). On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. MS m/z = 450.8 $[M+1]^+$. Calc'd for $C_{22}H_{16}ClFN_6O_2$: 450.8.



Example 521

(S)-6-(1-(6-(5-chloropyridin-2-yl)-8-fluoro-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-methoxy-1,6-naphthyridin-5(6H)-one

Prepared according to General Method N. Chiral separation by preparative SFC (ChiralCel® OD-H (20 x 250 mm 5m), 35% MeOH 0.2% DEA, 70 mL/min and 100bar system backpressure (t_r: 8.0 mins). On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. m/z = 450.8 $[M+1]^+$. Calc'd for $C_{22}H_{16}ClFN_6O_2$: 450.8.

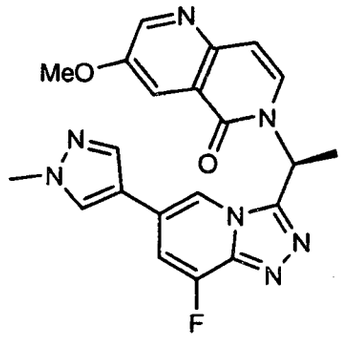


Example 522

***(R)*-6-(1-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-methoxy-1,6-naphthyridin-5(6H)-one**

Prepared according to General Method N. Chiral separation by preparative SFC (ChiralCel® OD-H (20 x 250 mm 5m), 40% EtOH 0.2% DEA, 70 mL/min and 100bar system backpressure

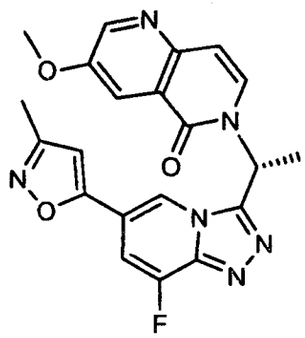
(t_r: 5.2 mins). On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. MS m/z = 419.8 $[M+1]^+$. Calc'd for $C_{21}H_{18}FN_7O_2$: 419.4.



Example 523

(*S*)-6-(1-(8-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-methoxy-1,6-naphthyridin-5(6H)-one

Prepared according to General Method N. Chiral separation by preparative SFC (ChiralCel® OD-H (20 x 250 mm 5m), 40% EtOH 0.2% DEA, 70 mL/min and 100bar system backpressure (t_r: 6.8 mins). On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. MS m/z = 419.8 $[M+1]^+$. Calc'd for $C_{21}H_{18}FN_7O_2$: 419.4.

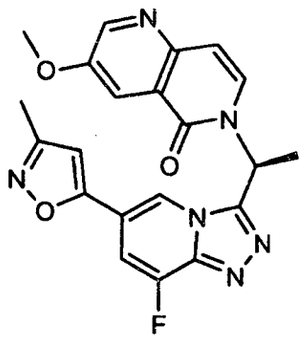


Example 524

(*R*)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-methoxy-1,6-naphthyridin-5(6H)-one

Prepared according to General Method N. Chiral separation by preparative SFC (ChiralPak® AD-H (20 x 250 mm 5m), 40% MeOH 0.2% DEA, 70 mL/min and 100bar system backpressure (t_r: 4.7 mins). On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. MS m/z = 420.8 $[M+1]^+$. Calc'd for $C_{21}H_{17}FN_6O_3$: 420.4. 1H NMR (400 MHz, DMSO-d_6) □ ppm 2.00 (d, *J*=7.04 Hz, 3 H) 2.31 (s, 3 H) 3.94 (s, 3 H)

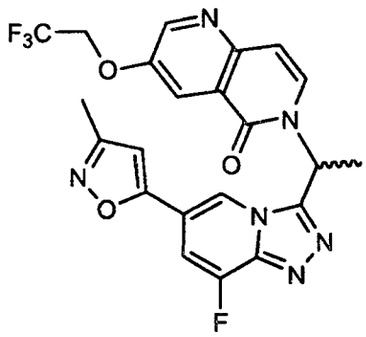
6.77 (dd, *J*=7.78, 0.54 Hz, 1 H) 6.94 - 7.05 (m, 2 H) 7.64 (d, *J*=7.82 Hz, 1 H) 7.76 - 7.89 (m, 1 H) 7.98 (dd, *J*=3.08, 0.54 Hz, 1 H) 8.68 (d, *J*=3.03 Hz, 1 H) 8.80 (d, *J*=1.08 Hz, 1 H).



Example 525

(*S*)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-methoxy-1,6-naphthyridin-5(6H)-one

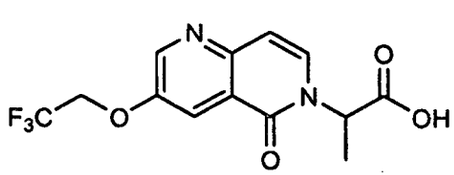
Prepared according to General Method N. Chiral separation by preparative SFC (ChiralPak® AD-H (20 x 250 mm 5m), 40% MeOH 0.2% DEA, 70 mL/min and 100bar system backpressure (t_r: 3.9 mins). On the basis of previous crystallographic data and potency recorded for related compounds in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. MS m/z = 420.8 $[M+1]^+$. Calc'd for $C_{21}H_{17}FN_6O_3$: 420.4.



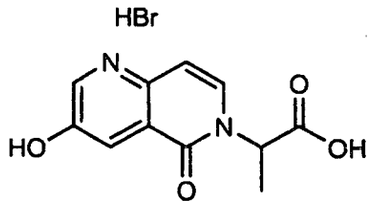
Example 526

6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-5(6H)-one

HCl

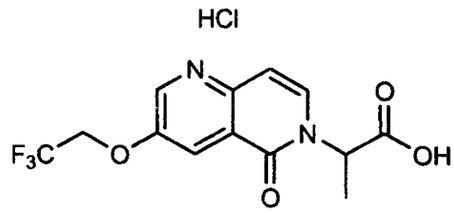


1. **2-(5-oxo-3-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride**



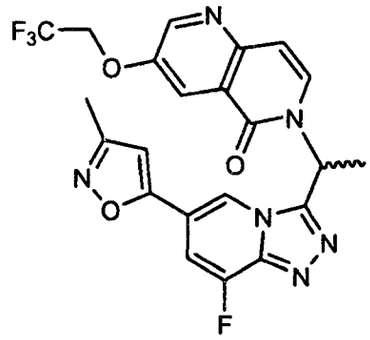
a. **2-(3-hydroxy-5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrobromide.**

A resealable pressure-resistant bottle was charged with ethyl 2-(3-methoxy-5-oxo-1,6-naphthyridin-6(5H)-yl)propanoate (0.83 g, 3.0 mmol) (Example 515) and conc. HBr (0.16 ml, 3.0 mmol). The vessel was sealed and the mixture was stirred at 130^{0}C for 20 hours. The reaction mixture was then concentrated to afford 2-(3-hydroxy-5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrobromide (0.95 g, 100% yield) as brown solid. This was carried through crude in the next step. Free base material MS m/z = 235.0 $[M+1]^+$. Calc'd for $C_{11}H_{11}BrN_2O_4$: 315.1.



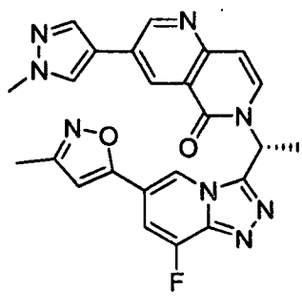
b. **2-(5-oxo-3-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride.**

A resealable pressurized vial was charged with 2-(3-hydroxy-5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrobromide (0.54 g, 2 mmol), cesium carbonate (2 g, 7 mmol), 2,2,2-trifluoroethyl trifluoromethanesulfonate (2 g, 7 mmol), and N,N-dimethylformamide (6 mL, 0.3M). The vessel was sealed and the mixture was stirred at 60^{0}C fo 1 hr. The reaction mixture was diluted with EtOAc and washed with water. The organic layer was collected, dried over sodium sulfate, and concentrated under reduced pressure to afford brown oil. This was purified via MPLC (10-50% EtOAC/Hexanes) to afford tan solid of bis alkylated material. This was suspended and refluxed in 5 mL of 6N HCl for 2 hours. Reaction mixture concentrated and dried under reduced pressure to afford 2-(5-oxo-3-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride (0.3 g, 50% yield). This was concentrated under reduced pressure to dryness to afford 2-(5-oxo-3-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride (0.3 g, 50% yield) as yellow solid. Free base material MS m/z = 317.0 $[M+1]^+$. Calc'd for $C_{13}H_{12}ClF_3N_2O_4$: 352.7.



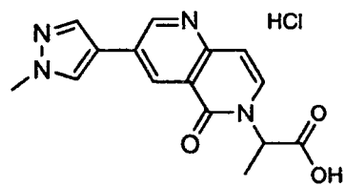
2. **6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-(2,2,2-trifluoroethoxy)-1,6-naphthyridin-5(6H)-one.**

Prepared according to General Method N. MS m/z = 488.8 $[M+1]^+$. Calc'd for $C_{22}H_{16}F_4N_6O_3$: 488.4. 1H NMR (400 MHz, DMSO-d_6) □ ppm 2.01 (d, *J*=7.04 Hz, 3 H) 2.25 - 2.38 (m, 3 H) 5.05 (q, *J*=8.77 Hz, 2 H) 6.74 - 6.83 (m, 1 H) 6.96 - 7.07 (m, 2 H) 7.71 (d, *J*=7.82 Hz, 1 H) 7.86 (dd, *J*=11.49, 1.12 Hz, 1 H) 8.20 (d, *J*=2.74 Hz, 1 H) 8.78 (d, *J*=3.03 Hz, 1 H) 8.83 (d, *J*=1.08 Hz, 1 H)



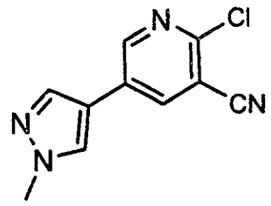
Example 527

6-((R)-1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-(1-methyl-1H-pyrazol-4-yl)-1,6-naphthyridin-5(6H)-one



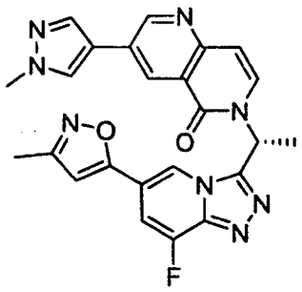
1. **2-(3-(1-methyl-1H-pyrazol-4-yl)-5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride**

All steps for the synthesis of this acid are the same as for 2-(3-(2-methoxyethoxy)-5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride (Example 514) with the following exception:



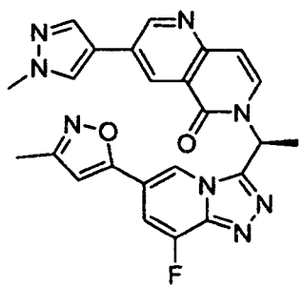
a. **2-chloro-5-(1-methyl-1H-pyrazol-4-yl)nicotinonitrile.**

A 48 mL tube was charged with 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (8.42 g, 40.5 mmol), 5-bromo-2-chloronicotinonitrile (8.00 g, 36.8 mmol), potassium carbonate (15.3 g, 110 mmol), $PdCl_2(dppf)$ (2.69 g, 3.68 mmol), 1,4-dioxane (135 mL, 1582 mmol) and water (23.9 mL, 1324 mmol), flushed with argon, sealed and then heated to 60^0C for 8 h. The reaction mixture was concentrated, adsorbed onto silica gel, and purified via MPLC eluting with 3% MeOH in DCM. 2-chloro-5-(1-methyl-1H-pyrazol-4-yl)nicotinonitrile (4.962 g, 61.7%) was obtained (with a small impurity). The material was taken forward crude.



2. **6-((R)-1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-(1-methyl-1H-pyrazol-4-yl)-1,6-naphthyridin-5(6H)-one.**

Synthesized using General Method N. Chiral separation by preparative SFC (Chiralpak® OJ-H 5 □m (20 x 250 mm, 5 □m), 45% MeOH, 55%, CO_2, 0.2% DEA, 70 mL/min; 120 bar system pressure; t_r : 8.3 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. M/Z = 471.2 [M+H], calc 470.16 for $C_{24}H_{19}FN_8O_2$. ^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 2.01 (d, *J*=7.04 Hz, 3 H) 2.31 (s, 3 H) 3.89 (s, 3 H) 6.78 (d, *J*=8.41 Hz, 1 H) 6.95 - 7.09 (m, 2 H) 7.72 (d, *J*=7.82 Hz, 1 H) 7.85 (d, *J*=12.62 Hz, 1 H) 8.12 (s, 1 H) 8.46 (s, 1 H) 8.67 (dd, *J*=2.35, 0.68 Hz, 1 H) 8.83 (d, *J*=1.08 Hz, 1 H) 9.20 (d, *J*=2.45 Hz, 1 H).

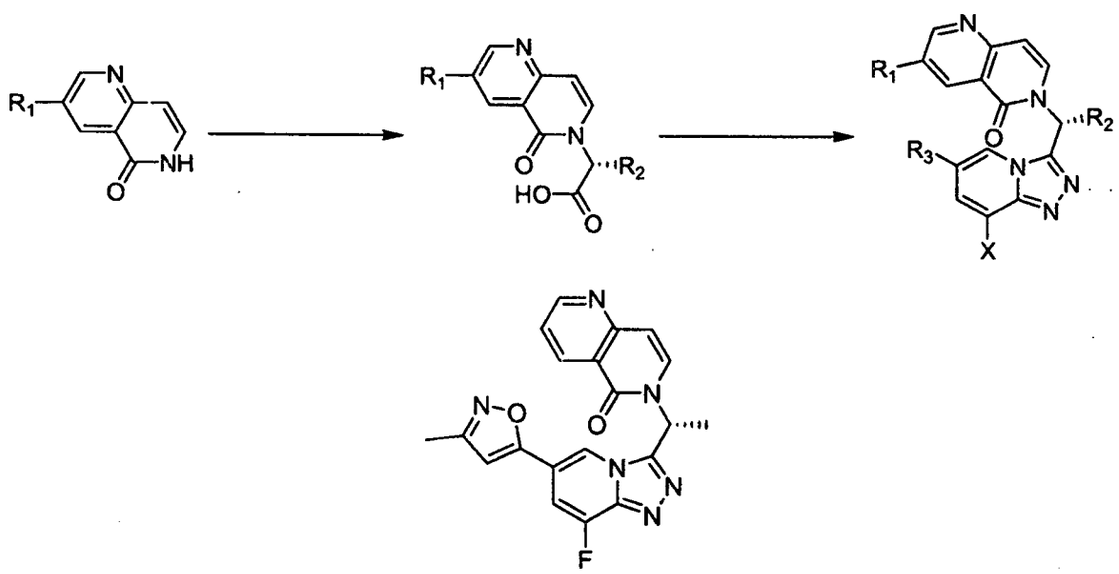


Example 528

6-((*S*)-1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-3-(1-methyl-1H-pyrazol-4-yl)-1,6-naphthyridin-5(6H)-one

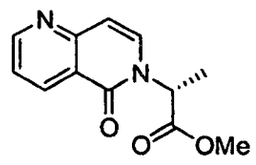
Prepared in the same general manner as that previously described for example 527 according to General Method N. Chiral separation by preparative SFC (Chiralpak® OJ-H 5 □m (20 x 250 mm, 5 □m), 45% MeOH, 55%, CO_2, 0.2% DEA, 70 mL/min; 120 bar system pressure; t_r : 7.2 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. M/Z = 471.2 [M+H], calc 470.16 for $C_{24}H_{19}FN_8O_2$.

General Method O.



Example 529

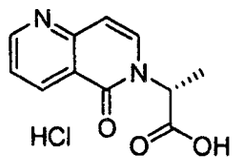
(R)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one



1. **(R)-methyl 2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoate.**

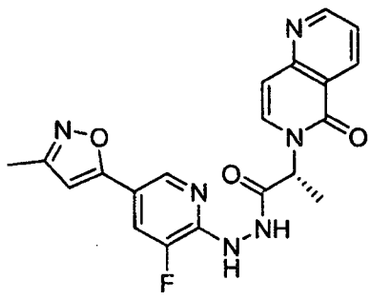
Dissolved 1,6-naphthyridin-5(6H)-one (10.6 g, 73 mmol), (S)-methyl 2-hydroxypropanoate (8.6 ml, 91 mmol) and triphenylphosphine (30 g, 116 mmol) in 144 mL THF (0.5M) and cooled to 0 °C. Then added DEAD (17 ml, 109 mmol) dropwise, monitoring temperature so as not to exceed 5 °C. Then let warm to room temperature over 1 hr, where reaction was complete by LCMS. The reaction was concentrated on silica and purified via MPLC, first with a gradient of Hexanes:EtOAc (removes most of PPh_3O); then gradient of 100% DCM to 90%

DCM:10% MeOH:1% NH_4OH to yield (R)-methyl 2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoate (16 g, 95% yield) where the ee was confirmed to be >95%.



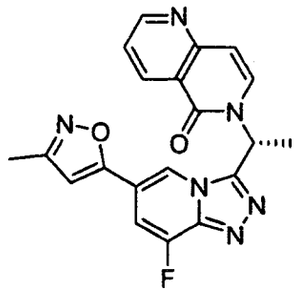
2. (R)-2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride.

Dissolved (R)-methyl 2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoate (3.20 g, 14 mmol) in 70 mL of THF and added 6 M HCl (23 ml, 138 mmol) and heated to 80 °C for 3 hrs until reaction was complete by LCMS. Reaction concentrated to remove water, and azeotroped 3 times with benzene to remove excess water, to yield (R)-2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride (3.4 g, 95% yield) which was >95% ee according to HPLC (conditions: 25/75 EtOH-TFA (0.1%):Heptane, ChiralPak AD-H, 1.0 mL/min, 20 min, 4.6X150 mm column). Obtained (R)-2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride as a yellow solid, which was taken on crude to the next step.



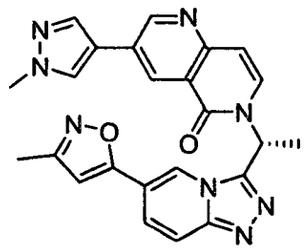
3. (2R)-N'-(3-fluoro-5-(3-methylisoxazol-5-yl)pyridin-2-yl)-2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanehydrazide.

HATU (9.0 g, 24 mmol), (R)-2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanoic acid hydrochloride and 1-(3-fluoro-5-(3-methylisoxazol-5-yl)pyridin-2-yl)hydrazine (3.6 g, 17 mmol) were taken up in acetonitrile (52 ml, 0.3 M) and cooled to 0 °C. DIPEA (8.2 ml, 47 mmol) was added dropwise and the reaction was allowed to stir to room temperature for 30 minutes until complete by LCMS. The crude material was concentrated onto silica gel and then purified via MPLC eluting with 100% DCM to 90% DCM:10% MeOH:1% NH_4OH to yield (2R)-N'-(3-fluoro-5-(3-methylisoxazol-5-yl)pyridin-2-yl)-2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanehydrazide (4.927 g, 77% yield).



4. **(R)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one.**

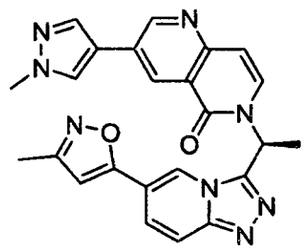
(2R)-N'-(3-fluoro-5-(3-methylisoxazol-5-yl)pyridin-2-yl)-2-(5-oxo-1,6-naphthyridin-6(5H)-yl)propanehydrazide (1.9 g, 4.7 mmol) and triphenylphosphine (1.8 g, 7.0 mmol) were taken up in THF (47 ml, 4.7 mmol). TMS-azide (0.93 ml, 7.0 mmol) was added, followed by slow addition of DEAD (1.1 ml, 7.0 mmol) and the reaction was stirred at room temperature for 50 minutes (monitored temperature so as not too exceed 30-40 °C) until reaction was complete. The reaction mixture was concentrated down, removing approximately ½ volume of THF. The material was then redissolved in EtOAc (~100 mL), and 2 M HCl (~30 mL) was added. The mixture was shaken vigorously, and the aqueous layer (with product) was set aside. The EtOAc layer was extracted x2 with HCl (30 mL) and all of the aqueous layers were combined. The aqueous layer was cooled to 0 °C, and to it was added 6 M NaOH dropwise until pH was 7-8 (desired product crashed out as an off-white solid). The solid was filtered over vacuum to remove desired product from water. The solid was then dissolved through the frit into a new flask with DCM/MeOH, and dried over $NaSO_4$ (to further dry). The product was then recrystallized from EtOH with heat, sonication and then cooling or scratching to promote rapid crystallization. (R)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one (1.5 g, 60-80% yield) was isolated as a white solid with >95% ee by HPLC (conditions: 50/50 EtOH:Heptane, ChiralPak® AD-H, 1.0 mL/min, 20 min, 4.6X150 mm column, tr 6.61 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. M/Z = 391.2 [M+H], calc 390.12 for $C_{20}H_{15}FN_6O_2$. ^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 2.00 (d, *J*=7.04 Hz, 3 H) 2.31 (s, 3 H) 6.78 (d, *J*=7.92 Hz, 1 H) 6.95 - 7.12 (m, 2 H) 7.54 (dd, *J*=8.22, 4.50 Hz, 1 H) 7.77 (d, *J*=7.73 Hz, 1 H) 7.85 (d, *J*=11.54 Hz, 1 H) 8.62 (d, *J*=9.59 Hz, 1 H) 8.82 (s, 1 H) 8.92 (dd, *J*=4.55, 1.71 Hz, 1 H).



Example 530

3-(1-methyl-1H-pyrazol-4-yl)-6-((R)-1-(6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

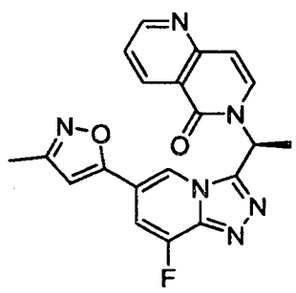
Prepared in the same general manner as that previously described for example 527 according to General Method N. Chiral separation by preparative SFC (ChiralCel OD-H (20 x 250 mm 5□), 35:65:0.2 MeOH:CO_2:DEA, 80 mL/min and 100 bar system backpressure (t_r: 12 mins).. On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. M/Z = 453.0 [M+H], calc 452.5 for $C_{24}H_{20}N_8O_2$.



Example 531

3-(1-methyl-1H-pyrazol-4-yl)-6-((S)-1-(6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

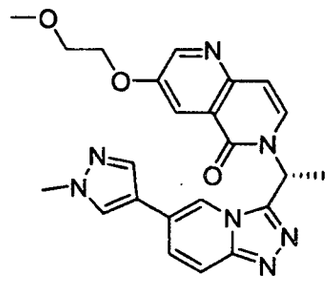
Prepared in the same general manner as that previously described for example 527 according to General Method N. Chiral separation by preparative SFC (ChiralCel OD-H (20 x 250 mm 5□), 35:65:0.2 MeOH:CO_2:DEA, 80 mL/min and 100 bar system backpressure (t_r: 18 mins).. On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. M/Z = 453.0 [M+H], calc 452.5 for $C_{24}H_{20}N_8O_2$.



Example 532

(S)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

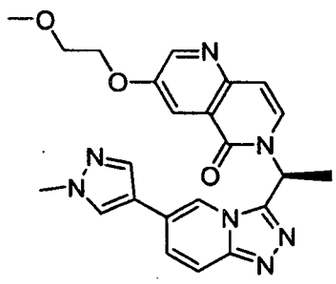
Synthesized according to General Method N. Seperated by preperative HPLC (ChiralPak® IA, (50 x 250 mm, 5 □m), 50% Heptane, 50% EtOH; 100 mL/min; t_r : 14.0 min) to yield (S)-6-(1-(8-fluoro-6-(3-methylisoxazol-5-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one. On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. M/Z = 391.2 [M+H], calc 390.12 for $C_{20}H_{15}FN_6O_2$.



Example 533

(R)-3-(2-methoxyethoxy)-6-(1-(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

Synthesized using General Method N. Chiral separation by preparative SFC (Chiralpak® OD-H (20 x 250 mm, 5 □m), 30% MeOH, 70%, CO_2, 0.2% DEA, 70 mL/min; 100 bar system pressure; t_r : 6.8 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *R* enantiomer. M/Z = 446.2 [M+H], calc 445.19 for $C_{23}H_{23}N_7O_3$.



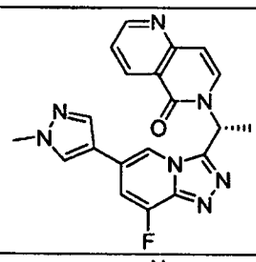
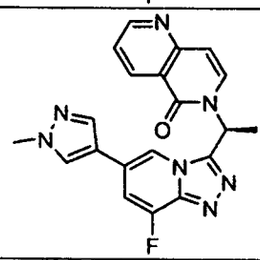
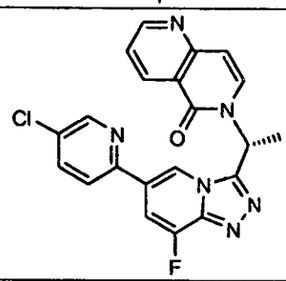
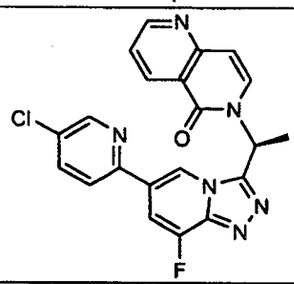
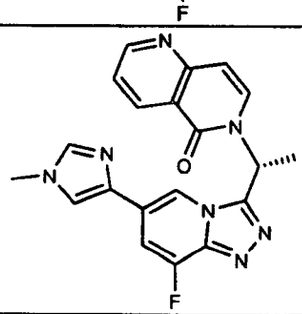
Example 534

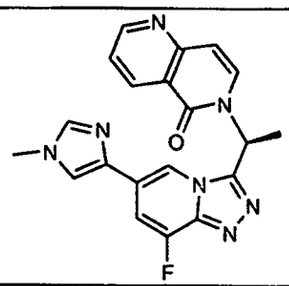
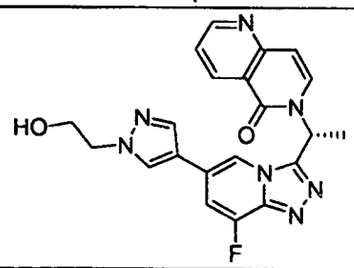
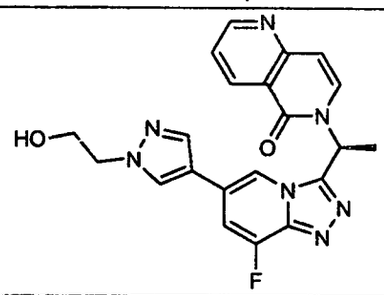
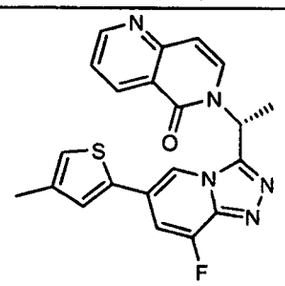
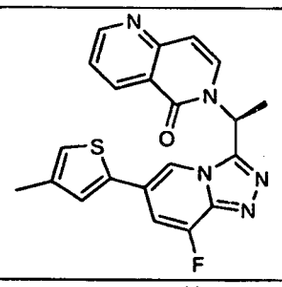
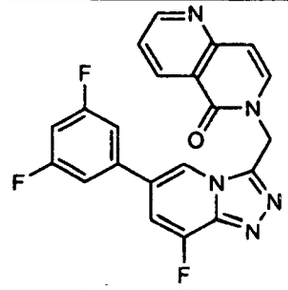
(S)-3-(2-methoxyethoxy)-6-(1-(6-(1-methyl-1H-pyrazol-4-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)ethyl)-1,6-naphthyridin-5(6H)-one

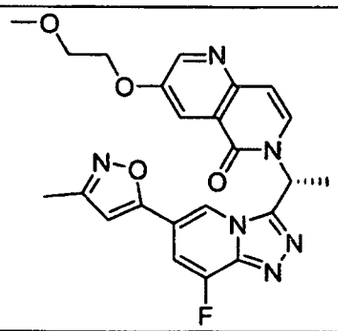
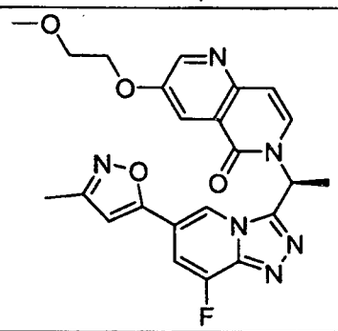
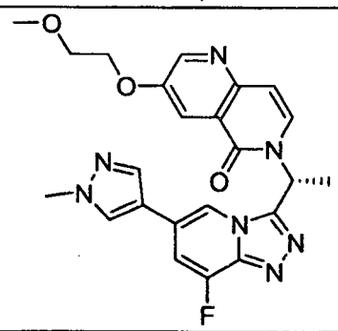
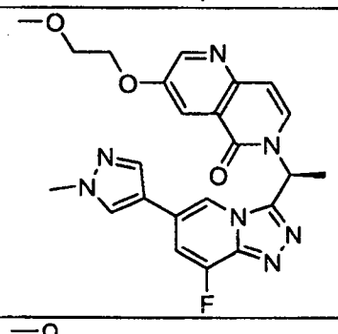
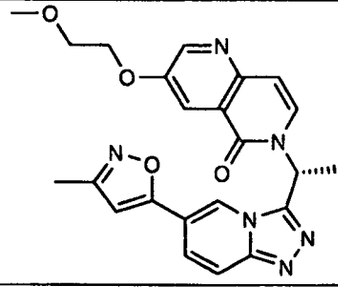
Prepared in the same general manner as that previously described for example 533 according to General Method N. Chiral separation by preparative SFC (Chiralpak® OD-H (20 x 250 mm, 5

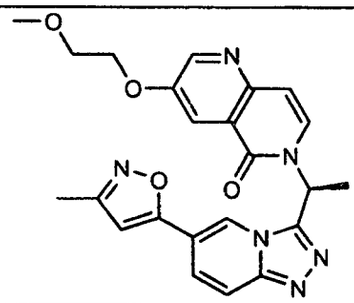
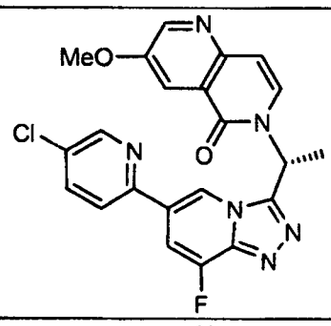
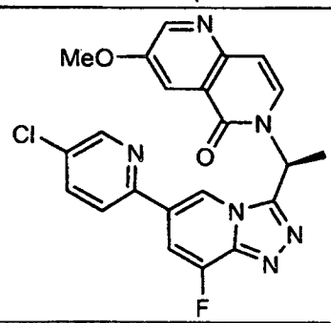
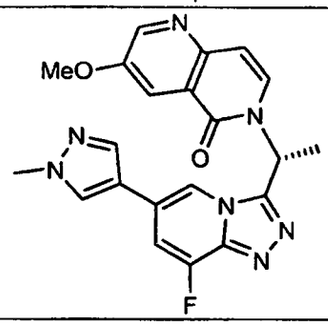
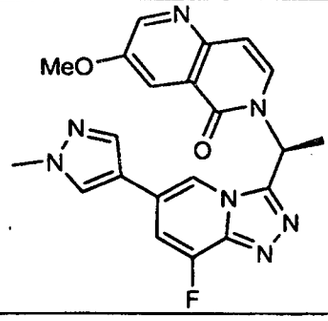
□m), 30% MeOH, 70%, CO_2, 0.2% DEA, 70 mL/min; 100 bar system pressure; t_r : 9.9 min). On the basis of previous crystallographic data and potency recorded for related compound in the same program, the absolute stereochemistry has been assigned to be the *S* enantiomer. M/Z = 446.2 [M+H], calc 445.19 for $C_{23}H_{23}N_7O_3$.

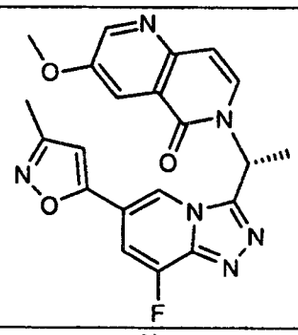
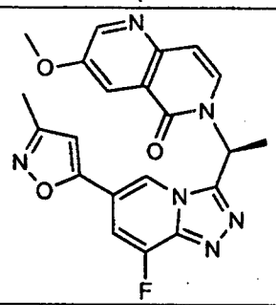
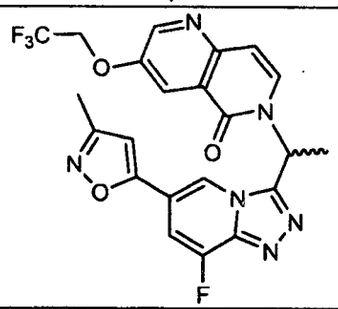
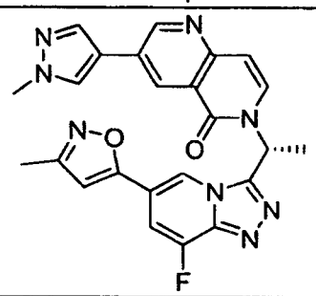
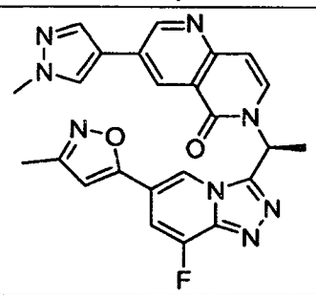
5

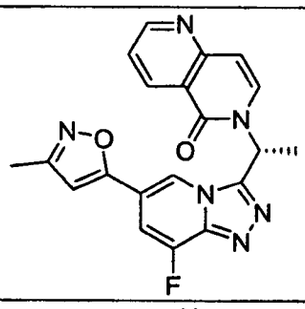
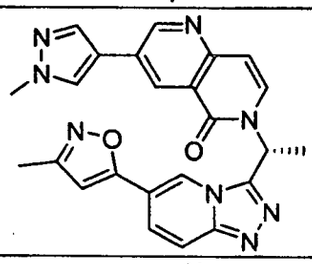
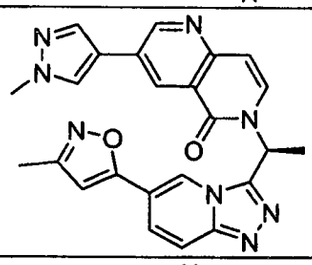
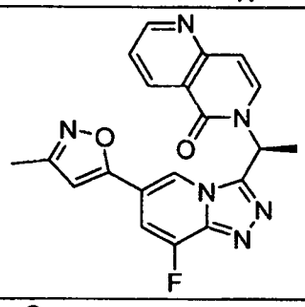
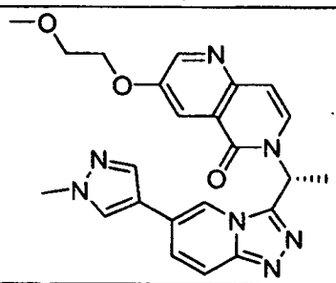
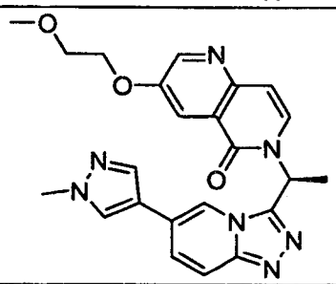
Ex	Structure	MW	Mass Found	General Method
503		389.4	390.2	N
504		389.4	390.2	N
505		420.8	420.8	N
506		420.8	420.8	N
507		389.4	389.8	N

Ex	Structure	MW	Mass Found	General Method
508		389.4	389.8	N
509		419.4	420.2	N
510		419.4	420.2	N
511		405.5	406.0	N
512		405.5	406.0	N
513		407.4	408.2	N

Ex	Structure	MW	Mass Found	General Method
514		464.5	465.2	N
515		464.5	465.2	N
516		463.2	464.2	N
517		463.2	464.2	N
518		446.5	447.2	N

Ex	Structure	MW	Mass Found	General Method
519		446.5	447.2	N
520		450.8	450.8	N
521		450.8	450.8	N
522		419.4	419.8	N
523		419.4	419.8	N

Ex	Structure	MW	Mass Found	General Method
524		420.4	420.8	N
525		420.4	420.8	N
526		488.4	488.8	N
527		470.2	471.2	N
528		470.2	471.2	N

Ex	Structure	MW	Mass Found	General Method
529		390.1	391.2	O
530		452.5	453.0	N
531		452.5	453.0	N
532		390.1	391.2	N
533		445.2	446.2	N
534		445.2	446.2	N

Example	1H NMR Data
348	1H NMR (400 MHz, DMSO-d_6) δ ppm 8.70 (d, *J*=2.74 Hz, 1 H), 8.53 (s, 1 H), 8.50 (d, *J*=5.28 Hz, 1 H), 8.35 (d, *J*=9.68 Hz, 1 H), 8.21 (d, *J*=0.78 Hz, 1 H), 8.17 (s, 1 H), 7.94 (d, *J*=2.64 Hz, 1 H), 7.69 - 7.73 (m, 1 H), 6.94 (d, *J*=5.38 Hz, 1 H), 5.15 (d, *J*=6.16 Hz, 2 H), 3.94 (s, 3 H)
351	1H NMR (400 MHz, CHLOROFORM-*d*) d ppm 8.66 (d, *J*=1.56 Hz, 1 H), 8.08 (d, *J*=8.51 Hz, 1 H), 7.83 - 7.93 (m, 2 H), 7.61 (s, 1 H), 7.53 (d, *J*=8.61 Hz, 1 H), 7.42 (d, *J*=9.78 Hz, 1 H), 7.33 (s, 1 H), 6.80 - 6.95 (m, 3 H), 4.78 (s, 2 H), 3.93 (s, 3 H).
352	1H NMR (400 MHz, CHLOROFORM-*d*) d ppm 8.67 (d, *J*=2.84 Hz, 1 H), 8.15 (d, *J*=8.51 Hz, 1 H), 7.94 - 7.99 (m, 1 H), 7.86 (dd, *J*=9.59 Hz, 1 H), 7.62 (s, 1 H), 7.56 (dd, *J*=8.61 Hz, 1 H), 7.34 - 7.43 (m, 2 H), 7.07 (s, 1 H), 4.77 (s, 2 H), 3.95 (s, 3 H), 2.51 (s, 3 H).
355	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 (s, 3 H) 5.19 (d, *J*=6.26 Hz, 2 H) 6.95 (d, *J*=5.38 Hz, 1 H) 7.71 (dd, *J*=8.51, 4.11 Hz, 1 H) 7.94 (d, *J*=9.78 Hz, 1 H) 8.04 (t, *J*=6.21 Hz, 1 H) 8.09 (s, 1 H) 8.21 (dd, *J*=8.51, 1.56 Hz, 1 H) 8.50 (d, *J*=5.28 Hz, 1 H) 8.54 (d, *J*=9.78 Hz, 1 H) 8.79 (dd, *J*=4.11, 1.56 Hz, 1 H).
359	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.51 (s, 3 H) 5.19 (d, *J*=6.06 Hz, 2 H) 6.96 (d, *J*=5.48 Hz, 1 H) 7.94 (d, *J*=9.68 Hz, 1 H) 8.05 (dd, *J*=10.03, 2.49 Hz, 1 H) 8.09 (s, 1 H) 8.22 (s, 1 H) 8.48 - 8.59 (m, 2 H) 8.85 (d, *J*=2.64 Hz, 1 H)
364	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.51 (s, 3 H) 5.17 (d, *J*=6.16 Hz, 2 H) 6.94 (d, *J*=5.38 Hz, 1 H) 7.53 (t, *J*=73.21 Hz, 1 H) 7.89 - 7.99 (m, 2 H) 8.09 (s, 1 H) 8.12 (t, *J*=6.26 Hz, 1 H) 8.51 (d, *J*=5.28 Hz, 1 H) 8.54 (d, *J*=9.68 Hz, 1 H) 8.70 (d, *J*=2.74 Hz, 1 H).
365	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 (s, 3 H) 3.33 (s, 3 H) 3.71 - 3.76 (m, 2 H) 4.27 - 4.31 (m, 2 H) 5.14 (d, *J*=6.16 Hz, 2 H) 6.82 (d, *J*=5.38 Hz, 1 H) 7.59 (d, *J*=2.74 Hz, 1 H) 7.94 (d, *J*=9.78 Hz, 2 H) 8.09 (s, 1 H) 8.41 (d, *J*=5.28 Hz, 1 H) 8.49 - 8.57 (m, 2 H)
370	1H NMR (400 MHz, MeOH) δ ppm 3.44 (s, 3 H) 3.82 - 3.87 (m, 2 H) 4.29 - 4.34 (m, 2 H) 5.40 (s, 2 H) 7.02 (d, *J*=5.97 Hz, 1 H) 7.19 - 7.27 (m, 1 H) 7.51 (d, *J*=2.64 Hz, 1 H) 7.75 - 7.86 (m, 2 H) 7.95 (d, *J*=9.88 Hz, 1 H) 8.33 (d, *J*=9.88 Hz, 1 H) 8.39 (d, *J*=6.26 Hz, 1 H) 8.59 (s, 1 H)
371	1H NMR (400 MHz, DMSO-d_6) δ ppm 5.02 (q, *J*=8.80 Hz, 2 H) 5.22 (d, *J*=6.26 Hz, 2 H) 6.91 (d, *J*=5.48 Hz, 1 H) 7.53 (t, *J*=9.15 Hz, 1 H) 7.79 (d, *J*=2.64 Hz, 1 H) 7.99 - 8.10 (m, 3 H) 8.21 (t, *J*=5.97 Hz, 1 H) 8.44 (d, *J*=5.28 Hz, 1 H) 8.51 (d, *J*=9.78 Hz, 1 H) 8.61 (d, *J*=2.64 Hz, 1 H)
372	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.52 (s, 3 H) 5.02 (q, *J*=8.90 Hz, 2 H) 5.15 (d, *J*=6.16 Hz, 2 H) 6.87 (d, *J*=5.38 Hz, 1 H) 7.80 (d, *J*=2.84 Hz, 1 H) 7.94 (d, *J*=9.78 Hz, 1 H) 8.01 (t, *J*=6.11 Hz, 1 H) 8.09 (s, 1 H) 8.45 (d, *J*=5.28 Hz, 1 H) 8.54 (d, *J*=9.78 Hz, 1 H) 8.62 (d, *J*=2.84 Hz, 1 H).

Example	1H NMR Data
383	1H NMR (400 MHz, DMSO-d_6) δ ppm 3.94 (s, 3 H) 4.50 - 4.62 (m, 2 H) 5.14 (d, *J*=6.16 Hz, 2 H) 6.30 - 6.64 (m, 1 H) 6.87 (d, *J*=5.48 Hz, 1 H) 7.66 - 7.74 (m, 2 H) 8.06 (t, *J*=6.11 Hz, 1 H) 8.21 (d, *J*=0.68 Hz, 1 H) 8.34 (d, *J*=9.68 Hz, 1 H) 8.44 (d, *J*=5.38 Hz, 1 H) 8.52 (s, 1 H) 8.59 (d, *J*=2.84 Hz, 1 H).
390	(400 MHz, DMSO-*d6)* δ ppm 8.64 (s, 1H), 8.51 (d, J = 2.8 Hz, 1H), 8.40 (d, J = 5.2 Hz, 1H), 8.35 (d, J = 9.6 Hz, 1Hz), 8.19 (s, 1H), 7.99 (t, J = 6.0 Hz, 1H), 7.72 (d, J = 10 Hz, 1H), 7.57 (d J = 2.8 Hz, 1H), 6.83 (d, J = 5.2 Hz, 1H), 5.12 (d, J = 6.0 Hz, 2H), 3.93 (s, 3H), 3.80-3.86 (m, 1H), 1.10-1015 (m, 2H), 1.00-1.08 (m, 2H).
399	1H NMR (400 MHz, DMSO-d_6) d ppm 8.49 - 8.55 (m, 2 H), 8.41 (d, *J*=5.38 Hz, 1 H), 8.24 (s, 1 H), 8.03 (d, *J*=9.68 Hz, 1 H), 7.94 (t, *J*=6.16 Hz, 1 H), 7.58 (d, *J*=2.84 Hz, 1 H), 6.83 (d, *J*=5.38 Hz, 1 H), 5.67 (t, *J*=5.77 Hz, 1 H), 5.15 (d, *J*=6.16 Hz, 2 H), 4.63 (d, *J*=5.67 Hz, 2 H), 3.93 (s, 3 H).
400	1H NMR (400 MHz, DMSO-d_6) δ ppm 5.26 (d, *J*=6.36 Hz, 2 H) 7.02 (d, *J*=5.38 Hz, 1 H) 7.96 - 8.10 (m, 2 H) 8.22 - 8.32 (m, 2 H) 8.48 - 8.57 (m, 3 H) 8.85 (d, *J*=2.84 Hz, 1 H)
405	1H NMR (400 MHz, DMSO-d_6) δ ppm 3.43 - 3.53 (m, 4 H) 3.70 - 3.80 (m, 4 H) 3.94 (s, 3 H) 5.16 (d, *J*=6.16 Hz, 2 H) 6.85 (d, *J*=5.28 Hz, 1 H) 7.57 (d, *J*=2.74 Hz, 1 H) 7.87 (s, 1 H) 7.90 (d, *J*=9.68 Hz, 1 H) 8.01 - 8.08 (m, 1 H) 8.35 - 8.45 (m, 2 H) 8.52 (d, *J*=2.64 Hz, 1 H)
406	1H NMR (400 MHz, DMSO-d_6) δ ppm 3.94 (s, 3 H) 5.19 (d, *J*=6.26 Hz, 2 H) 6.85 (d, *J*=5.38 Hz, 1 H) 7.57 (d, *J*=2.93 Hz, 1 H) 7.97 - 8.02 (m, 1 H) 8.05 (d, *J*=9.78 Hz, 1 H) 8.42 (d, *J*=5.28 Hz, 1 H) 8.45 (d, *J*=9.68 Hz, 1 H) 8.52 (d, *J*=2.84 Hz, 1 H) 8.71 (d, *J*=1.96 Hz, 1 H) 9.36 (d, *J*=1.96 Hz, 1 H)
408	1H NMR (400 MHz, DMSO-d_6) δ ppm 1.90 (d, *J*=7.04 Hz, 3 H) 2.44 (s, 3 H) 5.24 (q, *J*=7.01 Hz, 1 H) 7.51 (dd, *J*=8.27, 4.16 Hz, 1 H) 7.64 - 7.73 (m, 2 H) 7.81 (dd, *J*=8.75, 2.01 Hz, 1 H) 7.94 (d, *J*=1.96 Hz, 1 H) 8.00 (d, *J*=8.61 Hz, 1 H) 8.32 (d, *J*=8.41 Hz, 1 H) 8.64 (d, *J*=1.17 Hz, 1 H) 8.86 (dd, *J*=4.16, 1.71 Hz, 1 H)
409	1H NMR (400 MHz, DMSO-d_6) δ ppm 1.92 (d, *J*=7.14 Hz, 3 H) 5.26 (q, 1 H) 7.31 (t, *J*=9.29 Hz, 1 H) 7.49 (dd, *J*=8.36, 4.16 Hz, 2 H) 7.55 (d, *J*=8.61 Hz, 1 H) 7.77 - 7.86 (m, *J*=8.22 Hz, 2 H) 7.95 (s, 1 H) 7.99 (d, *J*=8.71 Hz, 1 H) 8.31 (d, *J*=7.24 Hz, 1 H) 8.68 (s, 1 H) 8.85 (dd, *J*=4.11, 1.66 Hz, 1 H)
411	1H NMR (400 MHz, DMSO-d_6) δ ppm 1.89 (d, *J*=7.04 Hz, 3 H) 2.27 (s, 3 H) 3.88 (s, 3 H) 5.22 (q, *J*=6.98 Hz, 1 H) 6.99 (s, 1 H) 7.63 (dd, *J*=8.71, 2.05 Hz, 1 H) 7.67 - 7.70 (m, 1 H) 7.72 (d, *J*=1.86 Hz, 1 H) 7.76 (dd, *J*=11.54, 1.17 Hz, 1 H) 7.93 (d, *J*=8.61 Hz, 1 H) 8.58 (d, *J*=2.93 Hz, 1 H) 8.64 (d, *J*=1.08 Hz, 1 H)
413	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.40 (s, 3 H) 2.44 (d, *J*=23.28 Hz, 3 H) 7.56 - 7.61 (m, 2 H) 7.75 (dd, *J*=8.90, 2.15 Hz, 1 H) 7.80 (dd, *J*=11.49, 1.22 Hz, 1 H) 8.02 (d, *J*=0.88 Hz, 1 H) 8.09 (d, *J*=8.90 Hz, 1 H) 8.12 (d, *J*=2.05 Hz, 1 H) 8.43 - 8.47 (m, 1 H) 8.95 (dd, *J*=4.21, 1.76 Hz, 1 H)

Example	1H NMR Data
418	1H NMR (400 MHz, DMSO-d_6) δ ppm 3.89 (s, 3 H) 4.88 (s, 2 H) 7.61 (dd, *J*=8.56, 2.01 Hz, 1 H) 7.68 (d, *J*=2.74 Hz, 1 H) 7.70 - 7.75 (m, 1 H) 7.83 (s, 1 H) 7.89 (dd, *J*=11.44, 1.08 Hz, 1 H) 7.93 (d, *J*=8.61 Hz, 1 H) 8.59 (d, *J*=2.84 Hz, 1 H) 9.17 (d, *J*=1.08 Hz, 1 H)
430	1H NMR (400 MHz, DMSO-d_6) δ ppm 8.84 (dd, *J*=4.25, 1.71 Hz, 1 H), 8.42 - 8.46 (m, 1 H), 8.26 (d, *J*=2.05 Hz, 1 H), 8.15 (d, *J*=9.49 Hz, 1 H), 7.94 (s, 1 H), 7.90 (d, *J*=8.80 Hz, 1 H), 7.67 - 7.76 (m, 4 H), 7.52 (dd, *J*=8.26, 4.25 Hz, 1 H), 7.38 - 7.44 (m, 1 H), 7.32 - 7.37 (m, 2 H), 6.17 (s, 1 H), 2.17 (s, 3 H)
431	1H NMR (400 MHz, DMSO-d_6) δ ppm 8.85 (dd, *J*=4.21, 1.76 Hz, 1 H), 8.31 - 8.35 (m, 1 H), 8.21 (d, *J*=9.59 Hz, 1 H), 8.04 - 8.08 (m, 2 H), 7.95 - 7.99 (m, 2 H), 7.75 - 7.83 (m, 3 H), 7.49 - 7.58 (m, 4 H), 4.62 (s, 2 H)
433	1H NMR (400 MHz, DMSO-d_6) δ ppm 9.01 (dd, *J*=4.21, 1.66 Hz, 1 H), 8.54 - 8.59 (m, 1 H), 8.47 (s, 1 H), 8.44 (d, *J*=9.59 Hz, 1 H), 8.16 (d, *J*=8.80 Hz, 1 H), 8.13 (s, 1 H), 8.00 (dd, *J*=8.90, 2.05 Hz, 1 H), 7.88 (d, *J*=9.59 Hz, 1 H), 7.64 (dd, *J*=8.31, 4.21 Hz, 1 H), 7.11 (s, 1 H), 2.33 (s, 3 H)
436	1H NMR (400 MHz, DMSO-d_6) δ ppm 8.46 (d, *J*=2.74 Hz, 1 H), 8.38 (d, *J*=5.38 Hz, 1 H), 8.29 (d, *J*=9.39 Hz, 1 H), 8.00 (s, 1 H), 7.76 - 7.82 (m, 3 H), 7.54 (d, *J*=2.84 Hz, 1 H), 6.79 (d, *J*=5.38 Hz, 1 H), 4.98 (d, *J*=6.36 Hz, 2 H), 3.91 (s, 3 H)
437	^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 4.80 (s, 2 H) 7.19 (dd, *J*=10.76, 1.17 Hz, 1 H) 7.31 - 7.35 (m, 2 H) 7.38 - 7.43 (m, 4 H) 7.65 - 7.71 (m, 3 H) 8.07 (dd, *J*=8.31, 0.88 Hz, 1 H) 8.11 (d, *J*=8.41 Hz, 1 H) 8.91 (dd, *J*=4.21, 1.66 Hz, 1 H).
438	^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm 3.88 (s, 3 H) 4.76 (s, 2 H) 7.52 - 7.59 (m, 1 H) 7.61 (s, 1 H) 7.65 (d, J=12.32 Hz, 1 H) 7.80 (s, 1 H) 7.91 (d, J=8.80 Hz, 1 H) 8.01 (s, 1 H) 8.27 (s, 1 H) 8.57 - 8.66 (m, 2 H) 10.59 (br. s., 1 H)
439	1H NMR (400 MHz, DMF) δ ppm 7.69 (tt, *J*=9.32, 2.27 Hz, 3 H) 7.99 (dd, *J*=8.31, 4.21 Hz, 1 H) 8.01 - 8.09 (m, 2 H) 8.43 (dd, *J*=8.90, 2.15 Hz, 1 H) 8.54 (d, *J* = 8.8 Hz 1 H) 8.83 - 8.95 (m, 2 H) 9.19 (d, *J*=2.25 Hz, 1 H) 9.37 (dd, *J*=4.25, 1.71 Hz, 1 H) 9.53 (d, *J*=2.25 Hz, 1 H). MS m/z = 410.0 $[M+1]^+$ Calc'd for $C_{22}H_{11}F_4N_3O$: 409.3.
442	1H NMR (400 MHz, DMSO-d_6) δ ppm 4.00 (s, 3 H) 5.24 (d, *J*=5.97 Hz, 2 H) 5.76 (d, *J*=46.46 Hz, 2 H) 7.64 (d, *J*=2.74 Hz, 1 H) 7.77 (s, 1 H) 8.01 (d, *J*=9.68 Hz, 1 H) 8.10 (t, *J*=6.26 Hz, 1 H) 8.48 (d, *J*=5.28 Hz, 1 H) 8.59 (d, *J*=2.74 Hz, 1 H) 8.64 (d, *J*=9.68 Hz, 1 H).
443	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.40 - 2.40 (m, 1 H) 7.58 (dd, *J*=8.31, 4.21 Hz, 1 H) 7.81 (s, 1 H) 8.00 (dd, *J*=8.90, 2.25 Hz, 1 H) 8.12 (d, *J*=8.90 Hz, 1 H) 8.44 (d, *J*=1.27 Hz, 1 H) 8.47 (dd, *J*=8.46, 1.03 Hz, 1 H) 8.70 (d, *J*=2.25 Hz, 1 H) 8.95 (dd, *J*=4.26, 1.71 Hz, 1 H) 9.07 (d, *J*=2.15 Hz, 1 H) .
444	1H NMR (400 MHz, DMSO-d_6) δ ppm 7.44 - 7.53 (m, 1 H) 7.68 (dd, *J*=8.31, 4.21 Hz, 1 H) 8.00 (td, *J*=7.78, 1.76 Hz, 1 H) 8.11 (dd, *J*=8.90, 2.05 Hz, 1 H) 8.25 (dd, *J*=15.60, 8.36 Hz, 2 H) 8.55 (s, 1 H) 8.58 (dd, *J*=8.41, 0.78 Hz, 1 H) 8.75 (dq, *J*=4.77, 0.82 Hz, 1 H) 9.01 - 9.11 (m, 2 H) 9.53 (d, *J*=2.15 Hz, 1 H).

Example	1H NMR Data
450	1H NMR (400 MHz, DMSO-d_6) δ ppm 7.35 - 7.45 (m, 1 H) 7.67 (dd, *J*=8.31, 4.21 Hz, 1 H) 7.73 - 7.85 (m, 2 H) 8.11 (dd, *J*= 8.9, 2.0 Hz, 1 H) 8.21 (d, *J*=8.90 Hz, 1 H) 8.48 (d, *J*=9.10 Hz, 1 H) 8.57 (s, 1 H) 8.60 (m, 2 H) 9.04 (dd, *J*=4.11, 1.56 Hz, 1 H).
460	1H NMR (400 MHz, DMSO-d_6) δ ppm 3.89 (s, 3H); 3.89 (s, 3 H); 4.01 - 4.02 (m, 1 H); 7.86 (dd, *J*=8.8, 2.2 Hz, 1 H); 7.91 (dd, *J*=12.0, 1.0 Hz, 1 H); 7.95 (d, *J*=2.7 Hz, 1 H); 8.11 (d, *J*=0.7 Hz, 1 H); 8.15 (d, *J*=8.7 Hz, 1 H); 8.32 (d, *J*=1.5 Hz, 1 H); 8.56 (d, *J*=0.7 Hz, 1 H); 8.78 (d, *J*=2.9 Hz, 1 H)
462	1H NMR (400 MHz, DMSO-d_6) δ ppm 1.93 - 2.07 (m, 2 H) 2.30 - 2.42 (m, 4 H) 2.43 - 2.49 (m, 2 H) 3.50 - 3.65 (m, 4 H) 3.89 (s, 3 H) 4.20 (t, *J*=6.41 Hz, 2 H) 7.86 (dd, *J*=8.75, 1.91 Hz, 1 H) 7.96 (s, 1 H) 7.98 (d, *J*=2.64 Hz, 1 H) 8.13 (s, 1 H) 8.15 (d, *J*=8.90 Hz, 1 H) 8.32 (s, 1 H) 8.46 (s, 1 H) 8.57 (s, 1 H) 8.78 (d, *J*=2.84 Hz, 1 H)
468	1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.41 (s, 3 H); 3.97 (s, 3 H); 6.54 (s, 1 H); 7.39 (dd, *J*=9.8, 1.2 Hz, 1 H); 7.47 (d, *J*=2.8 Hz, 1 H); 7.83 (dd, *J*=8.8, 2.1 Hz, 1 H); 8.17 (d, *J*=1.1 Hz, 1 H); 8.21 (d, *J*=8.7 Hz, 1 H) 8.75 - 8.84 (m, 2 H)
469	1H NMR (400 MHz, DMSO-d_6) □ ppm 3.95 (s, 3 H); 7.83 - 7.92 (m, 2 H); 7.93 - 8.03 (m, 2 H); 8.18 (d, *J*=5.6 Hz, 1 H); 8.34 (s, 1 H); 8.69 (s, 1 H); 8.80 (d, *J*=2.93 Hz, 1 H)
470	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.34 (s, 3 H); 7.26 (s, 1 H); 7.69 (dd, *J*=8.3, 4.2 Hz, 1 H); 8.05 (dd, *J*=8.8, 2.2 Hz, 1 H); 8.09 (dd, *J*=11.3, 1.1 Hz, 1 H); 8.25 (d, *J*=8.9 Hz, 1 H); 8.50 (d, *J*=1.7 Hz, 1 H); 8.60 (s, 1 H); 8.80 (d, *J*=1.0 Hz, 1 H); 9.08 (dd, *J*=4.3, 1.7 Hz, 1 H)
471	1H NMR (400 MHz, DMSO-d_6) δ ppm 3.70 (s, 3 H); 7.57 - 7.67 (m, 1 H); 7.72 (s, 1 H); 7.87 - 8.16 (m, 3 H); 8.29 (s, 1 H); 8.55 (s, 1 H); 8.70 (s, 1 H)
473	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.32 (s, 3 H); 3.47 (s, 1 H); 3.55 (dd, *J*=11.4, 2.01 Hz, 1 H); 3.67 (s, 2 H); 3.80 (s, 1 H); 3.89 (s, 1 H); 3.98 (s, 1 H); 4.16 (d, *J*=5.0 Hz, 2 H); 7.22 (s, 1 H); 7.87 (dd, *J*=8.9, 2.0 Hz, 1 H); 7.98 (d, *J*=2.8 Hz, 1 H); 8.05 (dd, *J*=11.3, 0.6 Hz, 1 H); 8.16 (d, *J*=8.8 Hz, 1 H); 8.31 (s, 1 H); 8.74 (s, 1 H); 8.81 (d, *J*=2.9 Hz, 1 H)
474	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.35 (s, 3 H); 3.94 (s, 3 H); 4.79 (d, *J*=5.97 Hz, 2 H); 6.76 (d, *J*=5.4 Hz, 1 H); 7.01 (s, 1 H); 7.57 (d, *J*=2.7 Hz, 1 H); 7.89 - 7.94 (m, 1 H); 7.93 (d, *J*=8.6 Hz, 1 H); 8.21 (d, *J*=8.6 Hz, 1 H); 8.34 (s, 1 H); 8.40 (d, *J*=5.4 Hz, 1 H); 8.51 (d, *J*=2.7 Hz, 1 H)
475	^{1}H NMR (400 MHz, DMSO-d_6) ppm 3.89 (s, 3 H) 7.68 (dd, J=8.28, 4.27 Hz, 1 H) 7.93 (d, J=12.05 Hz, 1 H) 8.04 (d, J=8.53 Hz, 1 H) 8.13 (s, 1 H) 8.23 (d, J=8.53 Hz, 1 H) 8.43 - 8.52 (m, 2 H) 8.55 - 8.63 (m, 2 H) 9.07 (d, J=4.02 Hz, 1 H).
476	^{1}H NMR (400 MHz, DMSO-d_6) d ppm 7.56 - 7.74 (m, 2 H) 7.99 (d, J=9.03 Hz, 1 H) 8.21 (d, J=8.53 Hz, 1 H) 8.40 (s, 1 H) 8.57 (d, J=8.03 Hz, 1 H) 8.63 (d, J=10.04 Hz, 1 H) 9.05 (d, J=4.02 Hz, 1 H)
477	^{1}H NMR (400 MHz, DMSO-d_6) d ppm 3.92 (s, 3 H) 3.94 (s, 3 H) 7.80 - 7.87 (m, 2 H) 8.01 - 8.07 (m, 1 H) 8.11 (d, J=9.04 Hz, 1 H) 8.37 (s, 1 H) 8.46 - 8.51 (m, 2 H) 8.75 (d, J=3.01 Hz, 1 H)

Example	1H NMR Data
478	^{1}H NMR (400 MHz, DMSO-d_6) d ppm 7.67 (dd, J=8.03, 4.02 Hz, 1 H) 7.80 - 7.89 (m, 2 H) 8.17 (dd, J=13.05, 9.54 Hz, 2 H) 8.54 (s, 1 H) 8.60 (d, J=8.53 Hz, 1 H) 8.69 (d, J=10.04 Hz, 1 H) 9.04 (d, J=3.51 Hz, 1 H)
484	^{1}H NMR (400 MHz, DMSO-d_6) d ppm 2.94 (t, J=7.78 Hz, 2 H) 3.03 - 3.14 (m, 2 H) 7.44 (d, J=8.03 Hz, 2 H) 7.68 (dd, J=8.28, 4.27 Hz, 1 H) 7.85 (br. s., 2 H) 7.95 (d, J=8.03 Hz, 2 H) 8.05 (d, J=8.53 Hz, 1 H) 8.12 (d, J=9.54 Hz, 1 H) 8.21 (d, J=8.53 Hz, 1 H) 8.49 (s, 1 H) 8.57 - 8.66 (m, 2 H) 9.05 (d, J=4.02 Hz, 1 H).
490	^{1}H NMR (300 MHz, CHLOROFORM-d) d ppm 2.10 (d, J=7.16 Hz, 3 H) 2.55 (s, 3 H) 5.04 (q, J=6.87 Hz, 1 H) 7.27 - 7.52 (m, 3 H) 7.82 (d, J=8.62 Hz, 1 H) 7.93 (s, 1 H) 8.05 (d, J=8.62 Hz, 1 H) 8.15 (d, J=9.21 Hz, 2 H) 8.85 (d, J=2.63 Hz, 1 H).
496	^{1}H NMR (300 MHz, CHLOROFORM-d)ppm 3.58 (s, 3 H) 4.78 (s, 2 H) 7.48 - 7.63 (m, 4 H) 7.66 (d, J=8.48 Hz, 1 H) 7.87 (d, J=7.16 Hz, 1 H) 7.91 - 8.06 (m, 3 H) 8.14 (d, J=9.65 Hz, 1 H) 8.47 (s, 1 H).
499	^{1}H NMR (300 MHz, CHLOROFORM-d) δ ppm 3.94 (s, 3 H) 4.73 (s, 2 H) 7.10 (d, J=9.65 Hz, 1 H) 7.33 (d, J=2.78 Hz, 1 H) 7.63 (d, J=10.67 Hz, 1 H) 7.76 (s, 1 H) 8.00 (d, J=8.48 Hz, 1 H) 8.07 (d, J=9.65 Hz, 1 H) 8.64 (d, J=2.92 Hz, 1 H).
501	^{1}H NMR (300 MHz, MeOH) d ppm 4.05 (s, 11 H) 4.82 (s, 7 H) 7.40 (dd, J=10.08, 1.46 Hz, 4 H) 7.81 (dd, J=8.77, 1.90 Hz, 4 H) 7.96 (d, J=0.88 Hz, 4 H) 8.05 (d, J=8.77 Hz, 4 H) 8.21 (d, J=2.78 Hz, 4 H) 8.50 (d, J=0.73 Hz, 3 H) 8.85 (d, J=2.92 Hz, 4 H).
502	^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.59 (s, 3 H) 3.93 (s, 3 H) 4.77 (s, 2 H) 7.34 (d, *J*=2.74 Hz, 1 H) 7.38 (d, *J*=9.68 Hz, 1 H) 7.46 (s, 1 H) 7.66 (dd, *J*=8.61, 2.05 Hz, 1 H) 7.84 (d, *J*=1.96 Hz, 1 H) 7.98 (d, *J*=8.61 Hz, 1 H) 8.16 (d, *J*=9.59 Hz, 1 H) 8.61 (d, *J*=2.93 Hz, 1 H).

Example	^{1}H NMR Data
503	^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.16 (d, *J*=5.18 Hz, 3 H) 3.97 (s, 3 H) 6.82 (d, *J*=6.55 Hz, 1 H) 7.01 - 7.13 (m, 2 H) 7.41 - 7.49 (m, 1 H) 7.54 (d, *J*=6.26 Hz, 1 H) 7.61 (s, 1 H) 7.71 (s, 1 H) 8.33 (s, 1 H) 8.78 (d, *J*=7.73 Hz, 1 H) 8.93 (s, 1 H).
505	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.01 (d, *J*=7.04 Hz, 3 H) 6.78 (d, *J*=7.82 Hz, 1 H) 7.03 (d, *J*=6.94 Hz, 1 H) 7.54 (dd, *J*=8.07, 4.55 Hz, 1 H) 7.78 (d, *J*=7.82 Hz, 1 H) 7.97 - 8.09 (m, 2 H) 8.16 (dd, *J*=8.56, 2.49 Hz, 1 H) 8.61 (dd, *J*=7.97, 1.71 Hz, 1 H) 8.70 - 8.78 (m, 1 H) 8.92 (dd, *J*=4.55, 1.81 Hz, 1 H) 9.03 (d, 1 H).
507	1H NMR (400 MHz, DMSO-d_6) δ ppm 1.97 (d, *J*=6.94 Hz, 3 H) 3.68 (s, 3 H) 6.75 (d, *J*=7.73 Hz, 1 H) 6.94 (d, *J*=6.85 Hz, 1 H) 7.52 - 7.59 (m, 1 H) 7.64 (dd, *J*=7.78, 0.54 Hz, 1 H) 7.69 - 7.75 (m, 3 H) 8.46 (s, 1 H) 8.63 (dt, *J*=8.12, 0.88 Hz, 1 H) 8.90 - 8.94 (m, 1 H)
509	^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.17 (d, *J*=7.14 Hz, 3 H) 4.00 - 4.09 (m, 2 H) 4.29 - 4.33 (m, 2 H) 6.91 (d, *J*=7.92 Hz, 1 H) 7.04 (dd, 1 H) 7.10 (dd, *J*=10.56, 1.17 Hz, 1 H) 7.51 (dd, *J*=8.17, 4.74 Hz, 1 H) 7.59 (d, *J*=7.82 Hz, 1 H) 7.72 (d, *J*=0.68 Hz, 1 H) 7.76 (d, *J*=0.78 Hz, 1 H) 8.34 (d, *J*=1.17 Hz, 1 H) 8.84 (dd, *J*=8.07, 1.22 Hz, 1 H) 8.92 (dd, *J*=4.74, 1.81 Hz, 1 H)

Example	^{1}H NMR Data
514	^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.17 (d, *J*=7.14 Hz, 3 H) 2.39 (s, 3 H) 3.49 (s, 3 H) 3.78 - 3.94 (m, 2 H) 4.23 - 4.43 (m, 2 H) 6.43 (s, 1 H) 6.85 (d, *J*=7.82 Hz, 1 H) 7.08 (q, *J*=7.11 Hz, 1 H) 7.29 (dd, *J*=10.07, 1.17 Hz, 1 H) 7.43 (d, *J*=7.82 Hz, 1 H) 8.17 (d, *J*=2.93 Hz, 1 H) 8.58 - 8.81 (m, 2 H).
516	^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.15 (d, *J*=7.14 Hz, 3 H) 3.49 (s, 3 H) 3.80 - 3.90 (m, 2 H) 3.97 (s, 3 H) 4.27 - 4.39 (m, 2 H) 6.83 (d, *J*=7.73 Hz, 1 H) 7.00 - 7.13 (m, 2 H) 7.42 (d, *J*=7.82 Hz, 1 H) 7.61 (s, 1 H) 7.72 (s, 1 H) 8.15 (d, *J*=2.84 Hz, 1 H) 8.31 (s, 1 H) 8.72 (d, *J*=3.03 Hz, 1 H).
518	1H NMR (400 MHz, DMSO-d_6) δ ppm 8.89 (t, 1 H), 8.68 (d, *J*=3.03 Hz, 1 H), 8.01 - 8.02 (m, 1 H), 7.96 (dd, *J*=9.59, 1.08 Hz, 1 H), 7.79 (dd, *J*=9.54, 1.61 Hz, 1 H), 7.60 (d, *J*=7.82 Hz, 1 H), 7.01 - 7.05 (m, 1 H), 6.99 (s, 1 H), 6.75 (d, *J*=7.63 Hz, 1 H), 4.29 - 4.32 (m, 2 H), 3.70 - 3.73 (m, 2 H), 3.32 (s, 3 H), 2.31 (s, 3 H), 1.99 (d, *J*=7.04 Hz, 3 H).
524	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.00 (d, *J*=7.04 Hz, 3 H) 2.31 (s, 3 H) 3.94 (s, 3 H) 6.77 (dd, *J*=7.78, 0.54 Hz, 1 H) 6.94 - 7.05 (m, 2 H) 7.64 (d, *J*=7.82 Hz, 1 H) 7.76 - 7.89 (m, 1 H) 7.98 (dd, *J*=3.08, 0.54 Hz, 1 H) 8.68 (d, *J*=3.03 Hz, 1 H) 8.80 (d, *J*=1.08 Hz, 1 H).
526	1H NMR (400 MHz, DMSO-d_6) δ ppm 2.01 (d, *J*=7.04 Hz, 3 H) 2.25 - 2.38 (m, 3 H) 5.05 (q, *J*=8.77 Hz, 2 H) 6.74 - 6.83 (m, 1 H) 6.96 - 7.07 (m, 2 H) 7.71 (d, *J*=7.82 Hz, 1 H) 7.86 (dd, *J*=11.49, 1.12 Hz, 1 H) 8.20 (d, *J*=2.74 Hz, 1 H) 8.78 (d, *J*=3.03 Hz, 1 H) 8.83 (d, *J*=1.08 Hz, 1 H)
527	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.01 (d, *J*=7.04 Hz, 3 H) 2.31 (s, 3 H) 3.89 (s, 3 H) 6.78 (d, *J*=8.41 Hz, 1 H) 6.95 - 7.09 (m, 2 H) 7.72 (d, *J*=7.82 Hz, 1 H) 7.85 (d, *J*=12.62 Hz, 1 H) 8.12 (s, 1 H) 8.46 (s, 1 H) 8.67 (dd, *J*=2.35, 0.68 Hz, 1 H) 8.83 (d, *J*=1.08 Hz, 1 H) 9.20 (d, *J*=2.45 Hz, 1 H)
529	^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.00 (d, *J*=7.04 Hz, 3 H) 2.31 (s, 3 H) 6.78 (d, *J*=7.92 Hz, 1 H) 6.95 - 7.12 (m, 2 H) 7.54 (dd, *J*=8.22, 4.50 Hz, 1 H) 7.77 (d, *J*=7.73 Hz, 1 H) 7.85 (d, *J*=11.54 Hz, 1 H) 8.62 (d, *J*=9.59 Hz, 1 H) 8.82 (s, 1 H) 8.92 (dd, *J*=4.55, 1.71 Hz, 1 H)

Although the pharmacological properties of the compounds of the current invention vary with structural change, in general, activity possessed by these compounds may be demonstrated *in vivo*. The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological *in vitro* assays. The exemplified pharmacological assays, which follow, have been carried out with the compounds according to the invention. The exemplified compounds of the present invention demonstrated a K_i between 20 μM and 0.1 nM. Illustrative activity values are provided in the following table.

Ex.	cMet K_i (μM)
373	0.0001

Ex.	cMet K_i (μM)
430	0.3480
437	0.0364
439	0.2531
440	0.1716
441	0.0286
447	0.0121
450	0.1823
466	0.6351

Ex.	cMet Ki (μM)
503	0.0015
505	0.0015
508	1.3438
509	0.0032
511	0.0005
514	0.0007
516	0.0061
518	0.0015
520	0.0011
522	0.0011
524	0.0009
525	0.0257
527	0.0003
529	0.0021

BIOLOGICAL TESTING

The efficacy of the compounds of the invention as inhibitors of HGF related activity is demonstrated as follows.

c-Met receptor assay

Cloning, Expression and Purification of c-Met Kinase Domain

1) A PCR product covering residues 1058-1365 of c-Met (c-Met kinase domain) is generated from Human Liver QuickClone™ cDNA (Invitrogen) as described in WO 08/008539.

2). The PCR product is cloned into a modified pFastBac1 expression vector (harboring the gene for *S. japonicum* glutathione S-transferase immediately upstream of the multiple cloning site) using standard molecular biological techniques. The GST-c-Met kinase domain fusion (GST-Met) gene is transposed into full-length baculovirus DNA using the

BacToBac™ system (Invitrogen). High5 cells are infected with the recombinant baculovirus for 72 h at 27°C. The infected cells are harvested by centrifugation and the pellet is stored at –80°C. The pellet is resuspended in buffer A (50 mM HEPES, pH 8.0, 0.25 M NaCl, 10 mM 2-mercaptoethanol, 10% (w/v) glycerol, 0.5 % (v/v) protease inhibitor cocktail (Sigma P8340), stirred at 4°C to homogeneity, and the cells are disrupted by microfluidization (Microfluidics) at 10,000 psi. The resulting lysate is centrifuged at 50,000 x *g* for 90 min at 4 °C, and the supernatant is adsorbed onto 10 mL of glutathione sepharose™ 4B (Amersham) by batch method. The slurry is rocked gently overnight at 4°C. The glutathione resin is harvested by centrifugation and washed three times with 40 mL buffer A by batch method. The resin is washed three times with buffer B (buffer A adjusted to 0.1 M NaCl, less protease inhibitors). The protein is eluted with buffer B containing 25 mM reduced glutathione. Eluted fractions are analyzed by SDS-PAGE and concentrated to <10 mL (~10 mg/mL total protein). The concentrated protein is separated by Superdex™ 200 (Amersham) size exclusion chromatography in buffer C (25 mM Tris, pH 7.5, 0.1 M NaCl, 10 mM 2-mercaptoethanol, 10% glycerol). The fractions are analyzed by SDS-PAGE and the appropriate fractions are pooled and concentrated to ~1 mg/mL. The protein is aliquotted and stored at –80°C.

Alternative purification of human GST-cMET from Baculovirus cells

Baculovirus cells are broken in 5x (volume/weight) of Lysis Buffer (50 mM HEPES, pH 8.0, 0.25 M NaCl, 5 mM mercaptoethanol, 10% glycerol plus Complete Protease Inhibitors (Roche (#10019600), 1 tablet per 50 mL buffer). The lysed cell suspension is centrifuged at 100,000 x g (29,300 rpm) in a Beckman ultracentrifuge Ti45 rotor for 1 h. The supernatant is incubated with 10 ml of Glutathione Sepharose 4B from Amersham Biosciences (#27-4574-01). Incubation is carried out overnight in a cold room (approximately 8°C). The resin and supernatant is poured into an appropriately sized disposable column and the flow through supernatant was collected. The resin is washed with 10 column volumes (100 mL) of Lysis Buffer. The GST-cMET is eluted with 45 mL of 10 mM Glutathione (Sigma #G-4251) in Lysis Buffer. The elution is collected as 15 mL fractions. Aliquots of the elution fractions are run on SDS PAGE (12% Tris Glycine gel, Invitrogen, #EC6005BOX). The gel is stained with 0.25% Coomassie Blue stain. Fractions with GST-cMET are concentrated with a Vivaspin 20 mL Concentrator (#VS2002; 10,00 MW cutoff) to a final volume less than 2.0 ml. The concentrated GST-cMET solution is applied to a Superdex 75 16/60 column (Amersham Biosciences #17-1068-01) equilibrated with 25 mM Tris, pH 7.5, 100 mM NaCl, 10 mM mercaptoethanol, 10% glycerol. The GST-cMET is eluted with an isocratic run of the above buffer, with the eluent collected in 1.0 mL fractions. Fractions with significant OD_{280} readings

are run on another 12% Tris Glycine gel. The peak tubes with GST-cMET are pooled and the OD_{280} is read with the column buffer listed above as the blank buffer.

Phosphorylation of the purified GST-cMET is performed by incubating the protein for 3 h at RT with the following:

	Final concentration
a) 100 mM ATP (Sigma #A7699)	25 mM
b) 1.0 M $MgCl_2$ (Sigma #M-0250)	100 mM
c) 200 mM Sodium Orthovanadate (Sigma #S-6508)	15 mM
d) 1.0 M Tris-HCl, pH 7.00 (in house)	50 mM
e) H_20	
f) GST-cMET	0.2 - 0.5 mg/mL

After incubation, the solution is concentrated in a Vivaspin 20 ml Concentrator to a volume less than 2.00 ml. The solution is applied to the same Superdex 75 16/60 column used above after re-equilibration. The GST-cMET is eluted as described above. The elution fractions corresponding to the first eluted peak on the chromatogram are run on a 12% Tris Glycine gel, as above, to identify the fractions with GST-cMET. Fractions are pooled and the OD_{280} is read with the column buffer used as the blank.

A Kinase reaction Buffer is prepared as follows:

			Per 1 L
60 mM HEPES pH 7.4	1 M stock	16.7 X	60 mL
50 mM NaCl	5 M stock	100 X	10 mL
20 mM $MgCl_2$	1 M stock	50 X	20 mL
5 mM $MnCl_2$	1 M stock	200 X	5 mL

When the assay is carried out, freshly add:

2 mM DTT	1 M stock	500 X
0.05 % BSA	5 % stock	100 X
0.1 mM Na_3OV_4	0.1 M stock	1000 X

The HTRF buffer contains:

50 mM Tris-HCl (pH 7.5), 100 mM NaCl, 0.1 % BSA, 0.05 % Tween 20,5mM EDTA

Fresh add SA-APC (PJ25S Phycolink Streptavidin-Allophycocyanin Conjugate, Prozyme Inc.) and Eu-PT66 (Eu-W1024 labeled anti-phosphorotyrosine antibody PT66, AD0069, Lot 168465, Perkin-Elmer Inc.) to reach the final concentration:

0.1 nM final Eu-PT66

11 nM final SA-APC

Methods:

1. Dilute GST-cMet (P) enzyme in kinase buffer as follows:

Prepare 8 nM GST-cMet (P) working solution (7.32 μM to 8 nM, 915 X, 10 μL to 9.15 mL). In a 96 well clear plate [Costar # 3365] add 100 μL in eleven columns, in one column add 100 μL kinase reaction buffer alone.

2. Assay plate preparation:

Use Biomek FX to transfer 10 μL 8 nM GST-cMet (P) enzyme, 48.4 μL kinase reaction buffer, 1.6 μL compound (in DMSO) (Start concentration at 10 mM, 1 mM and 0.1 mM, sequential dilution 1:3 to reach 10 test points) in a 96 well costar clear plate [Costar # 3365], mix several times. Then incubate the plate at RT for 30 min.

3. Prepare Gastrin and ATP working solution in kinase reaction buffer as follows:

Prepare 4 μM Gastrin and 16 μM ATP working solution

		Per 10 mL
Gastrin 4 μM stock	(500 μM to 4 μM, 125 X)	80 μL
ATP 16 μM stock	(1000 μM to 16 μM, 62.5 X)	160 μL

Use Biomek FX to add 20 μl ATP and Gastrin working solution to the assay plate to start reaction, incubate the plate at RT for 1 h.

4. Transfer 5 μL reaction product at the end of 1 h into 80 μL HTRF buffer in black plate [Costar # 3356], read on Discover after 30 min incubation.

Assay condition summary:

K_M ATP *	-	6 μM
[ATP]	-	4 μM
K_M Gastrin/p(EY)	-	3.8 μM

[gastrin] - 1 μM

[enzyme] - 1 nM

K_M ATP, K_M gastrin for various enzymes were determined by HTRF/^{33}P labeling and HTRF methods.

Examples 1-28, 30, 33-34, 36-37, and 39-48 exhibited activity with IC_{50} values less than 0.5 μM.

c-Met cell-based autophosphorylation assay

Human PC3 and mouse CT26 cells are available obtained from ATCC. The cells were cultured in a growth medium containing RPMI 1640, penicillin/streptomycin/glutamine (1X) and 5% FBS. 2 x 10^4 cells in medium were plated per well in a 96 well plate and incubated at 37 °C overnight. The cells were serum-starved by replacing the growth media with basic medium (DMEM low glucose + 0.1 BSA, 120 μL per well) at 37 °C for 16 h. Compounds (either 1 mM and 0.2 mM) in 100% DMSO were serially diluted (1:3) 3333 fold on a 96 well plate, diluting 1:3 with DMSO from column 1 to 11 (columns 6 and 12 receive no compound). Compound samples (2.4 μL per well) were diluted with basic medium (240 μL) in a 96 well plate. The cells were washed once with basic medium (GIBCO, DMEM 11885-076) then compound solution was added (100 μL). The cells were incubated at 37 °C for 1 h. A (2 mg/mL) solution of CHO-HGF (7.5 μL) was diluted with 30 mL basic medium to provide a final concentration of 500 ng/mL. This HGF-containing media (120 μL) was transferred to a 96 well plate. Compounds (1.2 μL) was added to the HGF-containing media and mixed well. The mixture of media/HGF/compound (100 μL) was added to the cells (final HGF concentration - 250 ng/mL) then incubated at 37 °C for 10 min. A cell lysate buffer (20 mL) was prepared containing 1% Triton X-100, 50 mM Tris pH 8.0, 100 mM NaCl, Protease inhibitor (Sigma, #P-8340) 200 μL, Roche Protease inhibitor (Complete, # 1-697-498) 2 tablets, Phosphatase Inhibitor II (Sigma, #P-5726) 200 μL, and a sodium vanadate solution (containing 900 μL PBS, 100 μL 300 mM $NaVO_3$, 6 μL H_2O_2 (30% stock) and stirred at RT for 15 min) (90 μL). The cells were washed once with ice cold 1X PBS (GIBCO, #14190-136), then lysis buffer (60 μL) was added and the cells were incubated on ice for 20 min.

The IGEN assay was performed as follows: Dynabeads M-280 streptavidin beads were pre-incubated with biotinylated anti-human HGFR (240 μL anti-human-HGFR (R&D system, BAF527 or BAF328) @ 100 μg/mL + 360 μL Beads (IGEN #10029 + 5.4 μL buffer – PBS/1% BSA/0.1% Tween20) by rotating for 30 min at RT. Antibody beads (25 μL) were transferred to a 96 well plate. Cell lysate solution (25 μL) was transferred added and the plate was shaken

at RT for 1 h. Anti-phosphotyrosine 4G10 (Upstate 05-321) (19.7 μL antibody + 6 mL 1X PBS) (12.5 μL) was added to each well, then incubated for 1 h at RT. Anti-mouse IgG ORI-Tag (ORIGEN #110087) (24 μL Antibody + 6 mL buffer) (12.5 μL) was added to each well, then incubated at RT for 30 min. 1X PBS (175 μL) was added to each well and the electrochemiluminescence was read by an IGEN M8. Raw data was analyzed using a 4-parameter fit equation in XLFit. IC_{50} values are then determined using Grafit software. Examples 2, 4, 6-8, 11, 13, 15-21, 23-26, 36-37, 39, 41, and 43-44 exhibited activity in PC3 cells with IC_{50} values less than 1.0 μM. Examples 2, 4, 6-8, 11-13, 15-21, 23-26, 36-37, 41, and 43-44 exhibited activity in CT26 cells with IC_{50} values less than 1.0 μM.

rHu-bFGF: Stock concentration of 180 ng/μL: R&D rHu- bFGF: Added 139 μL of the appropriate vehicle above to the 25 μg vial lyophilized vial. 13.3 μL of the [180 ng/μL] stock vial and added 26.6 μL of vehicle to yield a final concentration of 3.75 μM concentration.

Nitro-cellulose disk preparation: The tip of a 20-gauge needle was cut off square and beveled with emery paper to create a punch. This tip was then used to cut out ≅ 0.5 mm diameter disks from a nitrocellulose filter paper sheet (Gelman Sciences). Prepared disks were then placed into Eppendorf microfuge tubes containing solutions of either 0.1% BSA in PBS vehicle, 10 μM rHu-VEGF (R&D Systems, Minneapolis, MN), or 3.75 μM rHu-bFGF (R&D Systems, Minneapolis, MN) and allowed to soak for 45-60 min before use. Each nitrocellulose filter disk absorbs approximately 0.1 μL of solution.

In the rat micropocket assay, compounds of the present invention will inhibit angiogenesis at a dose of less than 50 mg/kg/day.

Tumor model

A431 cells (ATCC) are expanded in culture, harvested and injected subcutaneously into 5-8 week old female nude mice (CD1 nu/nu, Charles River Labs) (n = 5-15). Subsequent administration of compound by oral gavage (10 - 200 mpk/dose) begins anywhere from day 0 to day 29 post tumor cell challenge and generally continues either once or twice a day for the duration of the experiment. Progression of tumor growth is followed by three dimensional caliper measurements and recorded as a function of time. Initial statistical analysis is done by repeated measures analysis of variance (RMANOVA), followed by Scheffe post hoc testing for multiple comparisons. Vehicle alone (Ora-Plus, pH 2.0) is the negative control. Compounds of the present invention will be active at doses less than 150 mpk.

Tumor models

Human glioma tumor cells (U87MG cells, ATCC) are expanded in culture, harvested and injected subcutaneously into 5-8 week old female nude mice (CD1 nu/nu, Charles River Labs) (n=10). Subsequent administration of compound by oral gavage or by IP (10-100 mpk/dose) begins anywhere from day 0 to day 29 post tumor cell challenge and generally continues either once or twice a day for the duration of the experiment. Progression of tumor growth is followed by three dimensional caliper measurements and recorded as a function of time. Initial statistical analysis is done by repeated measures analysis of variance (RMANOVA), followed by Scheffe post hoc testing for multiple comparisons. Vehicle alone (captisol, or the like) is the negative control. Compounds of the present invention will be active at 150 mpk.

Human gastric adenocarcinoma tumor cells (MKN45 cells, ATCC) are expanded in culture, harvested and injected subcutaneously into 5-8 week old female nude mice (CD1 nu/nu, Charles River Labs) (n=10). Subsequent administration of compound by oral gavage or by IP (10-100 mpk/dose) begins anywhere from day 0 to day 29 post tumor cell challenge and generally continues either once or twice a day for the duration of the experiment. Progression of tumor growth is followed by three dimensional caliper measurements and recorded as a function of time. Initial statistical analysis is done by repeated measures analysis of variance (RMANOVA), followed by Scheffe post hoc testing for multiple comparisons. Vehicle alone (captisol, or the like) is the negative control. Compounds of the present invention will be active at 150 mpk.

FORMULATIONS

Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of the current invention in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and compositions of the present invention may, for example, be administered orally, mucosally, topically, rectally, pulmonarily such as by inhalation spray, or parentally including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly intrasternally and infusion techniques, in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles.

The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, including humans and other mammals.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. For example, these may contain an amount of active ingredient from about 1 to 2000 mg, preferably from about 1 to 500 mg. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, once again, can be determined using routine methods.

The amount of compounds which are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the type of disease, the severity of the disease, the route and frequency of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. A daily dose of about 0.01 to 500 mg/kg, preferably between about 0.01 and about 50 mg/kg, and more preferably about 0.01 and about 30 mg/kg body weight may be appropriate. The daily dose can be administered in one to four doses per day.

For therapeutic purposes, the active compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose.

In the case of psoriasis and other skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (*e.g.*, liniments, lotions, ointments, creams, or pastes) and drops suitable for administration to the eye, ear, or nose. A suitable topical dose of active ingredient of a compound of the invention is 0.1 mg to 150 mg

administered one to four, preferably one or two times daily. For topical administration, the active ingredient may comprise from 0.001% to 10% w/w, *e.g.*, from 1% to 2% by weight of the formulation, although it may comprise as much as 10% w/w, but preferably not more than 5% w/w, and more preferably from 0.1% to 1% of the formulation.

When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound, which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include DMSO and related analogs.

The compounds of this invention can also be administered by a transdermal device. Preferably transdermal administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier, which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base, which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, sodium lauryl sulfate, glyceryl distearate alone or with a wax, or other materials well known in the art.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a

non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules using one or more of the carriers or diluents mentioned for use in the formulations for oral administration or by using other suitable dispersing or wetting agents and suspending agents. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art. The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water, or with cyclodextrin (ie. Captisol), cosolvent solubilization (ie. propylene glycol) or micellar solubilization (ie. Tween 80).

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-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed 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.

For pulmonary administration, the pharmaceutical composition may be administered in the form of an aerosol or with an inhaler including dry powder aerosol.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene glycols that are

solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. Tablets and pills can additionally be prepared with enteric coatings. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes, which are obvious to one skilled in the art are intended to be within the scope and nature of the invention, which are defined, in the appended claims.

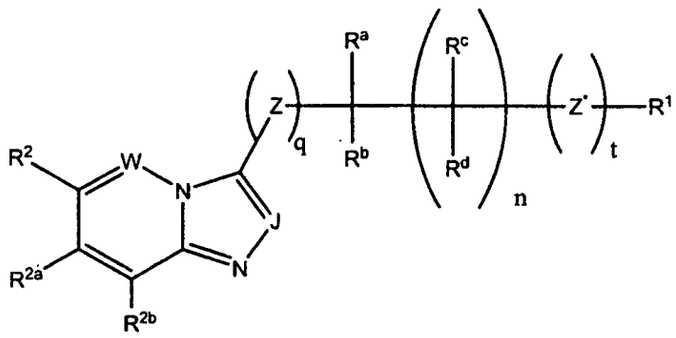
From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

No unacceptable toxological effects are expected when compounds of the present invention are administered in accordance with the present invention.

All mentioned references, patents, applications and publications, are hereby incorporated by reference in their entirety, as if here written.

WE CLAIM:

1. A compound of formula I



I

wherein

J is N or CR^3;

W is CR^{2b} or N;

Z and Z* are independently -O-, $-S(O)_v-$, or $-NR^5-$;

R^a, R^b, R^c and R^d are each independently H, halo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, $-NO_2$, -CN, $-NR^5R^{5a}$, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$; $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-OC(=O)NR^5R^{5a}$, $-S(O)_vR^4$, $-S(O)_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$ any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

or R^a and R^b together with the carbon atom to which they are bonded may combine to form a 3-10 membered cycloalkyl, a 3-10membered cycloalkenyl ring, or a heterocyclo ring, any of which may be optionally substituted with one or more R^{10} groups as allowed by valance.;

or R^c and R^d together with the carbon atom to which they are bonded may combine to form a 3-10 membered cycloalkyl, a 3-10membered cycloalkenyl ring, or a heterocyclo ring, any of which may be optionally substituted with one or more R^{10} groups as allowed by valance;

or R^a and/or R^b may combine with any R^c or R^d to form a partially or fully saturated 3-8 membered cycloalkyl ring or heterocyclo ring, either of which may be optionally substituted with one or more R^{10} groups as allowed by valance;

or R^a and R^b may combine to form a carbonyl group;

or R^c and R^d attached to the same carbon atom may combine to form a carbonyl group;

R^1 is aryl, heteroaryl or heterocyclo any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

R^2 is

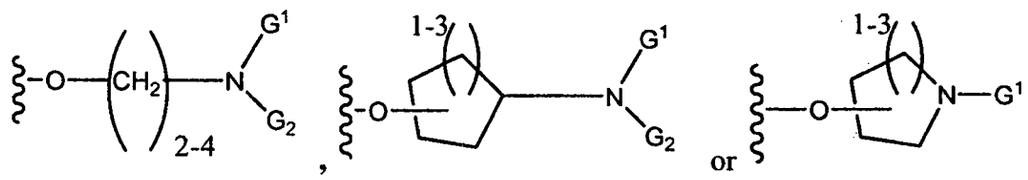
(i) H, halo, cyano, nitro, or

(ii) alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-OR^4$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, any of which may be optionally independently substituted with one or more R^{10} as allowed by valance,

provided that in compounds of formula I when W and J are both N, R^2 is other than

(c) $-NR^5R^{5a}$ where R^5 and R^{5a} are independently H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, and cycloalkylalkyl; and

(d) phenyl substituted with a group



or

where G^1 and G^2 are independently alkyl, cycloalkyl, or G^1 and G^2 together with the nitrogen atom to which they are attached combine to form a 5- to 8-membered heterocyclo ring;

R^{2a}, R^{2b} and R^3 are independently selected at each occurrence from H, halo, cyano, nitro, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-OR^4$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

R^4 is independently selected at each occurrence from H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, and cycloalkylalkyl, any of which may be optionally independently substituted as allowed by valance with one or more R^{10} groups;

R^5 and R^{5a} are independently selected at each occurrence from H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, and cycloalkylalkyl, any of which may be optionally substituted as allowed by valance with one or more R^{10};

or R^5 and R^{5a} may combine to form a heterocyclo ring optionally substituted with one or more R^{10};

R^{10} at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-(alkylene)_m-OR^4$, $-(alkylene)_m-S(O)_vR^4$, $-(alkylene)_m-NR^5R^{5a}$, $-(alkylene)_m-C(=O)R^4$, $-(alkylene)_m-C(=S)R^4$, $-(alkylene)_m-C(=O)OR^4$, $-(alkylene)_m-OC(=O)R^4$, $-(alkylene)_m-C(=S)OR^4$, $-(alkylene)_m-C(=O)NR^5R^{5a}$, $-(alkylene)_m-C(=S)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=S)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)R^4$, $-(alkylene)_m-N(R^5)C(=S)R^4$, $-(alkylene)_m-OC(=O)NR^5R^{5a}$, $-(alkylene)_m-OC(=S)NR^5R^{5a}$, $-(alkylene)_m-SO_2NR^5R^{5a}$, $-(alkylene)_m-N(R^5)SO_2R^4$, $-(alkylene)_m-N(R^5)SO_2NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)OR^4$, $-(alkylene)_m-N(R^5)C(=S)OR^4$, or $-(alkylene)_m-N(R^5)SO_2R^4$;

wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more $-(alkylene)_m-OR^4$, $-(alkylene)_m-S(O)_vR^4$, $-(alkylene)_m-NR^5R^{5a}$, $-(alkylene)_m-C(=O)R^4$, $-(alkylene)_m-C(=S)R^4$, $-(alkylene)_m-C(=O)OR^4$, $-(alkylene)_m-OC(=O)R^4$, $-(alkylene)_m-C(=S)OR^4$, $-(alkylene)_m-C(=O)NR^5R^{5a}$, $-(alkylene)_m-C(=S)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=S)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)R^4$, $-(alkylene)_m-N(R^5)C(=S)R^4$, $-(alkylene)_m-OC(=O)NR^5R^{5a}$, $-(alkylene)_m-OC(=S)NR^5R^{5a}$, $-(alkylene)_m-SO_2NR^5R^{5a}$, $-(alkylene)_m-N(R^5)SO_2R^4$, $-(alkylene)_m-N(R^5)SO_2NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)OR^4$, $-(alkylene)_m-N(R^5)C(=S)OR^4$, or $-(alkylene)_m-N(R^5)SO_2R^4$;

and further wherein any two R^{10} groups attached to the same atom or attached to adjacent atoms may combine to form an optionally substituted 3- to 8 membered ring system;

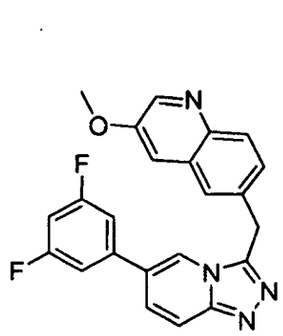
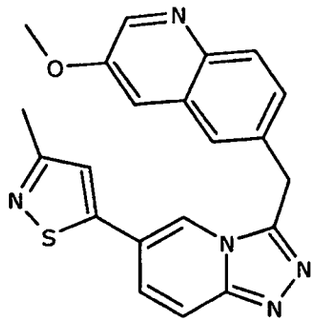
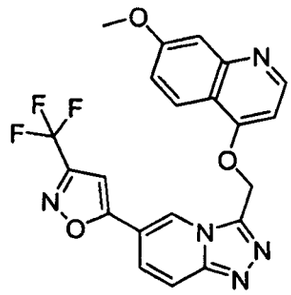
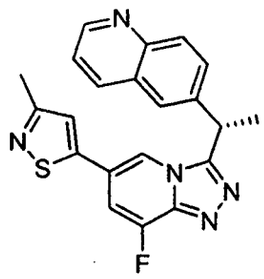
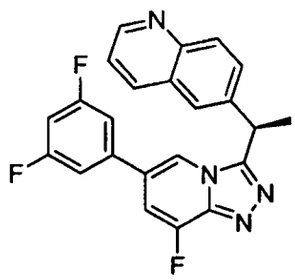
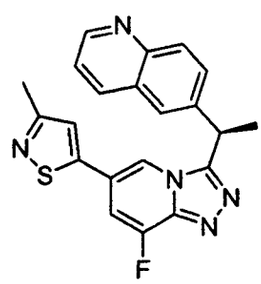
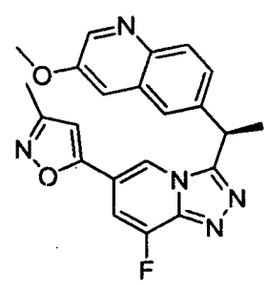
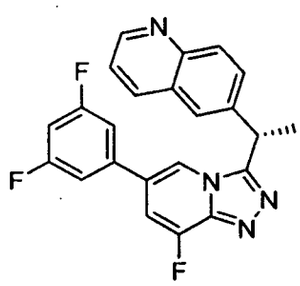
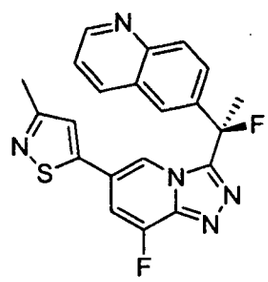
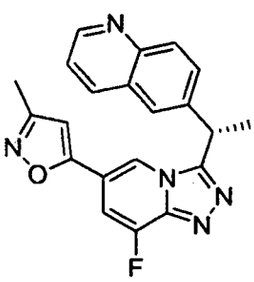
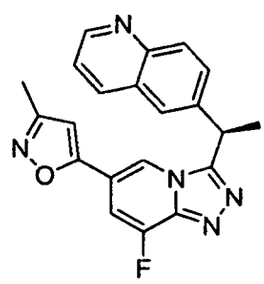
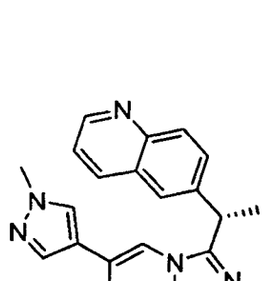
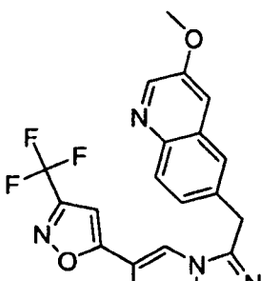
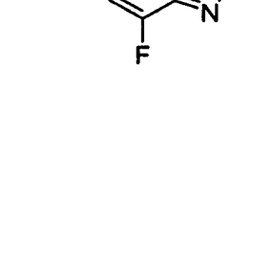
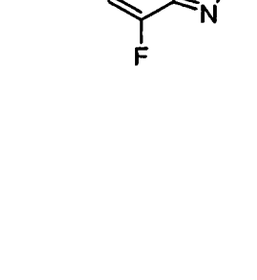
m is 0 or 1;

n is 0, 1 or 2;

q and t are each independently 0 or 1;

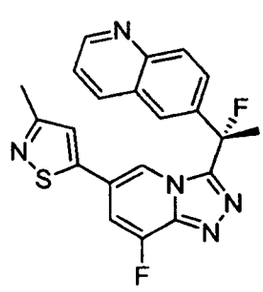
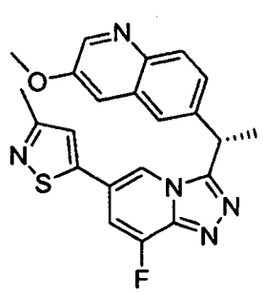
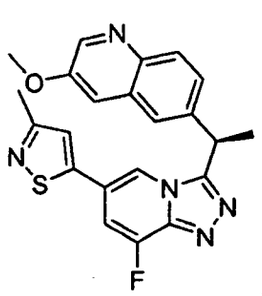
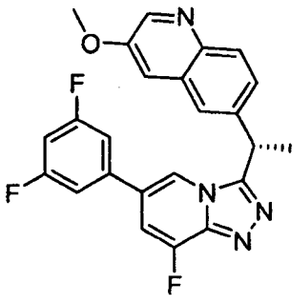
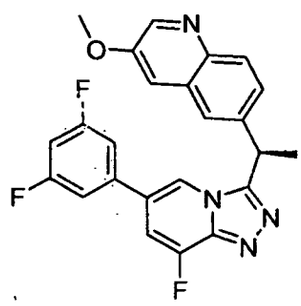
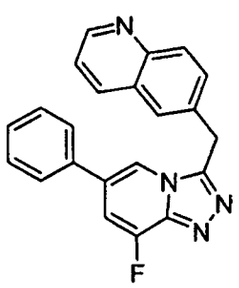
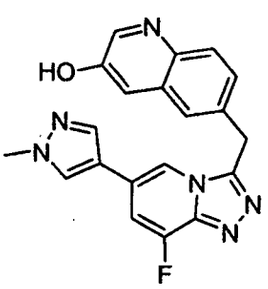
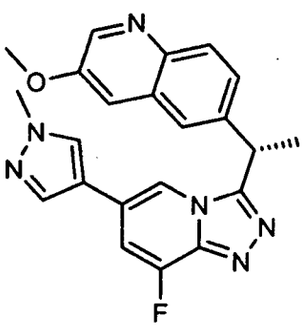
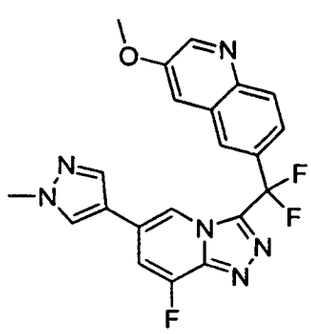
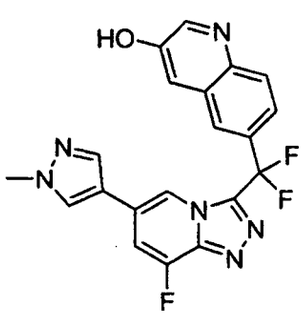
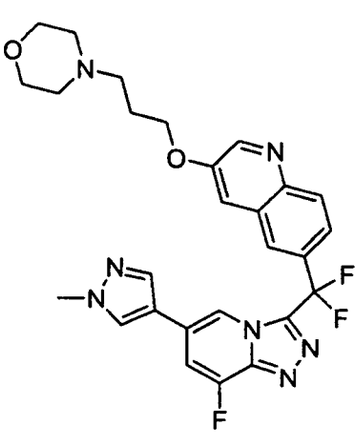
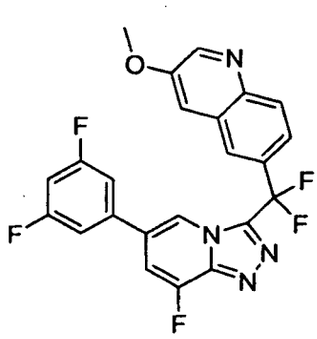
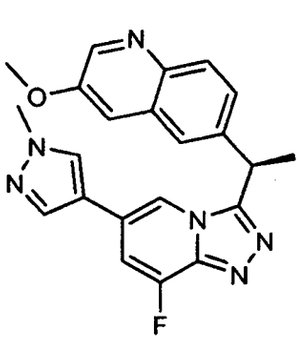
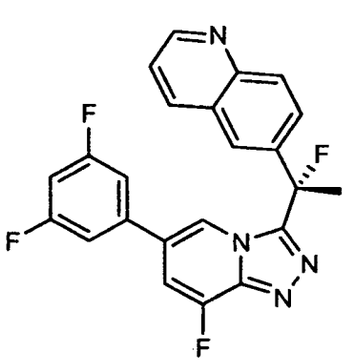
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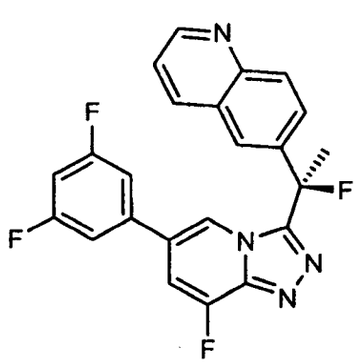
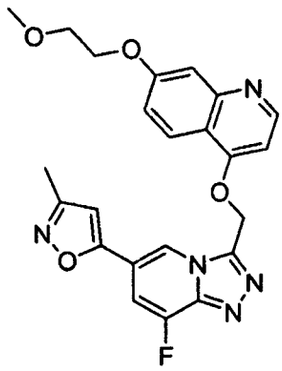
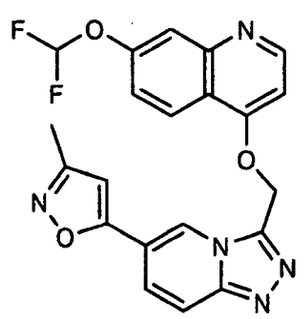
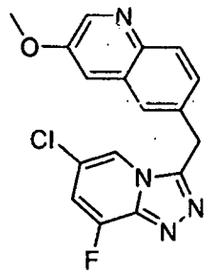
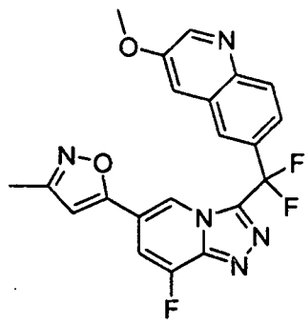
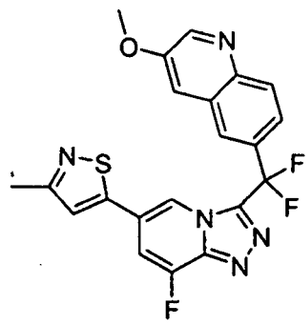
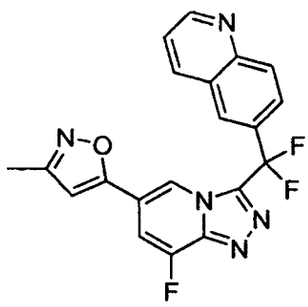
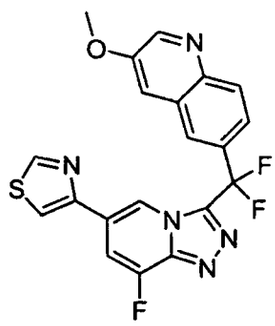
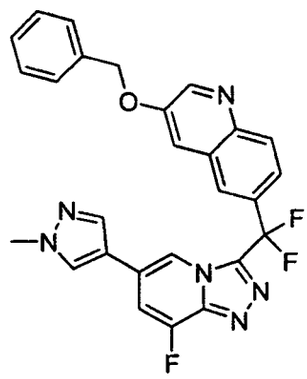
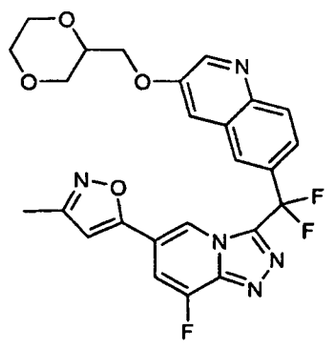
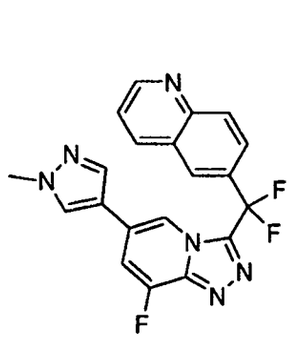
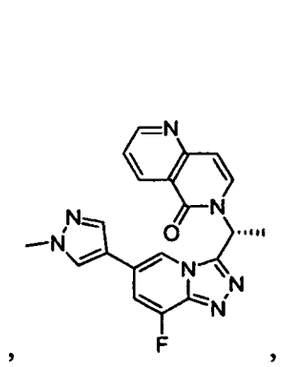
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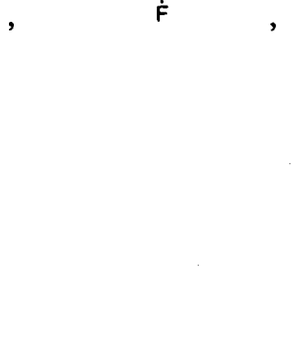
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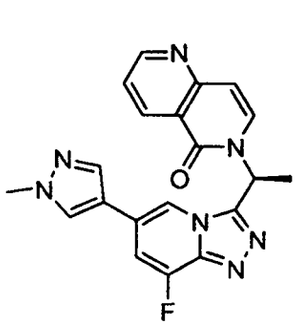
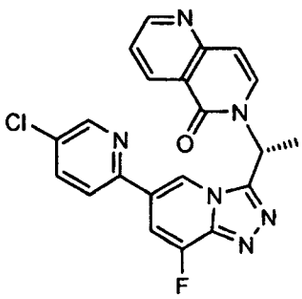
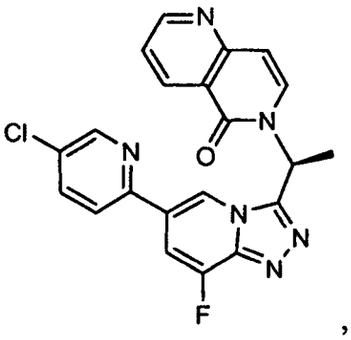
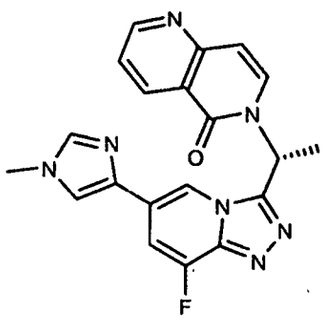
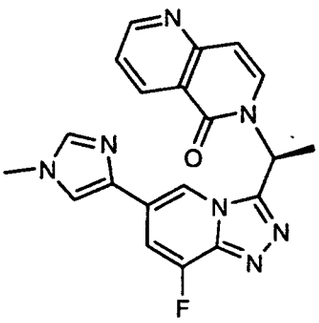
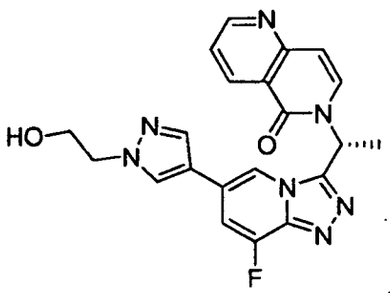
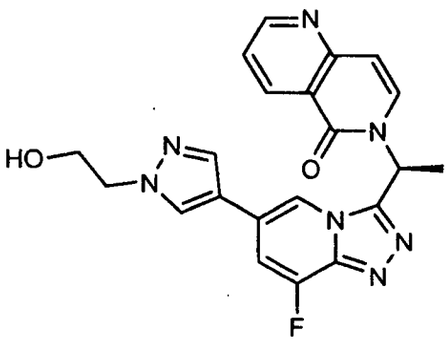
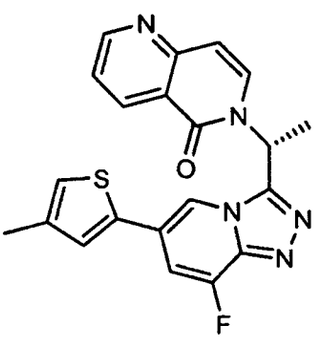
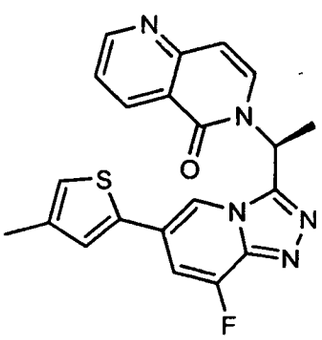
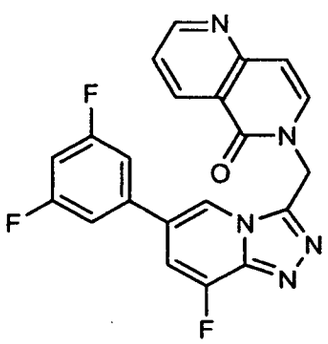
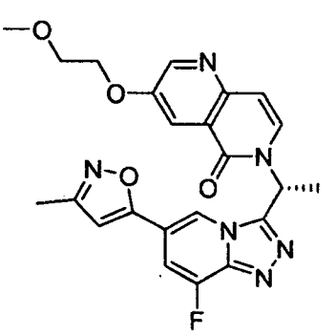
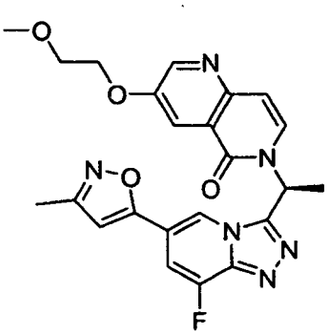
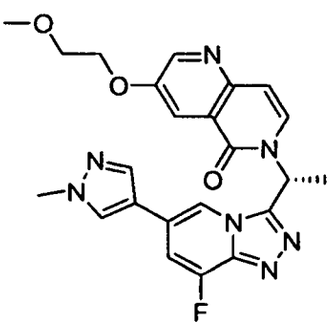
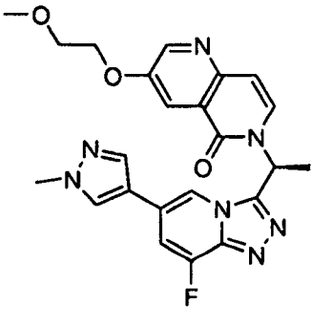
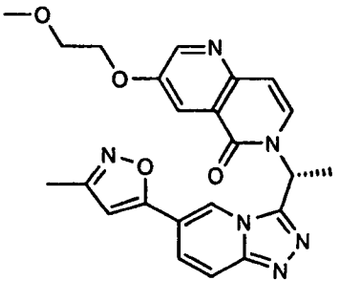
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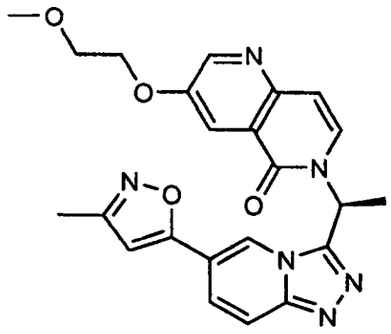
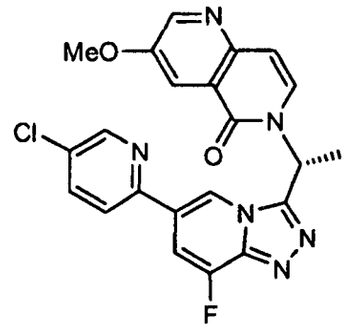
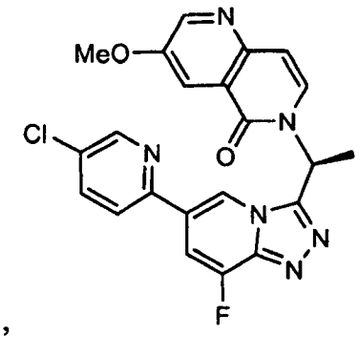
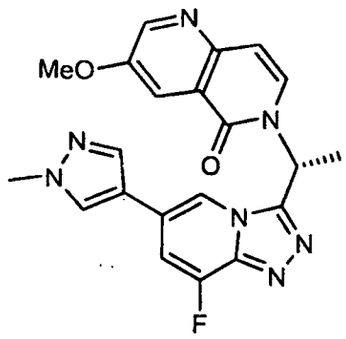
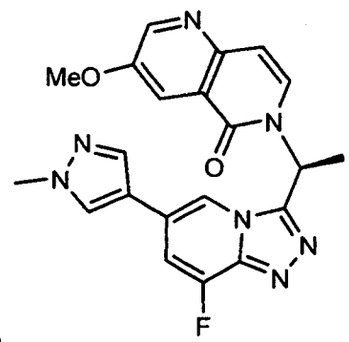
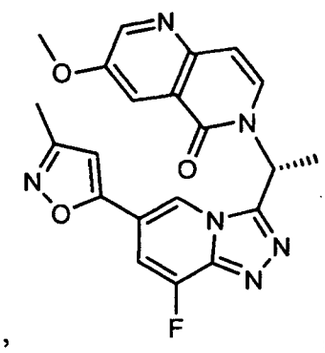
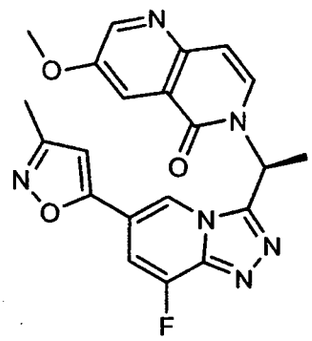
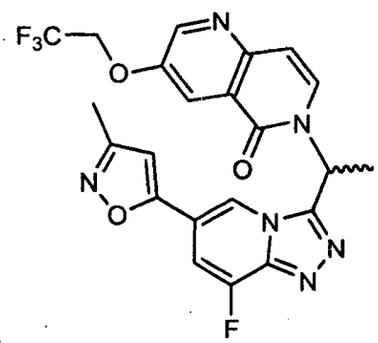
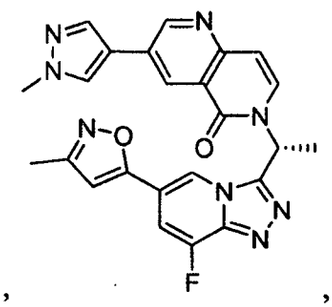
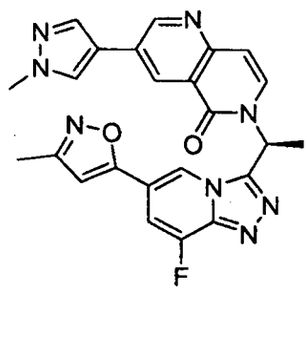
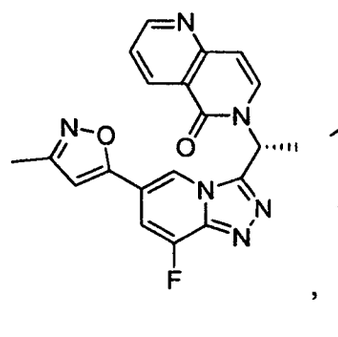
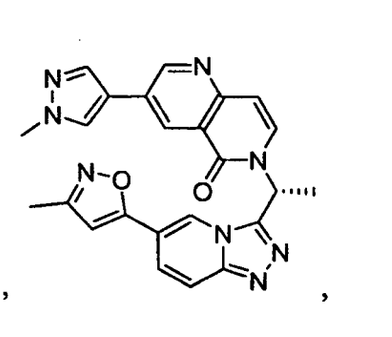

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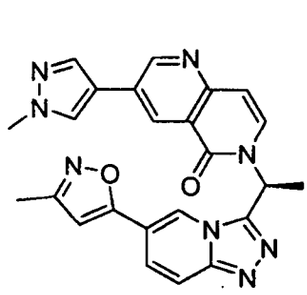
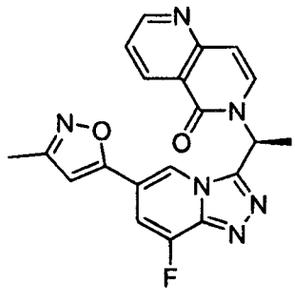
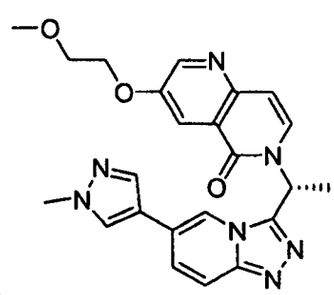
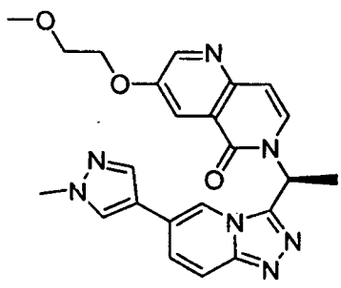

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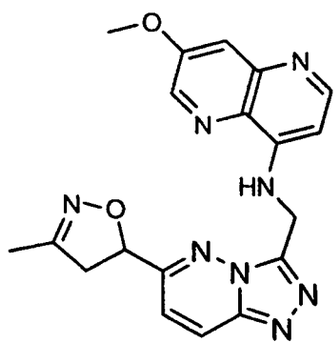
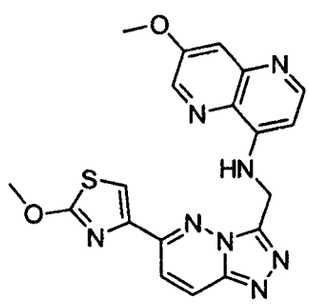
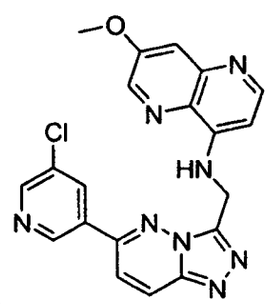
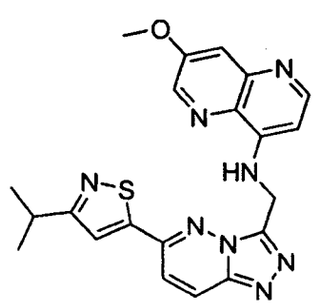
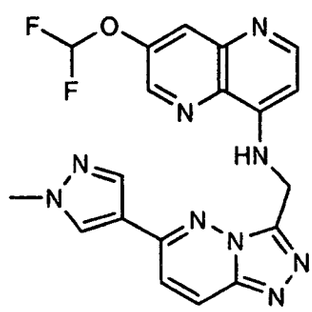
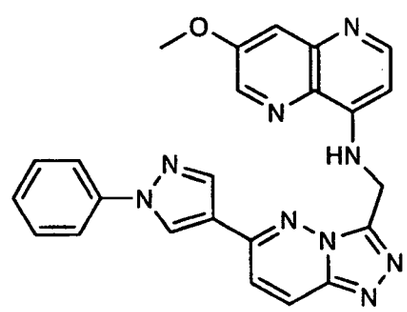
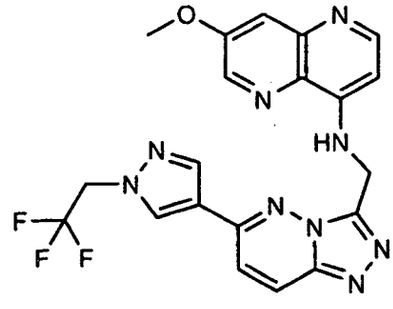
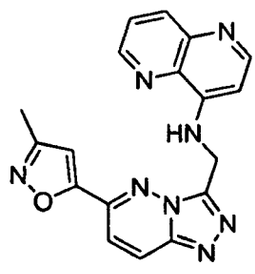
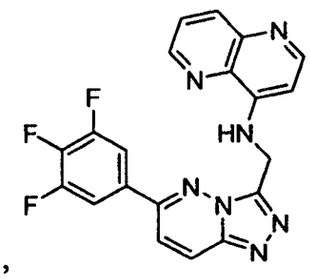
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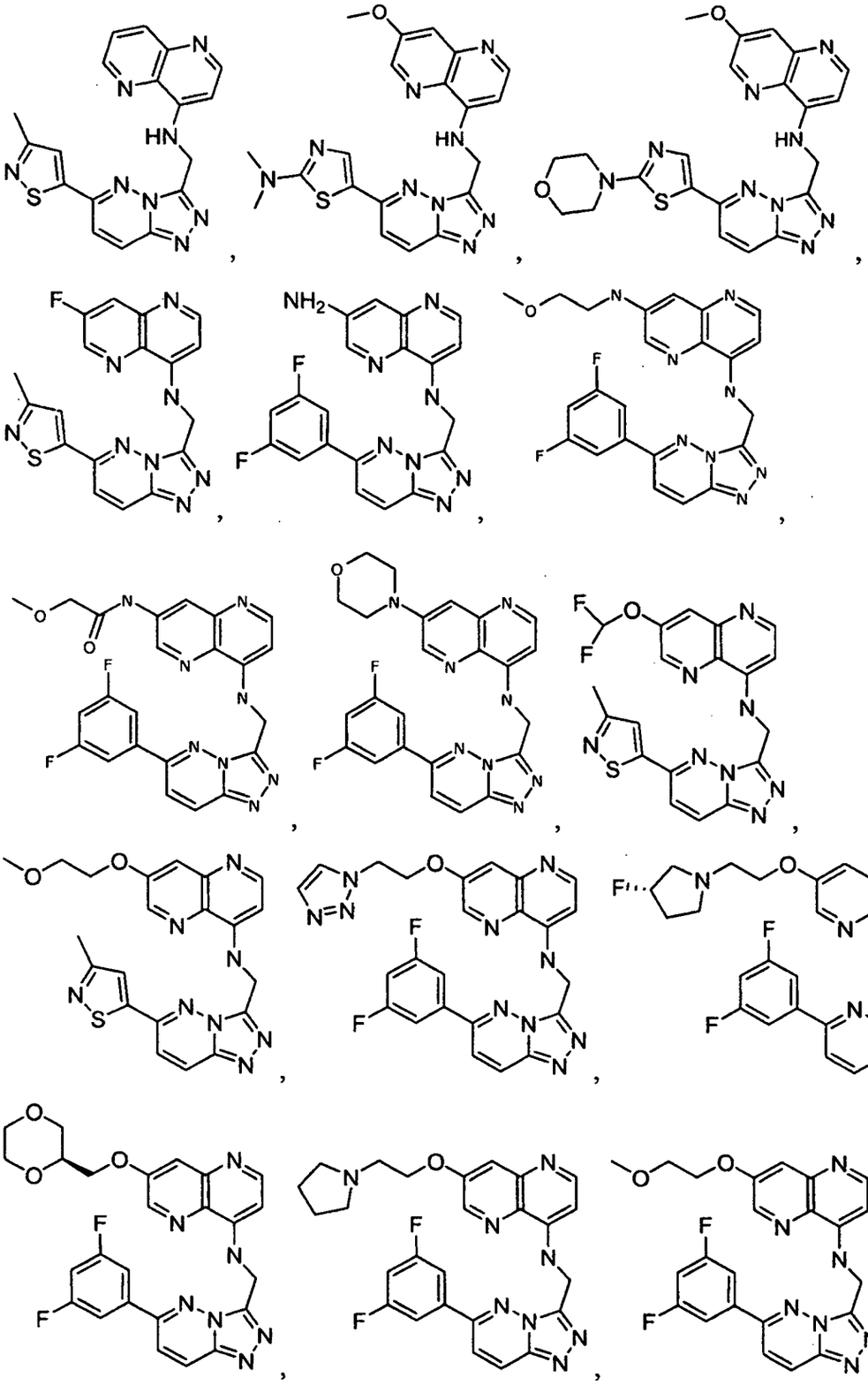
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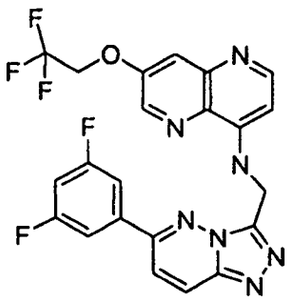
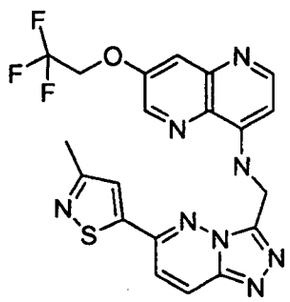
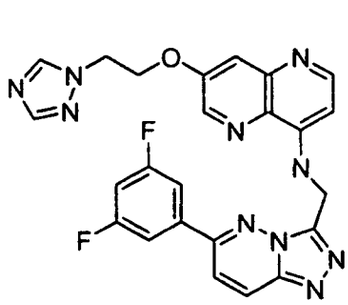
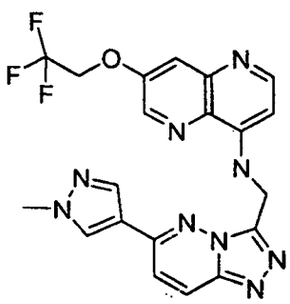
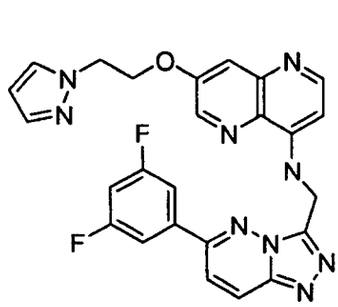
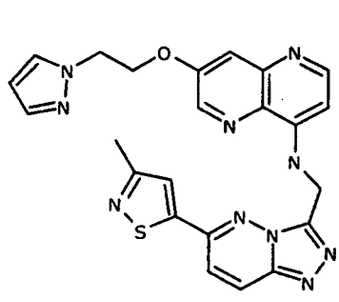
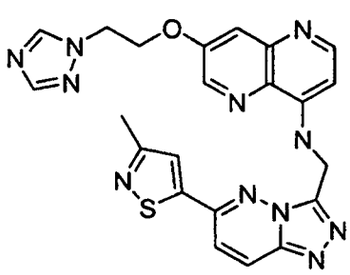
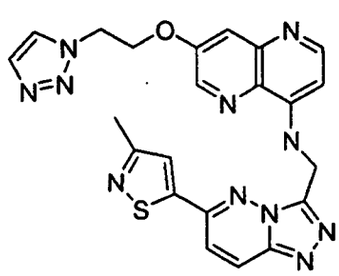
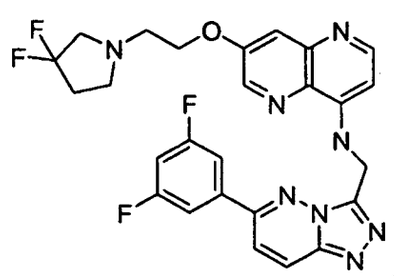
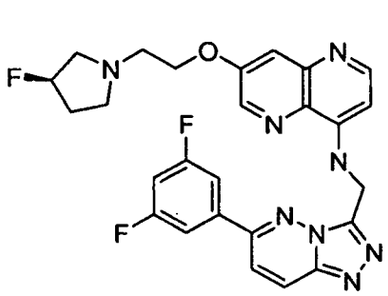
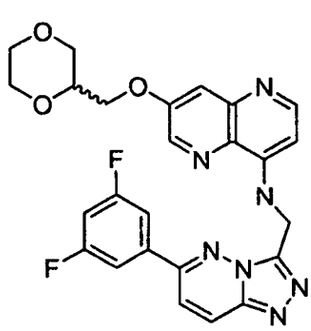
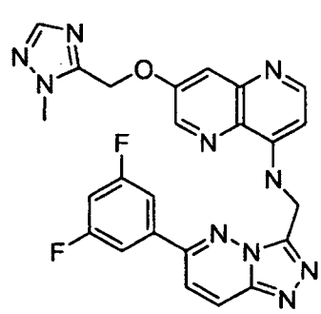
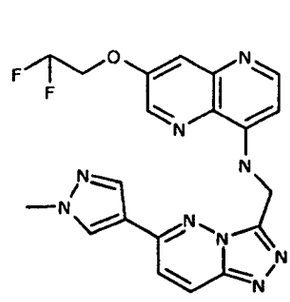
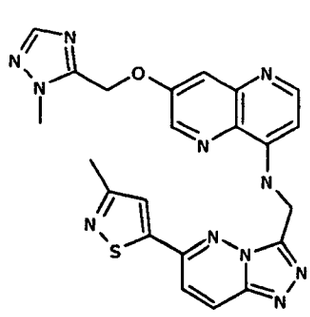
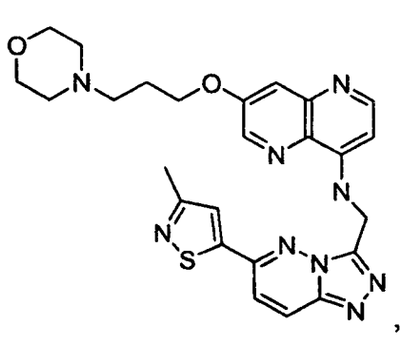

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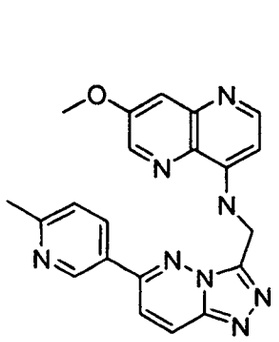
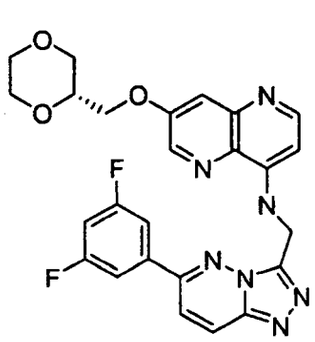
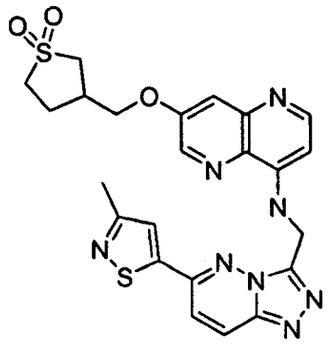
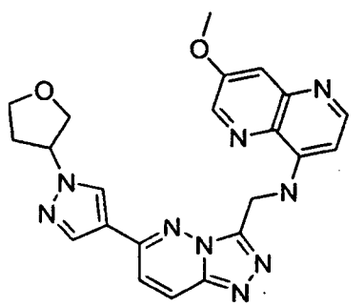
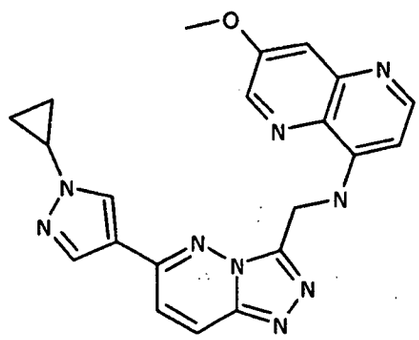
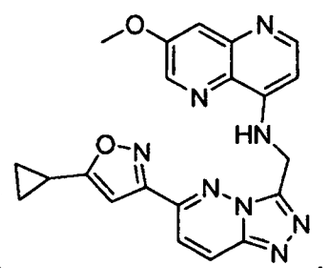
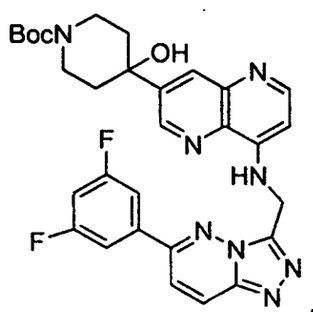
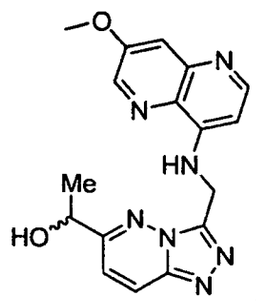
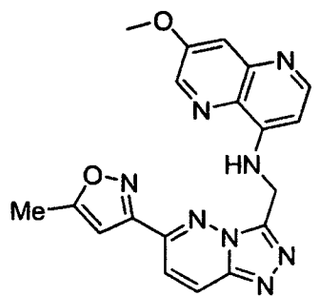
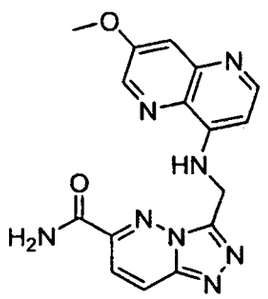
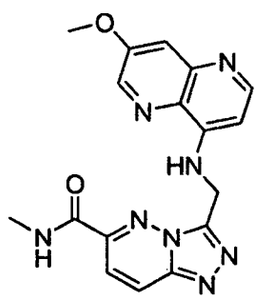
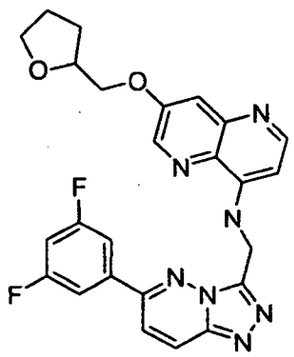
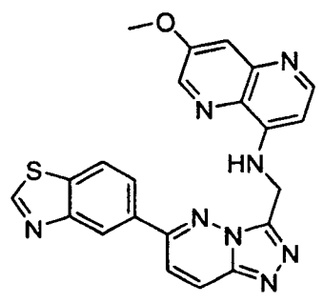
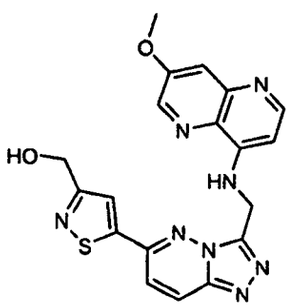
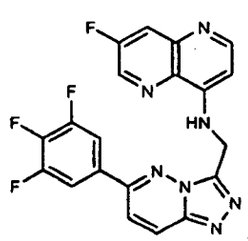
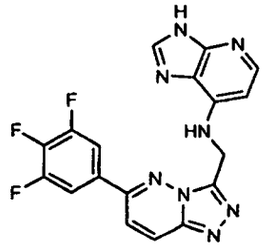

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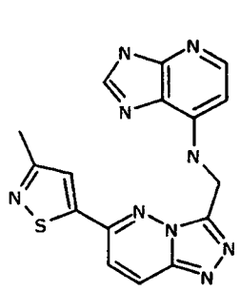
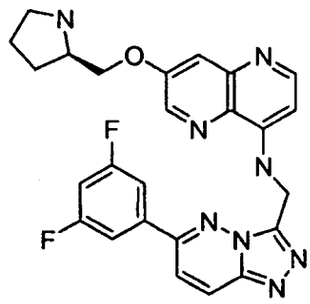
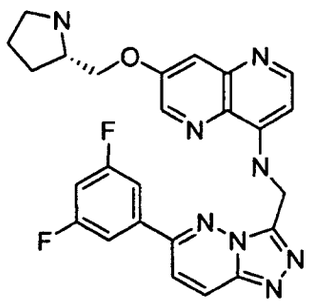
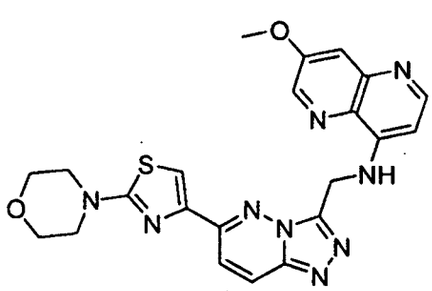
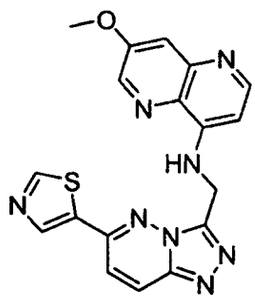
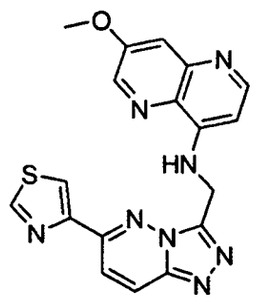
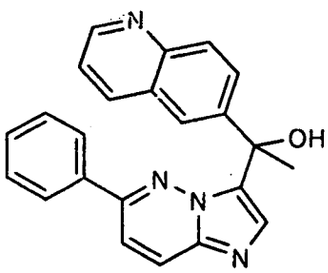
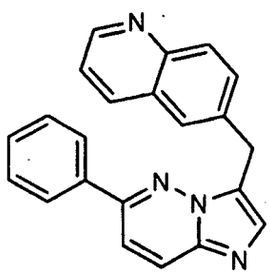
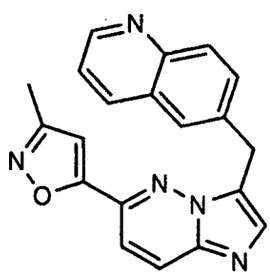
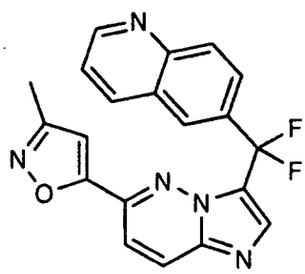
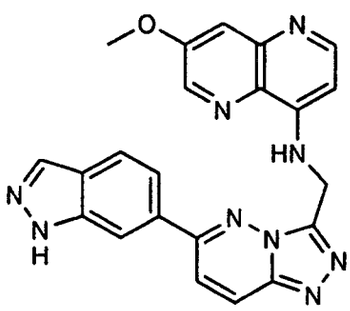
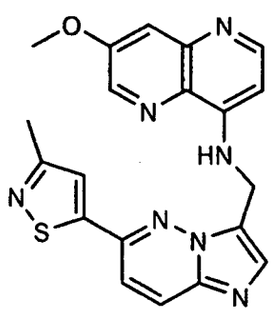
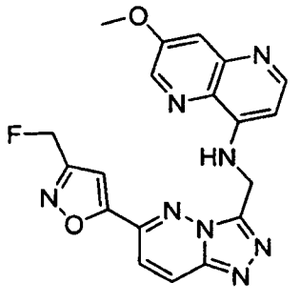
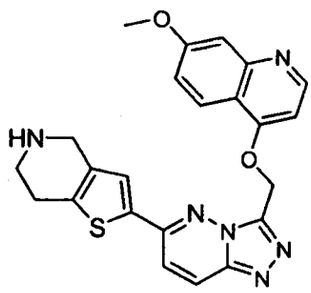
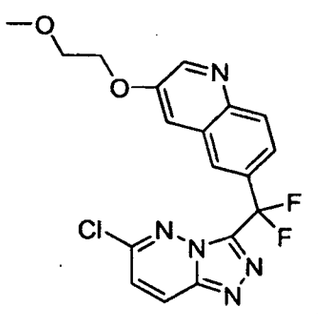

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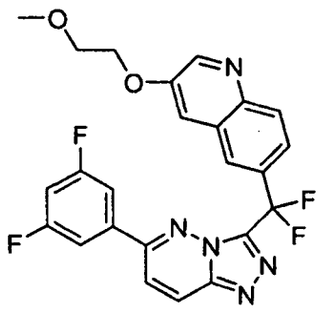
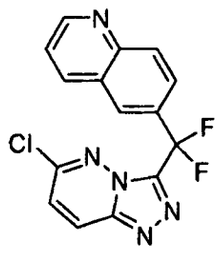
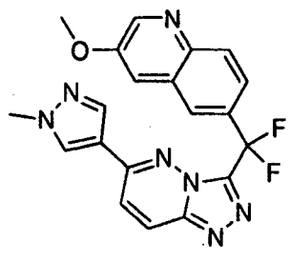
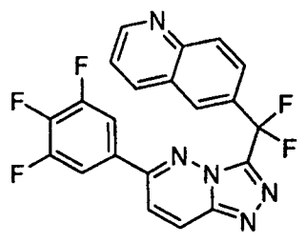
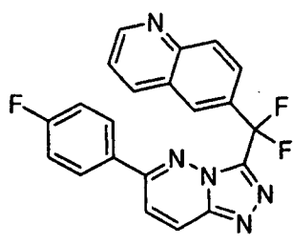
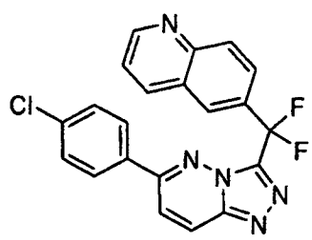
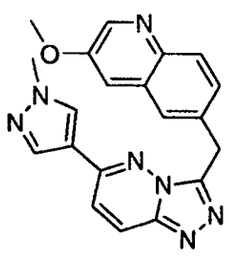
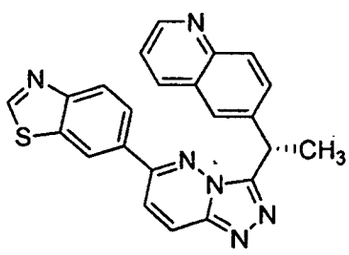
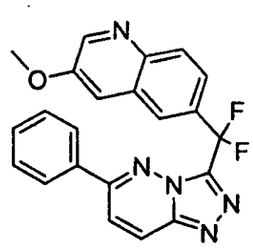
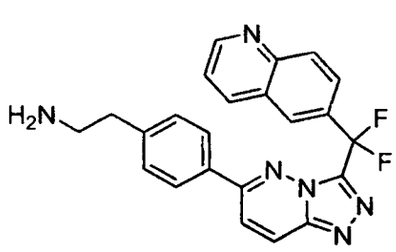
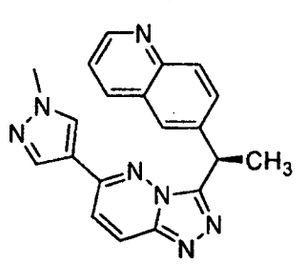
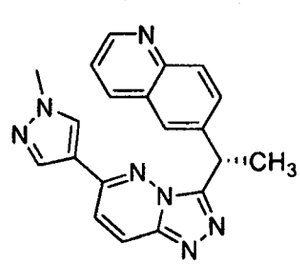
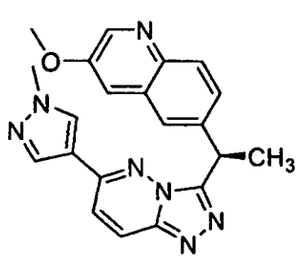
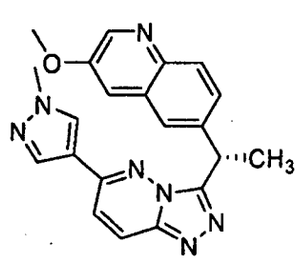
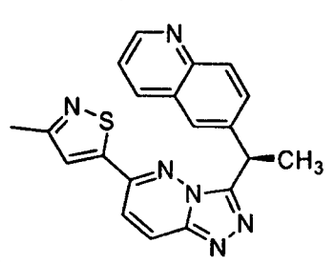
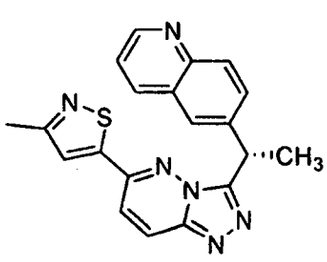
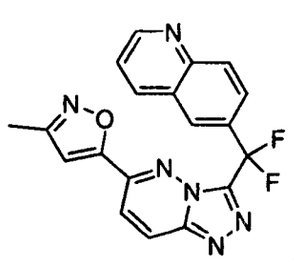
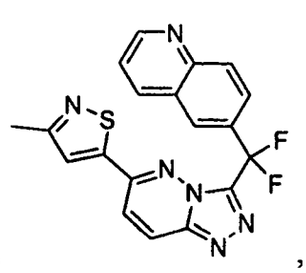


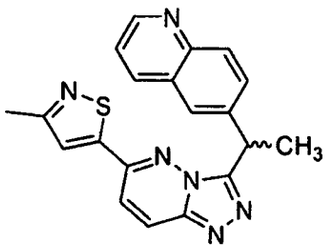
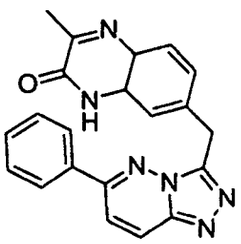
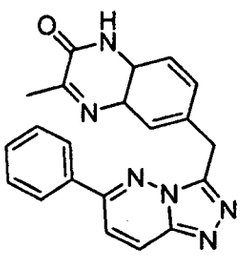
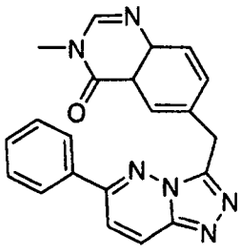
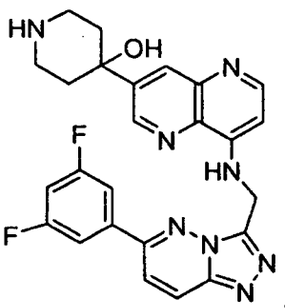
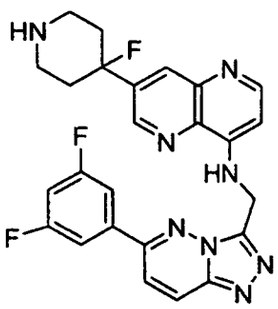
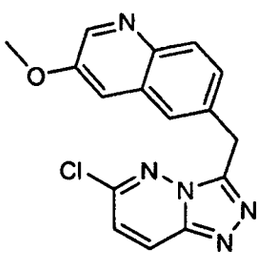
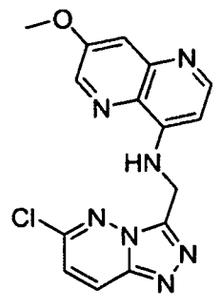
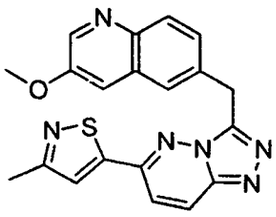

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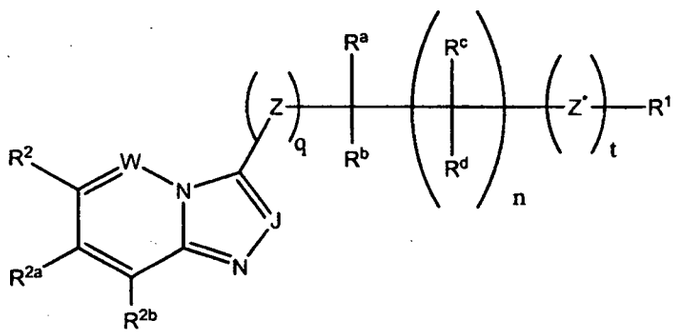

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and salts thereof.

2. A compound of Formula I



I

enantiomers, diastereomers, salts and solvates thereof wherein

J is N or CR^3;

W is CR^{2b} or N;

Z and Z* are independently -O-, $-S(O)_v-$, or $-NR^5-$;

q is 0;

R^a, R^b, R^c and R^d are each independently H, halo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, $-NO_2$, -CN, $-NR^5R^{5a}$, $-OR^4$,

$-C(=O)R^4$, $-C(=O)OR^4$; $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-OC(=O)NR^5R^{5a}$, $-S(O)_vR^4$, $-S(O)_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$ any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

or R^a and R^b together with the carbon atom to which they are bonded may combine to form a 3-10 membered cycloalkyl, a 3-10membered cycloalkenyl ring, or a heterocyclo ring, any of which may be optionally substituted with one or more R^{10} groups as allowed by valance.;

or R^c and R^d together with the carbon atom to which they are bonded may combine to form a 3-10 membered cycloalkyl, a 3-10membered cycloalkenyl ring, or a heterocyclo ring, any of which may be optionally substituted with one or more R^{10} groups as allowed by valance;

or R^a and/or R^b may combine with any R^c or R^d to form a partially or fully saturated 3-8 membered cycloalkyl ring or heterocyclo ring, either of which may be optionally substituted with one or more R^{10} groups as allowed by valance;

or R^a and R^b may combine to form a carbonyl group;

or R^c and R^d attached to the same carbon atom may combine to form a carbonyl group;

R^1 is an oxo-substituted heteroaryl or oxo-substituted heterocyclo selected from naphthyridinonyl, dihydronaphthyridinonyl, pyridopyrimidinonyl, dihydropyridopyrimidinonyl, imidazopyridinonyl, dihydroimidazopyridinonyl, oxazolopyridinonyl, dihydrooxazolopyridinonyl, thiazolopyridinonyl, dihydrothiazolopyridinonyl, pyrazolopyrazinonyl, dihydropyrazolopyrazinonyl, triazolopyrazinonyl, dihydrotriazolopyrazinonyl, triazolopyridinonyl or dihydrotriazolopyridinonyl any of which may be optionally further independently substituted with one or more R^{10} groups as allowed by valance.

R^2 is

(i) H, halo, cyano, nitro, or

(ii) alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-OR^4$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, any of which may be optionally independently substituted with one or more R^{10} as allowed by valance,

R^{2a}, R^{2b} and R^3 are independently selected at each occurrence from H, halo, cyano, nitro, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-OR^4$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

R^4 is independently selected at each occurrence from H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, and cycloalkylalkyl, any of which may be optionally independently substituted as allowed by valance with one or more R^{10} groups;

R^5 and R^{5a} are independently selected at each occurrence from H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, and cycloalkylalkyl, any of which may be optionally substituted as allowed by valance with one or more R^{10};

or R^5 and R^{5a} may combine to form a heterocyclo ring optionally substituted with one or more R^{10};

R^{10} at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-(alkylene)_m-OR^4$, $-(alkylene)_m-S(O)_vR^4$, $-(alkylene)_m-NR^5R^{5a}$, $-(alkylene)_m-C(=O)R^4$, $-(alkylene)_m-C(=S)R^4$, $-(alkylene)_m-C(=O)OR^4$, $-(alkylene)_m-OC(=O)R^4$, $-(alkylene)_m-C(=S)OR^4$, $-(alkylene)_m-C(=O)NR^5R^{5a}$, $-(alkylene)_m-C(=S)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=S)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)R^4$, $-(alkylene)_m-N(R^5)C(=S)R^4$, $-(alkylene)_m-OC(=O)NR^5R^{5a}$, $-(alkylene)_m-OC(=S)NR^5R^{5a}$, $-(alkylene)_m-SO_2NR^5R^{5a}$, $-(alkylene)_m-N(R^5)SO_2R^4$, $-(alkylene)_m-N(R^5)SO_2NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)OR^4$, $-(alkylene)_m-N(R^5)C(=S)OR^4$, or $-(alkylene)_m-N(R^5)SO_2R^4$;

wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more $-(alkylene)_m-OR^4$, $-(alkylene)_m-S(O)_vR^4$, $-(alkylene)_m-NR^5R^{5a}$, $-(alkylene)_m-C(=O)R^4$,

-(alkylene)$_m$-C(=S)R^4, -(alkylene)$_m$-C(=O)OR^4, -(alkylene)$_m$-OC(=O)R^4, -(alkylene)$_m$-C(=S)OR^4, —(alkylene)$_m$-C(=O)NR^5R^{5a}, -(alkylene)$_m$-C(=S)NR^5R^{5a}, -(alkylene)$_m$-N(R^5)C(=O)NR^5R^{5a}, -(alkylene)$_m$-N(R^5)C(=S)NR^5R^{5a}, -(alkylene)$_m$-N(R^5)C(=O)R^4, -(alkylene)$_m$-N(R^5)C(=S)R^4, -(alkylene)$_m$-OC(=O)NR^5R^{5a}, -(alkylene)$_m$-OC(=S)NR^5R^{5a}, -(alkylene)$_m$-$SO_2NR^5R^{5a}$, -(alkylene)$_m$-N(R^5)SO_2R^4, -(alkylene)$_m$-N(R^5)$SO_2NR^5R^{5a}$, -(alkylene)$_m$-N(R^5)C(=O)OR^4, -(alkylene)$_m$-N(R^5)C(=S)OR^4, or -(alkylene)$_m$-N(R^5)SO_2R^4;

and further wherein any two R^{10} groups attached to the same atom or attached to adjacent atoms may combine to form an optionally substituted 3- to 8 membered ring system;

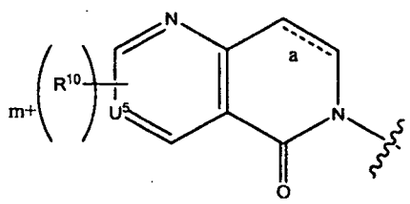
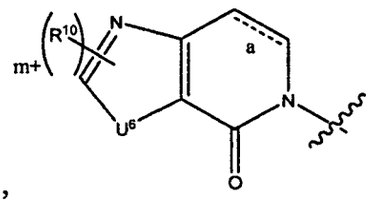
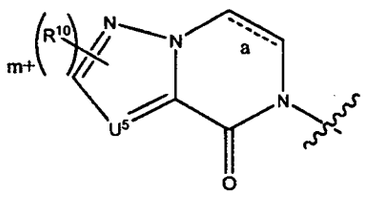
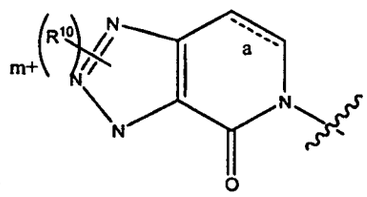
m is 0 or 1;

n is 0, 1 or 2;

t is 0 or 1;

v is 0, 1 or 2.

3. A compound of claim 2 wherein R^1 is

, or

a is a bond or is absent;

U^5 is C or N;

U^6 is NH, O or S;

m+ is 0, 1, 2 or 3 .

4. A compound of claim 2 wherein R^2 is H, halo, cyano, alkynyl, -C(=O)NR^5R^{5a}, -N(R^5)C(=O)R^4, -N(R^5)C(=O)OR^4, phenyl, naphthyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, tetrahydropyridinyl, pyridinonyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, indolinyl, indolinonyl, isoidolinyl, isoindolinonyl, dihydrobenzofuranyl,

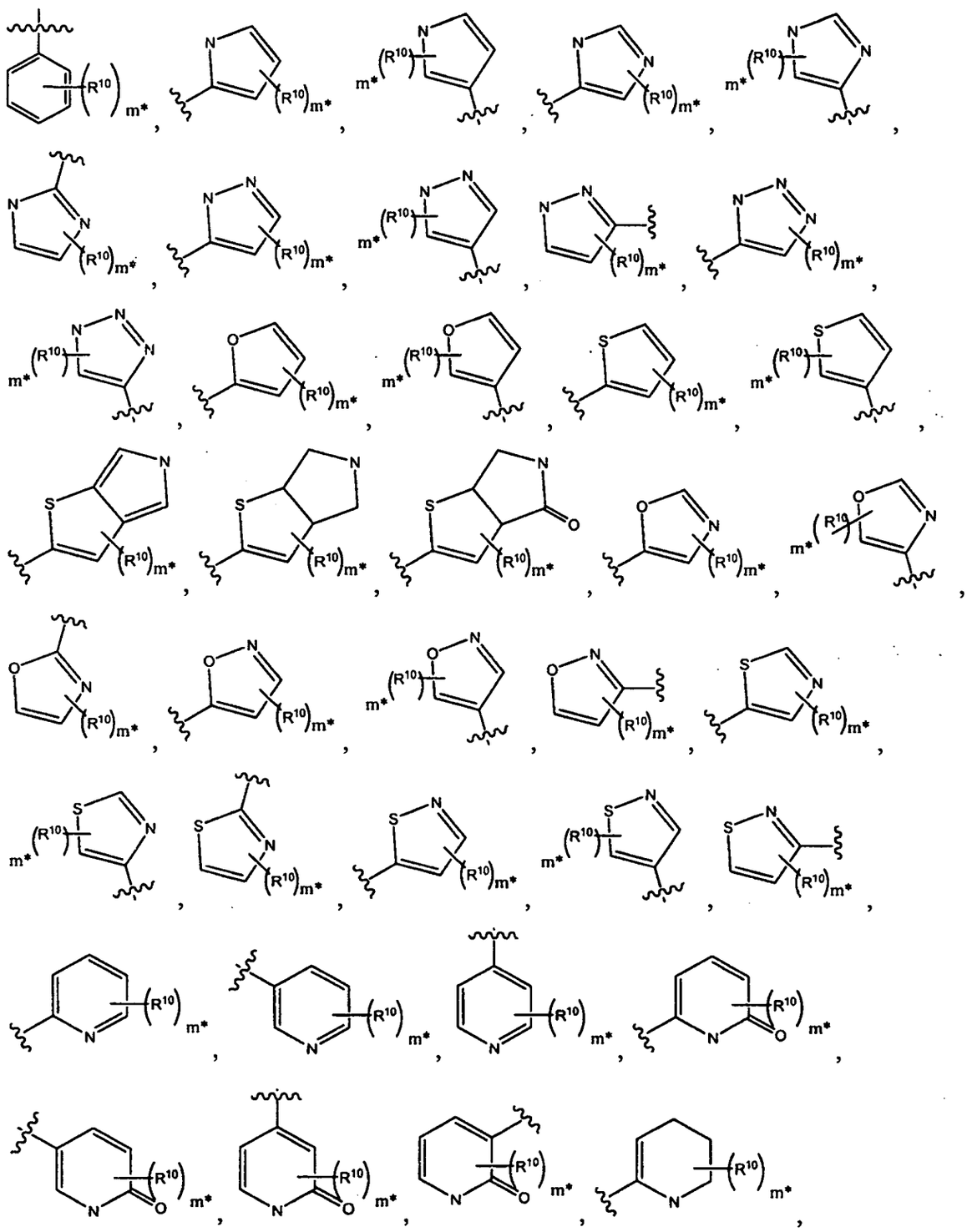
dihydroisobenzofuranyl, benzofuranyl, isobenzofuranyl, quinolinyl, isoquinolinyl, quinazolinyl, quinazolinonyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, quinoxalinyl, tetrahydroquinoxalinyl, benzomorpholinyl, dihydrobenzodioxinyl, imidazopyridinyl, naphthyridinyl, benzotriazinyl, triazolopyridinyl, triazolopyrimidinyl, triazolopyridazinyl, imidazopyridinyl, imidazopyrimidinyl, imidazopyridazinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, pyrrolopyridazinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrazolopyridazinyl, cinnolinyl, thienopyrrolyl, tetrahydrothienopyrrolyl, dihydrothienopyrrolonyl, thienopyridinyl, thienopyrimidinyl, thienopyridazinyl, furopyridinyl, furopyrimidinyl, furopyrazidinyl, benzofuranyl, benzoimidazolyl, benzoisoxazolyl, benzothiazolyl, or benzoisothiazolyl any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance.

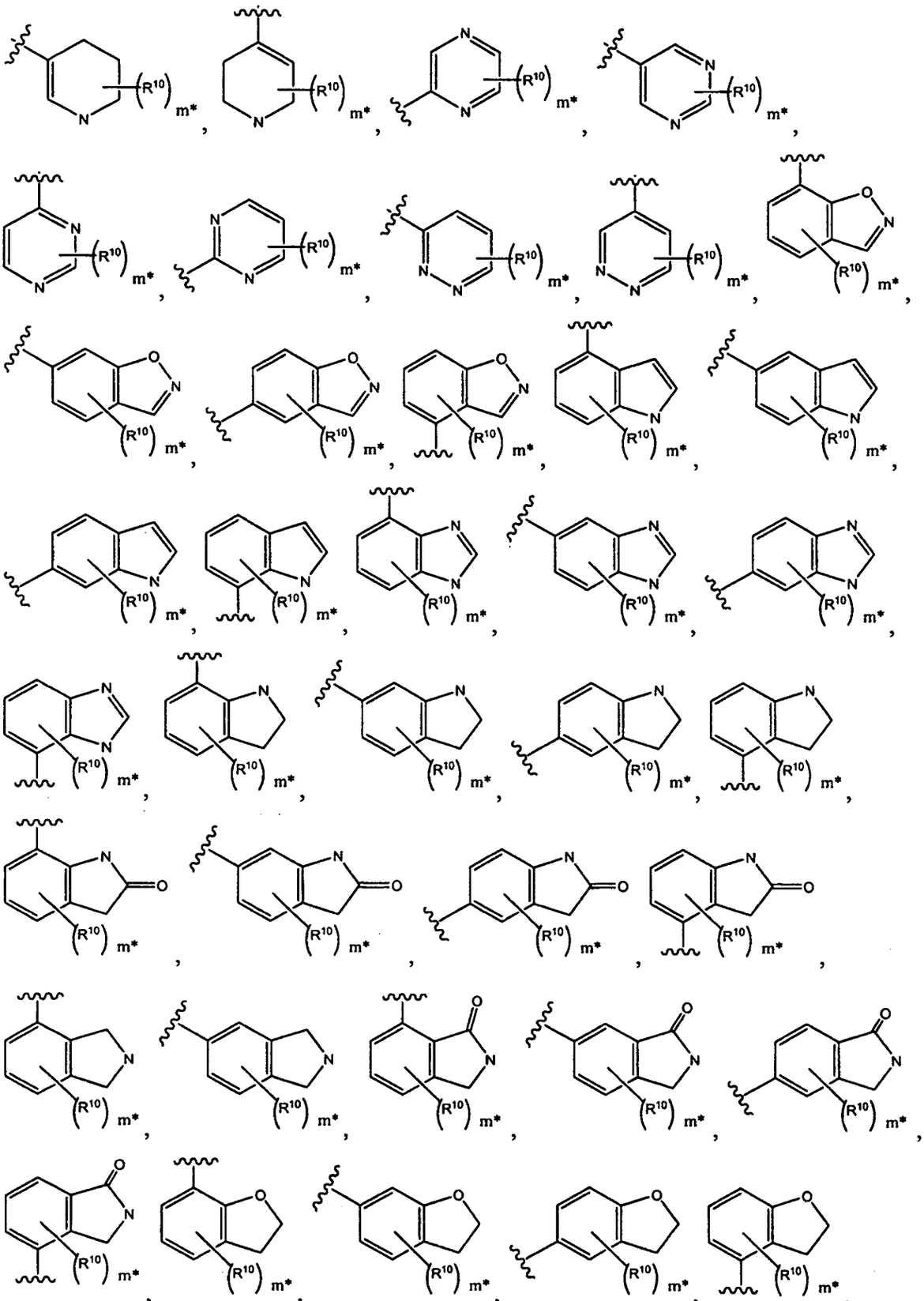
5. A compound of claim 3 wherein R^2 is H, halo, cyano, alkynyl, $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=O)OR^4$, phenyl, naphthyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, tetrahydropyridinyl, pyridinonyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, indolinyl, indolinonyl, isoidolinyl, isoindolinonyl, dihydrobenzofuranyl, dihydroisobenzofuranyl, benzofuranyl, isobenzofuranyl, quinolinyl, isoquinolinyl, quinazolinyl, quinazolinonyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, quinoxalinyl, tetrahydroquinoxalinyl, benzomorpholinyl, dihydrobenzodioxinyl, imidazopyridinyl, naphthyridinyl, benzotriazinyl, triazolopyridinyl, triazolopyrimidinyl, triazolopyridazinyl, imidazopyridinyl, imidazopyrimidinyl, imidazopyridazinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, pyrrolopyridazinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrazolopyridazinyl, cinnolinyl, thienopyrrolyl, tetrahydrothienopyrrolyl, dihydrothienopyrrolonyl, thienopyridinyl, thienopyrimidinyl, thienopyridazinyl, furopyridinyl, furopyrimidinyl, furopyrazidinyl, benzofuranyl, benzoimidazolyl, benzoisoxazolyl, benzothiazolyl, or benzoisothiazolyl any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance.

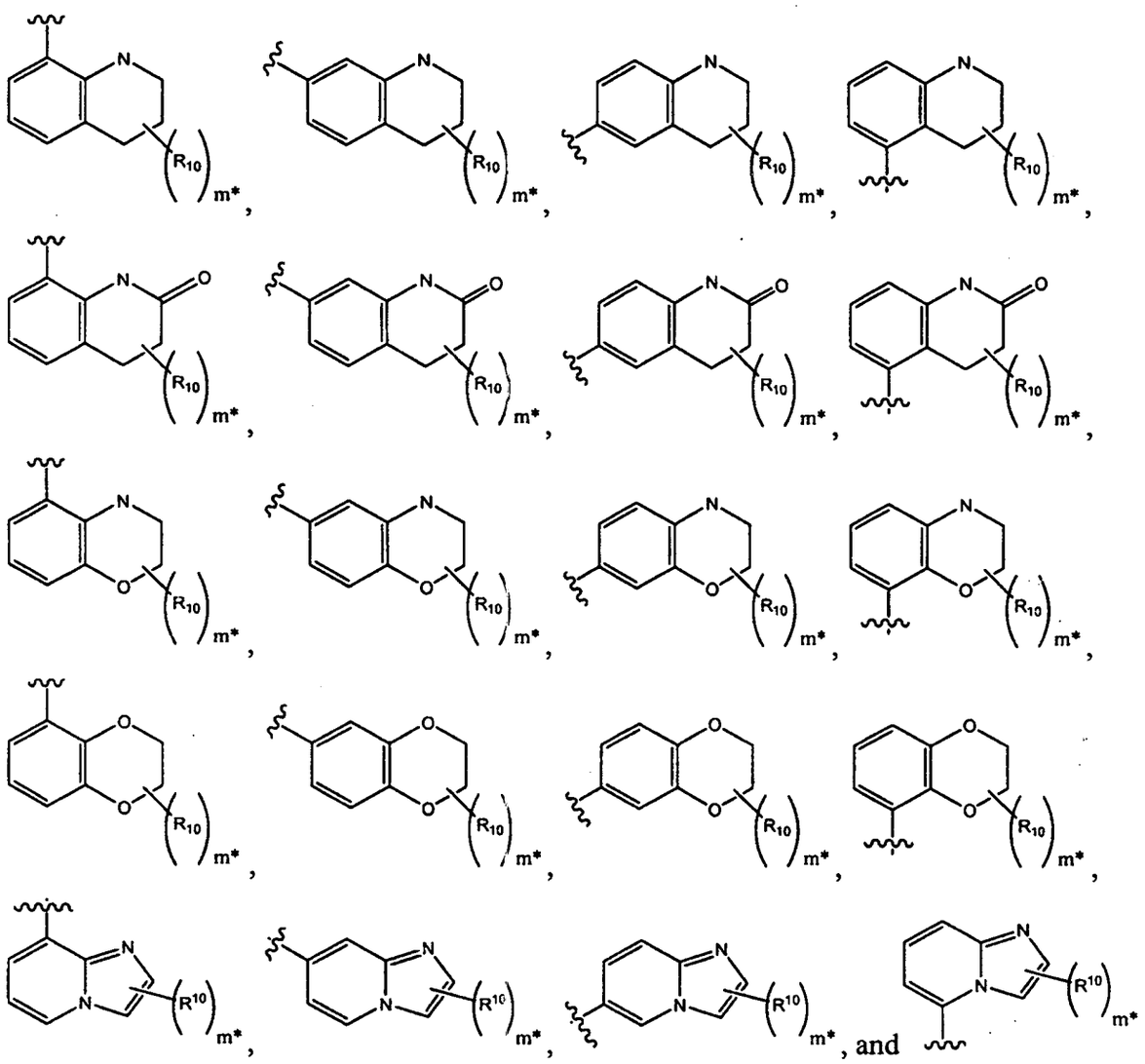
6. A compound of claim 5 wherein R^2 is

(a) halo, alkynyl, $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$ or $-N(R^5)C(=O)OR^4$ any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance; or

(b) an aryl, heteroaryl or heterocyclo ring system selected from

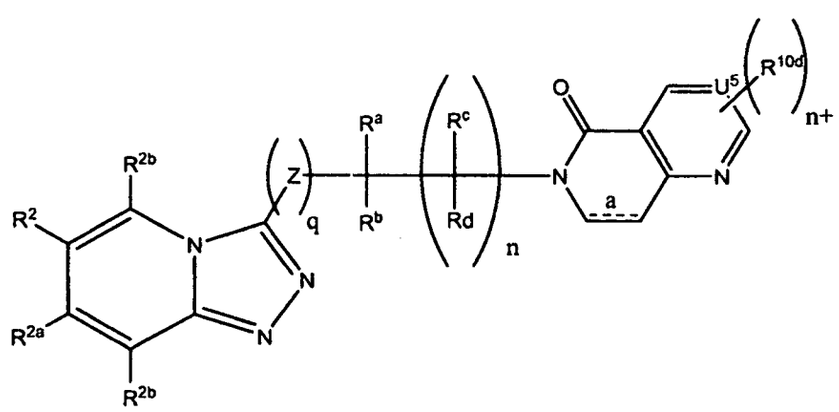






where m* is 0, 1, 2, 3, 4, 5 or 6, as allowed by valence.

7. A compound having the following formula IJ



IJ

a is a bond or is absent;

U^5 is C or N;

Z is -O-, $-S(O)_v-$, or $-NR^5-$;

R^a, R^b, R^c and R^d are each independently H, halo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, $-NO_2$, -CN, $-NR^5R^{5a}$, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$; $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-OC(=O)NR^5R^{5a}$, $-S(O)_vR^4$, $-S(O)_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$ any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

or R^a and R^b together with the carbon atom to which they are bonded may combine to form a 3-10 membered cycloalkyl, a 3-10membered cycloalkenyl ring, or a heterocyclo ring, any of which may be optionally substituted with one or more R^{10} groups as allowed by valance.;

or R^c and R^d together with the carbon atom to which they are bonded may combine to form a 3-10 membered cycloalkyl, a 3-10membered cycloalkenyl ring, or a heterocyclo ring, any of which may be optionally substituted with one or more R^{10} groups as allowed by valance;

or R^a and/or R^b may combine with any R^c or R^d to form a partially or fully saturated 3-8 membered cycloalkyl ring or heterocyclo ring, either of which may be optionally substituted with one or more R^{10} groups as allowed by valance;

or R^a and R^b may combine to form a carbonyl group;

or R^c and R^d attached to the same carbon atom may combine to form a carbonyl group;

provided that when q is 1, R^a and R^b are independently other than halo, $-NO_2$, -CN, $-NR^5R^{5a}$, $-OR^4$, $-N(R^5)C(=O)NR^5R^{5a}$, $-OC(=O)NR^5R^{5a}$, $-S(O)_vR^4$, $-S(O)_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$;

R^2 is

(i) H, halo, cyano, nitro, or

(ii) alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-OR^4$, $-NR^5R^{5a}$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$,

$-N(R^5)SO_2R^4$, any of which may be optionally independently substituted with one or more R^{10} as allowed by valance,

R^{2a} and R^{2b} are independently selected at each occurrence from H, halo, cyano, nitro, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-OR^4$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

R^4 is independently selected at each occurrence from H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, and cycloalkylalkyl, any of which may be optionally independently substituted as allowed by valance with one or more R^{10} groups;

R^5 and R^{5a} are independently selected at each occurrence from H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, and cycloalkylalkyl, any of which may be optionally substituted as allowed by valance with one or more R^{10};

or R^5 and R^{5a} may combine to form a heterocyclo ring optionally substituted with one or more R^{10};

R^{10} and R^{10d} at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-(alkylene)_m-OR^4$, $-(alkylene)_m-S(O)_vR^4$, $-(alkylene)_m-NR^5R^{5a}$, $-(alkylene)_m-C(=O)R^4$, $-(alkylene)_m-C(=S)R^4$, $-(alkylene)_m-C(=O)OR^4$, $-(alkylene)_m-OC(=O)R^4$, $-(alkylene)_m-C(=S)OR^4$, $-(alkylene)_m-C(=O)NR^5R^{5a}$, $-(alkylene)_m-C(=S)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=S)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)R^4$, $-(alkylene)_m-N(R^5)C(=S)R^4$, $-(alkylene)_m-OC(=O)NR^5R^{5a}$, $-(alkylene)_m-OC(=S)NR^5R^{5a}$, $-(alkylene)_m-SO_2NR^5R^{5a}$, $-(alkylene)_m-N(R^5)SO_2R^4$, $-(alkylene)_m-N(R^5)SO_2NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)OR^4$, $-(alkylene)_m-N(R^5)C(=S)OR^4$, or $-(alkylene)_m-N(R^5)SO_2R^4$;

wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may

be further independently substituted with one or more -(alkylene)$_m$-OR^4, -(alkylene)$_m$-S(O)$_v$R^4, -(alkylene)$_m$-NR^{5}R^{5a}, -(alkylene)$_m$-C(=O)R^4, -(alkylene)$_m$-C(=S)R^4, -(alkylene)$_m$-C(=O)OR^4, -(alkylene)$_m$-OC(=O)R^4, -(alkylene)$_m$-C(=S)OR^4, —(alkylene)$_m$-C(=O)NR^{5}R^{5a}, -(alkylene)$_m$-C(=S)NR^{5}R^{5a}, -(alkylene)$_m$-N(R^5)C(=O)NR^{5}R^{5a}, -(alkylene)$_m$-N(R^5)C(=S)NR^{5}R^{5a}, -(alkylene)$_m$-N(R^5)C(=O)R^4, -(alkylene)$_m$-N(R^5)C(=S)R^4, -(alkylene)$_m$-OC(=O)NR^{5}R^{5a}, -(alkylene)$_m$-OC(=S)NR^{5}R^{5a}, -(alkylene)$_m$-SO$_2$NR^{5}R^{5a}, -(alkylene)$_m$-N(R^5)SO$_2$R^4, -(alkylene)$_m$-N(R^5)SO$_2$NR^{5}R^{5a}, -(alkylene)$_m$-N(R^5)C(=O)OR^4, -(alkylene)$_m$-N(R^5)C(=S)OR^4, or -(alkylene)$_m$-N(R^5)SO$_2$R^4;

and further wherein any two R^{10} groups attached to the same atom or attached to adjacent atoms may combine to form an optionally substituted 3- to 8 membered ring system;

m is 0 or 1;

n is 0, 1 or 2;

n+ is 0, 1, 2 or 3;

q is 0 or 1;

v is 0, 1 or 2.

8. A compound of claim 7 wherein q and n are each zero, and a is a bond.

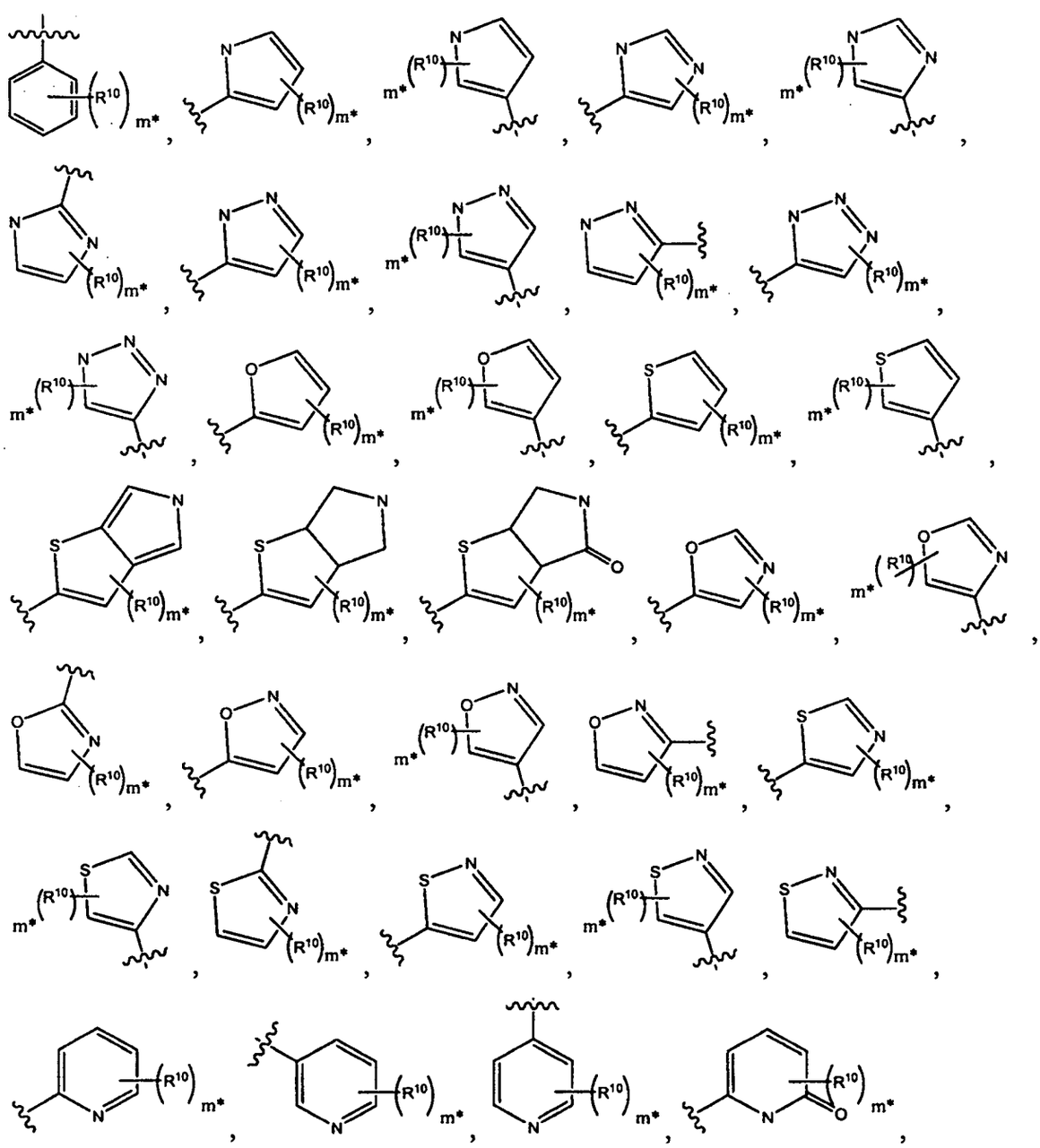
9. A compound of claim 7 wherein R^2 is H, halo, cyano, alkynyl, –NR^{5}R^{5a}, -C(=O)NR^{5}R^{5a}, -N(R^5)C(=O)R^4, -N(R^5)C(=O)OR^4, phenyl, naphthyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, tetrahydropyridinyl, pyridinonyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, indolinyl, indolinonyl, isoidolinyl, isoindolinonyl, dihydrobenzofuranyl, dihydroisobenzofuranyl, benzofuranyl, isobenzofuranyl, quinolinyl, isoquinolinyl, quinazolinyl, quinazolinonyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, quinoxalinyl, tetrahydroquinoxalinyl, benzomorpholinyl, dihydrobenzodioxinyl, imidazopyridinyl, naphthyridinyl, benzotriazinyl, triazolopyridinyl, triazolopyrimidinyl, triazolopyridazinyl, imidazopyridinyl, imidazopyrimidinyl, imidazopyridazinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, pyrrolopyridazinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrazolopyridazinyl, cinnolinyl, thienopyrrolyl, tetrahydrothienopyrrolyl, dihydrothienopyrrolonyl, thienopyridinyl, thienopyrimidinyl, thienopyridazinyl, furopyridinyl, furopyrimidinyl, furopyrazidinyl,

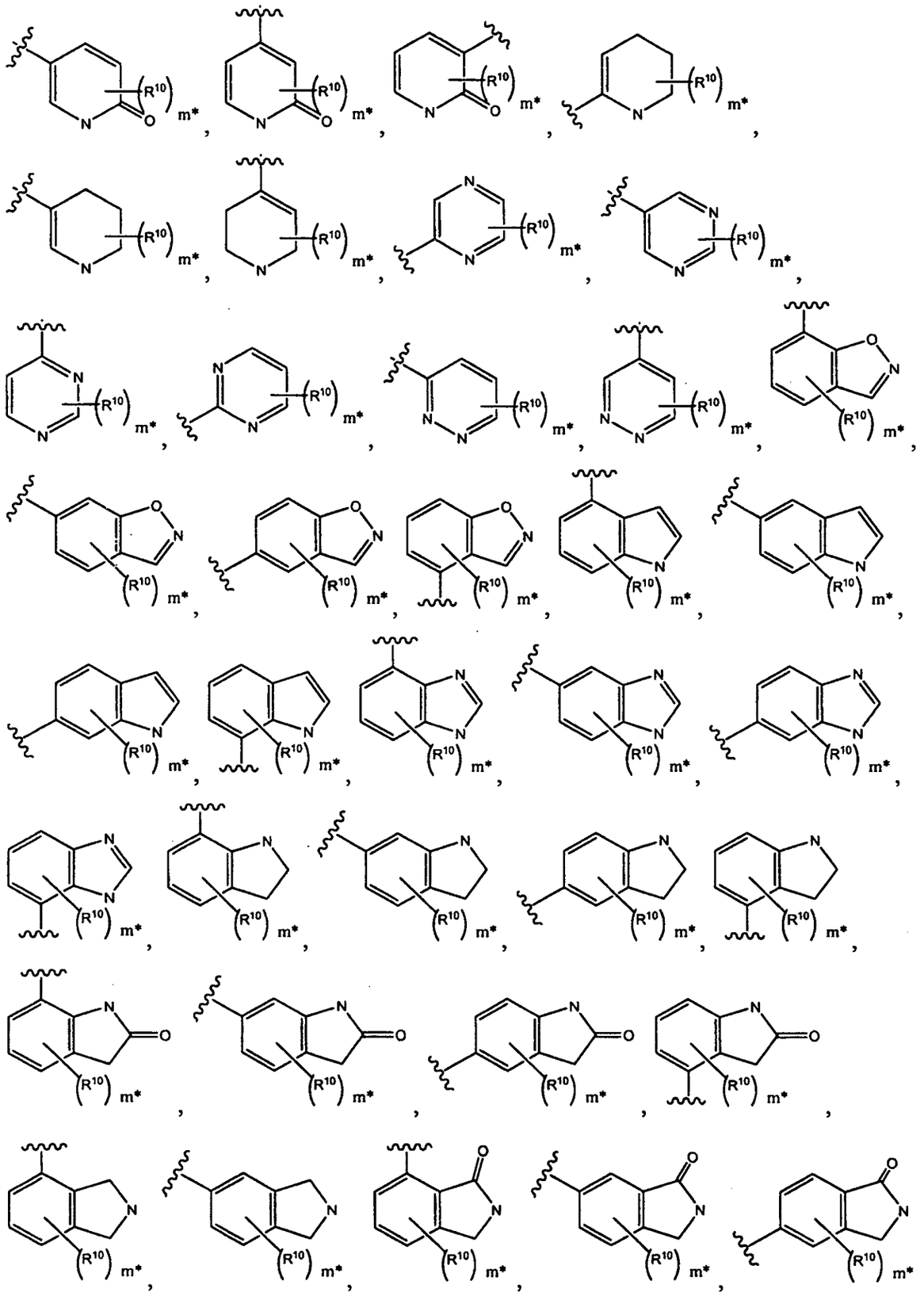
benzofuranyl, benzoimidazolyl, benzoisoxazolyl, benzothiazolyl, or benzoisothiazolyl any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance.

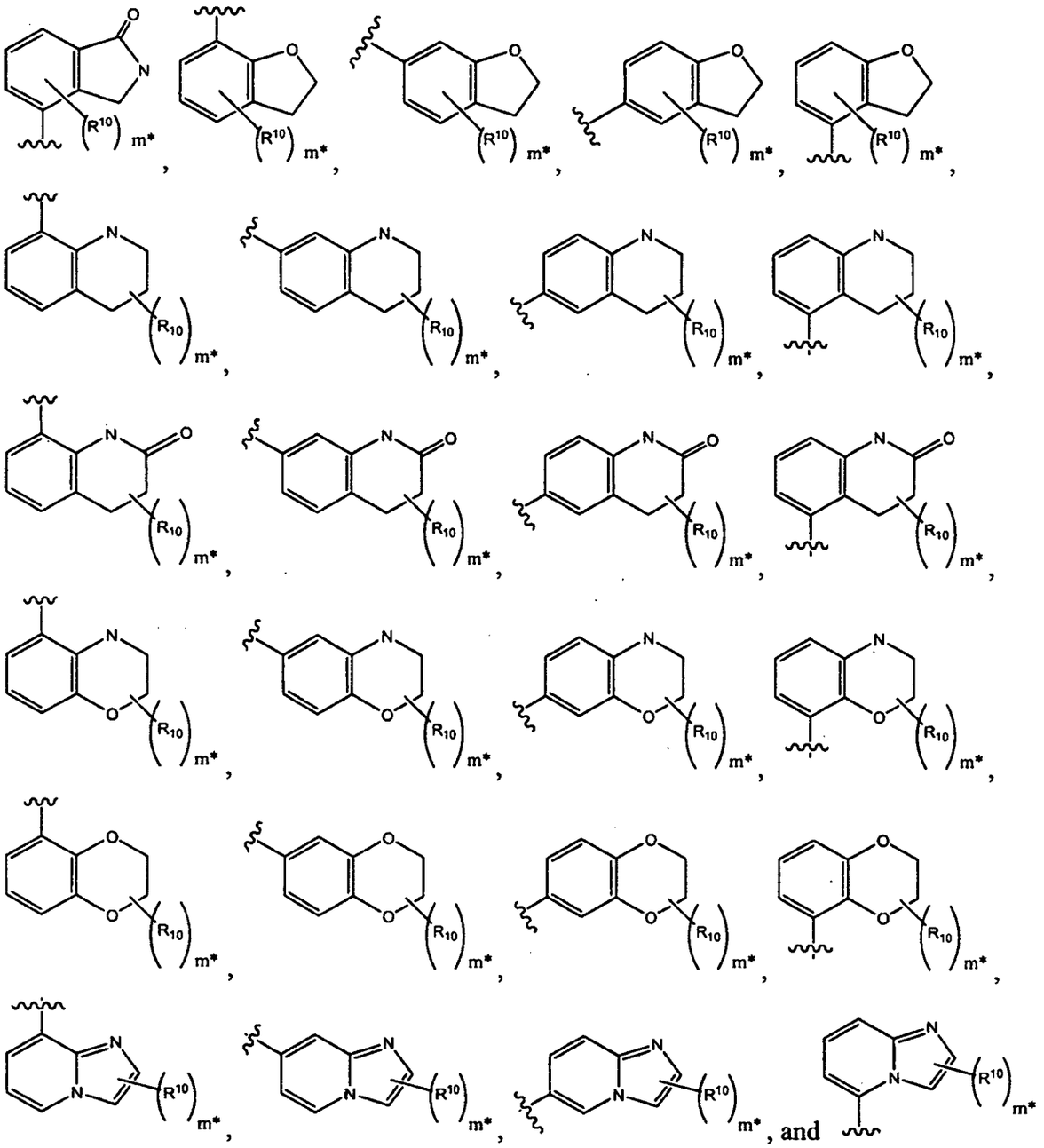
10. A compound of claim 9 wherein R^2 is

(a) halo, alkynyl, $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$ or $-N(R^5)C(=O)OR^4$ any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance; or

(b) an aryl, heteroaryl or heterocyclo ring system selected from

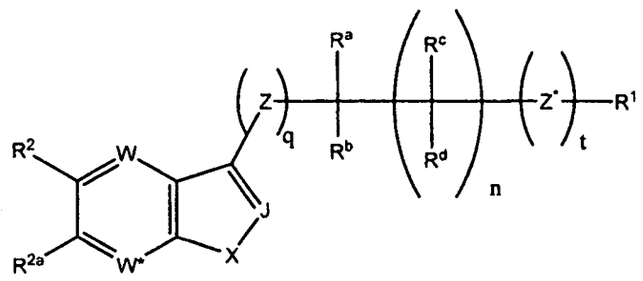






where m* is 0, 1, 2, 3, 4, 5 or 6, as allowed by valence.

11. A compound of Formula VII



VII

enantiomers, diastereomers, salts and solvates thereof wherein

J is N or CR^3;

W is CR^{2b};

W* is N or CR^{2b};

X is O or S;

Z and Z* are independently -O-, $-S(O)_v-$, or $-NR^5-$;

R^a, R^b, R^c and R^d are each independently H, halo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, $-NO_2$, -CN, $-NR^5R^{5a}$, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$; $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-OC(=O)NR^5R^{5a}$, $-S(O)_vR^4$, $-S(O)_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$ any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

or R^a and R^b together with the carbon atom to which they are bonded may combine to form a 3-10 membered cycloalkyl, a 3-10membered cycloalkenyl ring, or a heterocyclo ring, any of which may be optionally substituted with one or more R^{10} groups as allowed by valance.;

or R^c and R^d together with the carbon atom to which they are bonded may combine to form a 3-10 membered cycloalkyl, a 3-10membered cycloalkenyl ring, or a heterocyclo ring, any of which may be optionally substituted with one or more R^{10} groups as allowed by valance;

or R^a and/or R^b may combine with any R^c or R^d to form a partially or fully saturated 3-8 membered cycloalkyl ring or heterocyclo ring, either of which may be optionally substituted with one or more R^{10} groups as allowed by valance;

or R^a and R^b may combine to form a carbonyl group;

or R^c and R^d attached to the same carbon atom may combine to form a carbonyl group;

R^1 is aryl, heteroaryl or heterocyclo any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

R^2 is

(i) H, halo, cyano, nitro, or

(ii) alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-OR^4$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, any of which may be optionally independently substituted with one or more R^{10} as allowed by valance,

R^{2a}, R^{2b} and R^3 are independently selected at each occurrence from H, halo, cyano, nitro, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-OR^4$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, any of which may be optionally independently substituted with one or more R^{10} groups as allowed by valance;

R^4 is independently selected at each occurrence from H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, and cycloalkylalkyl, any of which may be optionally independently substituted as allowed by valance with one or more R^{10} groups;

R^5 and R^{5a} are independently selected at each occurrence from H, alkyl, haloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl, heterocycloalkyl, and cycloalkylalkyl, any of which may be optionally substituted as allowed by valance with one or more R^{10};

or R^5 and R^{5a} may combine to form a heterocyclo ring optionally substituted with one or more R^{10};

R^{10} at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, $-(alkylene)_m-OR^4$, $-(alkylene)_m-S(O)_vR^4$, $-(alkylene)_m-NR^5R^{5a}$, $-(alkylene)_m-C(=O)R^4$, $-(alkylene)_m-C(=S)R^4$, $-(alkylene)_m-C(=O)OR^4$, $-(alkylene)_m-OC(=O)R^4$, $-(alkylene)_m-C(=S)OR^4$, $-(alkylene)_m-C(=O)NR^5R^{5a}$, $-(alkylene)_m-C(=S)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=S)NR^5R^{5a}$, $-(alkylene)_m-N(R^5)C(=O)R^4$, $-(alkylene)_m-N(R^5)C(=S)R^4$,

-(alkylene)$_m$-OC(=O)NR^{5}R^{5a}, -(alkylene)$_m$-OC(=S)NR^{5}R^{5a}, -(alkylene)$_m$-SO$_2$NR^{5}R^{5a}, -(alkylene)$_m$-N(R^5)SO$_2$R^4, -(alkylene)$_m$-N(R^5)SO$_2$NR^{5}R^{5a}, -(alkylene)$_m$-N(R^5)C(=O)OR^4, -(alkylene)$_m$-N(R^5)C(=S)OR^4, or -(alkylene)$_m$-N(R^5)SO$_2$R^4;

wherein said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more -(alkylene)$_m$-OR^4, -(alkylene)$_m$-S(O)$_v$R^4, -(alkylene)$_m$-NR^{5}R^{5a}, -(alkylene)$_m$-C(=O)R^4, -(alkylene)$_m$-C(=S)R^4, -(alkylene)$_m$-C(=O)OR^4, -(alkylene)$_m$-OC(=O)R^4, -(alkylene)$_m$-C(=S)OR^4, -(alkylene)$_m$-C(=O)NR^{5}R^{5a}, -(alkylene)$_m$-C(=S)NR^{5}R^{5a}, -(alkylene)$_m$-N(R^5)C(=O)NR^{5}R^{5a}, -(alkylene)$_m$-N(R^5)C(=S)NR^{5}R^{5a}, -(alkylene)$_m$-N(R^5)C(=O)R^4, -(alkylene)$_m$-N(R^5)C(=S)R^4, -(alkylene)$_m$-OC(=O)NR^{5}R^{5a}, -(alkylene)$_m$-OC(=S)NR^{5}R^{5a}, -(alkylene)$_m$-SO$_2$NR^{5}R^{5a}, -(alkylene)$_m$-N(R^5)SO$_2$R^4, -(alkylene)$_m$-N(R^5)SO$_2$NR^{5}R^{5a}, -(alkylene)$_m$-N(R^5)C(=O)OR^4, -(alkylene)$_m$-N(R^5)C(=S)OR^4, or -(alkylene)$_m$-N(R^5)SO$_2$R^4;

and further wherein any two R^{10} groups attached to the same atom or attached to adjacent atoms may combine to form an optionally substituted 3- to 8 membered ring system;

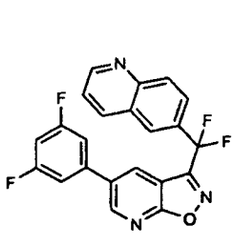
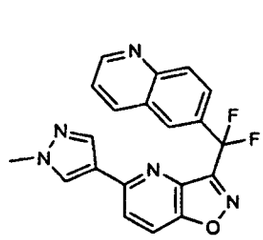
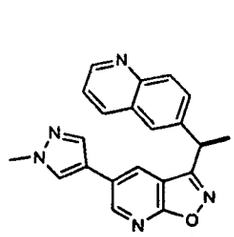
m is 0 or 1;

n is 0, 1 or 2;

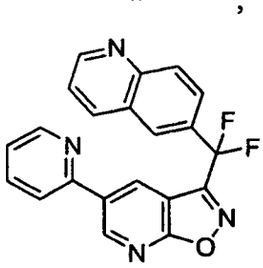
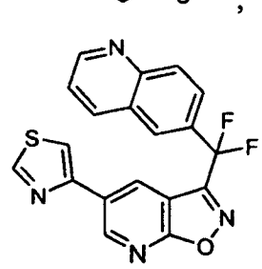
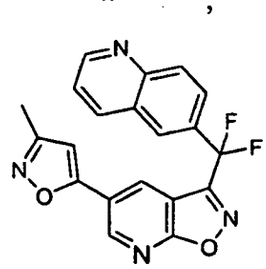
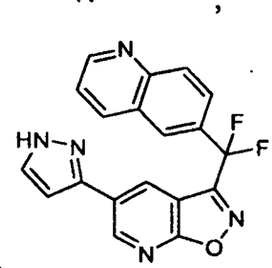
q and t are each independently 0 or 1;

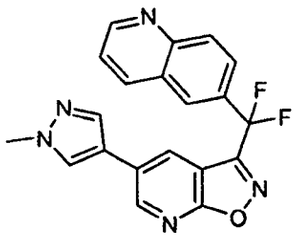
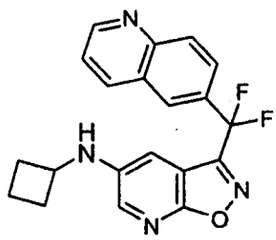
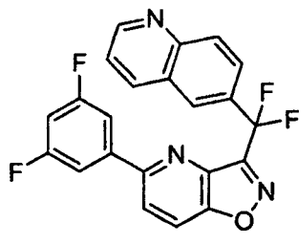
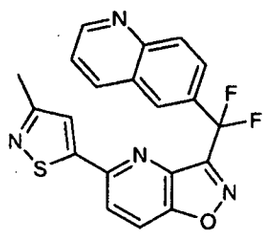
v is 0, 1 or 2;

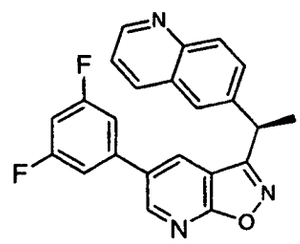
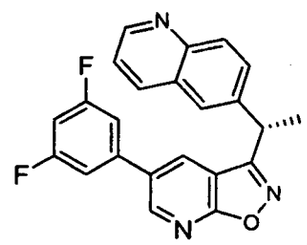
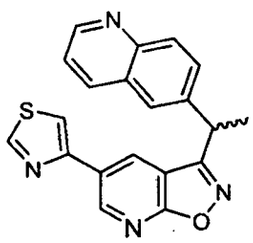
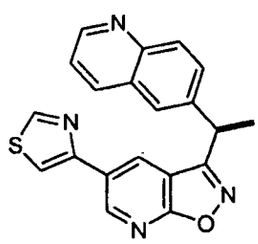
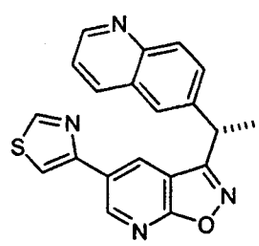
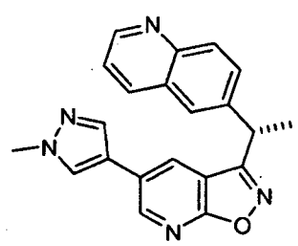
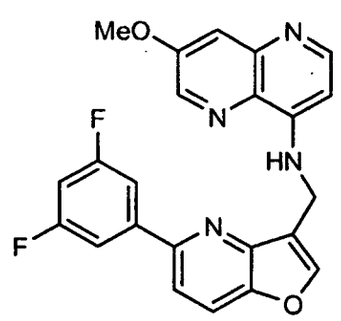
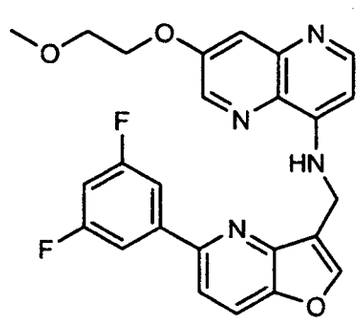
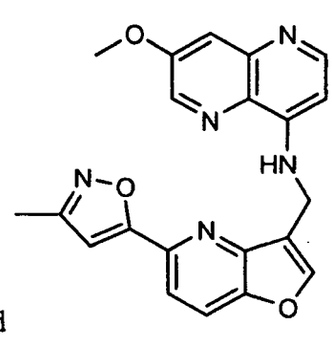
wherein said compound is selected from


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and salts thereof.

11. A pharmaceutical composition comprising a compound of either claim 1 or claim 7 together with a pharmaceutically acceptable vehicle or carrier.

12. A method of treating cancer in a subject, said method comprising administering an effective amount of a compound as in either claim 1 or claim 7.

13. The method of claim 12 wherein said compound is administered in combination with at least one compound selected from antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents and miscellaneous agents.

14. A method of reducing tumor size in a subject, said method comprising administering an effective amount of a compound as in claim 1.

15. A method of treating HGF mediated disorders in a subject, said method comprising administering an effective amount of a compound as in claim 1.

16. A method of reducing metastasis in a tumor in a subject, said method comprising administering an effective amount of a compound as in claim 1.

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DERIVADOS HETEROCÍCLICOS FUSIONADOS Y MÉTODOS DE USO COMO INHIBIDORES C-MET

CAMPO DE LA INVENCIÓN

Esta invención se refiere al campo de los agentes farmacéuticos y específicamente se refiere a compuestos, composiciones, usos y métodos para tratar cáncer.

ANTECEDENTES DE LA INVENCIÓN

Las protein quinasas representan una gran familia de proteínas, que cumplen una función central en la regulación de una amplia variedad de procesos celulares, manteniendo el control sobre la función celular. Una lista parcial de dichas quinasas incluye ab1, Akt, bcr–ab1, Blk, Brk, Btk, c–kit, c–Met, c–src, c–fms, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK10, cRaf1, CSF1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, Erk, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, flt–1, Fps, Frk, Fyn, Hck, IGF–1R, INS–R, Jak, KDR, Lck, Lyn, MEK, p38, PDGFR, PIK, PKC, PYK2, ros, tie, tie2, TRK, Yes, y Zap70. La inhibición de dichas quinasas se ha convertido en un importante objetivo terapéutico.

El receptor factor de crecimiento hepatocítico ("c–Met") es un notable receptor tirosin quinasa que se ha demostrado que está hiperexpresado en una variedad de tumores malignos. c–Met comprende típicamente, en su forma natural, una proteína tirosin quinasa que abarca una membrana heterodimérica de 190 kDa (una cadena α de 50–kDa y una cadena β de 145–kDa ligada a disulfuro) (Proc. Natl. Acad. Sci. USA, 84:6379–6383 (1987)). c–Met está expresado principalmente en células epiteliales y la estimulación de c–Met conduce a difusión, angiogénesis, proliferación y metástasis. (Ver Cytokine and Growth Factor Reviews, 13:41–59 (2002)).

A.F. 222.118

El ligando para c–Met es el factor de crecimiento de hepatocitos (conocido también como factor de difusión, HGF y SF). HGF es una proteína heterodimérica secretada por células de origen mesodérmico (Nature, 327:239–242 (1987); J. Cell Biol., 111:2097–2108 (1990)).

Varias actividades biológicas han sido descritas para HGF a través de la interacción con c– met (Factor de Crecimiento de Hepatocitos – Factor de Fusión (HGF–SF) y el Receptor c–Met, Goldberg and Rosen, eds., Birkhauser Verlag–Basel, 67–79 (1993). El efecto biológico de HGF/ SF puede depender en parte de la célula diana. HGF induce un espectro de actividades biológicas en las células epitelaliales, incluyendo mitogénesis, estimulación de la motilidad de las células y promoción de invasión de matriz (Biochem. Biophys. Res. Comm., 122:1450–1459 (1984); Proc. Natl. Acad. Sci. U.S.A., 88:415–419 (1991)). Estimula la motilidad e invasividad de las células de carcinoma, estando implicada la primera, en la migración de células requerida para metástasis. HGF puede actuar también como un "factor de difusión" que promueve la disociación de células epiteliales y vasculares endoteliales (Nature, 327:239–242 (1987); J. Cell Biol., 111:2097–2108 (1990); EMBO J., 10:2867–2878 (1991); Proc. Natl. Acad. Sci. USA, 90:649–653 (1993)). Por lo tanto, se cree

que HGF es importante en la invasión de tumores (Hepatocyte Growth Factor–Scatter Factor (HGF–SF) y C–Met Receptor, Goldberg and Rosen, eds., Birkhauser Verlag–Basel, 131–165 (1993)).

HGF y c–Met se expresan a niveles anormalmente altos en una gran variedad de tumores sólidos. Se han observado altos niveles de HGF y/ o c–Met en tumores de hígado, mama, páncreas, pulmón, riñón vejiga, ovario, cerebro, próstata, vesícula y mieloma, además de muchos otros. La función de HGF/c–Met en metástasis ha sido investigada en ratones usando líneas celulares transformadas con HGF/c–Met (J. Mol. Med., 74:505–513 (1996)). Se ha sugerido también que la hiperexpresión del oncogen c–Met cumple una función en la patogénesis y avance de tumores de tiroides derivados del epitelio folicular (Oncogen, 7:2549–2553 (1992)). HGF es un morfógeno (Development, 110:1271–1284 (1990); Cell, 66:697–711 (1991)) y un potente factor angiogénico (J. Cell Biol., 119:629–641 (1992)).

Un reciente trabajo sobre la relación entre la inhibición de la angiogénesis y la supresión o reversión del avance de tumores, muestra ser sumamente promisorio en el tratamiento del cáncer (Nature, 390:404–407 (1997)), especialmente en el uso de inhibidores de angiogénesis múltiple, si se compara con el efecto de un solo inhibidor. La angiogénesis puede ser estimulada por HGF, así como también por el factor de crecimiento vascular endotelial (VEGF) y el factor de crecimiento fibroblástico básico (bFGF).

La angiogénesis, el proceso de renovación de nuevos vasos sanguíneos de la vasculatura existente, y la arteriogénesis, la remodelación de pequeños vasos en vasos de conductos más grandes, son ambas aspectos fisiológicamente importantes del crecimiento vascular de tejidos en adultos. Estos procedimientos de crecimiento vascular son requeridos para procesos beneficiosos tales como reparación tisular, curación de heridas, recuperación de isquemia tisular y del ciclo menstrual. También son requeridos para el desarrollo de trastornos patológicos tales como el crecimiento de neoplasias, retinopatía diabética, artritis reumatoidea, psoriasis, ciertas formas de degeneración macular, y ciertas patologías inflamatorias. La inhibición del crecimiento vascular en estos contextos ha mostrado también efectos beneficiosos en modelos preclínicos en animales. Por ejemplo, la inhibición de angiogénesis mediante el bloqueo del factor de crecimiento endotelial vascular o su receptor ha dado como resultado la inhibición del crecimiento del tumor y de la retinopatía. Asimismo, el desarrollo de tejido de granulación sinovial patológico en artritis reumatoide involucra angiogénesis y podría ser bloqueado por los inhibidores de angiogénesis.

La capacidad de estimular el crecimiento vascular tiene utilidad potencial para el tratamiento de patologías inducidas por isquemia, tales como infarto de miocardio, enfermedad de las arterias coronarias, enfermedad vascular periférica y accidentes cerebro vasculares. El brote de nuevos vasos y/o la expansión de pequeños vasos en tejidos isquémicos previene la muerte del tejido isquemico e induce a la reparación del tejido. Se sabe que ciertas enfermedades están asociadas con angiogénesis desregulada, por ejemplo, neovascularización ocular, tales como retinopatías (incluyendo retinopatía diabética),

degeneración macular relacionada con la edad, psoriasis, hemangioblastoma, hemangioma, arteriosclerosis, enfermedades de inflamaciones tales como enfermedad reumatoidea o de inflamación reumática, especialmente artritis (incluyendo artritis reumatoidea), u otros trastornos de inflamaciones tales como asma crónico, aterosclerosis arterial o post–transplantacional, endometriosis, y enfermedades neoplásicas, por ejemplos, los denominados tumores sólidos y tumores líquidos (tales como leucemias). El tratamiento de malaria y enfermedades virales relacionadas, puede ser también intermediadas por HGF y cMet.

También se han observado niveles elevados de HGF y c–Met en episodios no–oncológicos, tales como hipertensión, infarto de miocardio y artritis reumatoidea. Se ha observado que los niveles de HGF aumentan en el plasma de pacientes con insuficiencia hepática (Gohda et al., supra) y en el plasma (Hepatol., 13:734–750 (1991)) o suero (J. Biochem., 109:8–13 (1991)) de animales con daño hepático inducido experimentalmente. También se ha demostrado que el HFG es un mitógeno para ciertos tipos de células, incluyendo melanocitos, células tubulares renales, queratinocitos, ciertas células endoteliales y células de origen epitelial (Biochem. Biophys. Res. Commun., 176:45–51 (1991); Biochem. Biophys. Res. Commun., 174:831–838 (1991); Biochem., 30:9768–9780 (1991); Proc. Natl. Acad. Sci. USA, 88:415–419 (1991)). Se ha postulado que tanto el HGF como el proto–oncogen c–Met actuan en las reacciones microgliales para las lesiones al SNC (Oncogen, 8:219–222 (1993)).

Las células metastáticas SCC hiperexpresan c–Met y tienen tumorgénesis y metástasis realzadas in vivo [G. Gong et al., Oncogen, 23:6199–6208 (2004)]. Se requiere C–Met para la supervivencia de células tumorales [N. Shinomiya et al., Cancer Research, 64:7962–7970 (2004)]. Para una revisión general ver C. Birchmeier et al., Nature Reviews/Molecular Biology 4:915–925 (2003).

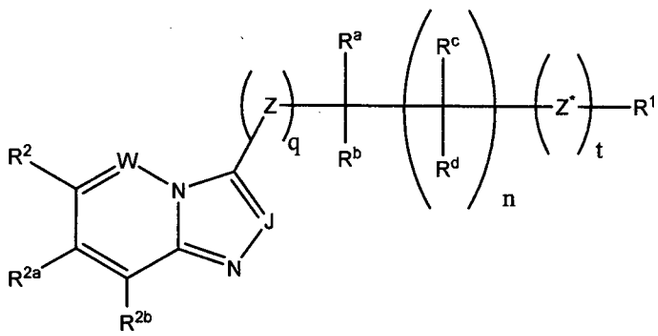
En vista de la función del HGF y/ o c–Met en la potenciación o promoción de dichas enfermedades o trastornos patológicos, sería útil tener los medios para reducir o inhibir sustancialmente uno o más de los efectos biológicos de HGF y su receptor. Por lo tanto un compuesto que reduce el efecto de HGF sería un compuesto útil. Los compuestos de la presente invención no han sido previamente descritos como inhibidores de angiogénesis, para el tratamiento de cáncer.

La solicitud Sugen WO 05/010005 describe ciertos compuestos de Triazolotriazina que son inhibidores de c–met. La solicitud WO 83/00864 de Diamon Shamrock Corp. describe ciertos compuestos de Triazolotriazina que son útiles como agentes anti–inflamatorios. Las solicitudes de EP 1481955 y US 2005/0261297 de Yamanouchi, describen ciertos compuestos heterocíclicos que contienen nitrógeno que son agentes terapéuticos que tienen un efecto estimulador para la formación de huesos.

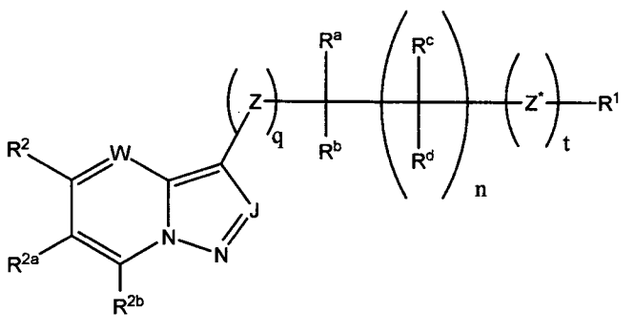
Los compuestos de la presente invención son inhibidores de c–Met.

DESCRIPCIÓN DE LA INVENCIÓN

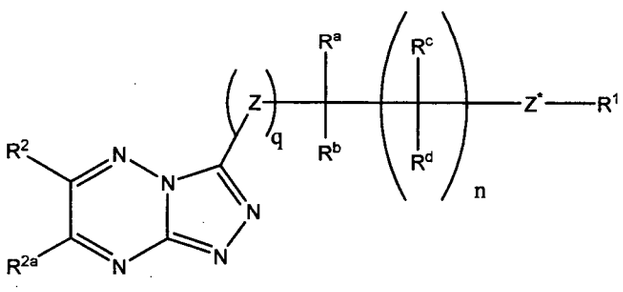
Se define una clase de compuestos útiles en el tratamiento de cáncer y angiogénesis mediante las Fórmulas I, II, III, IV, V, VI y VII



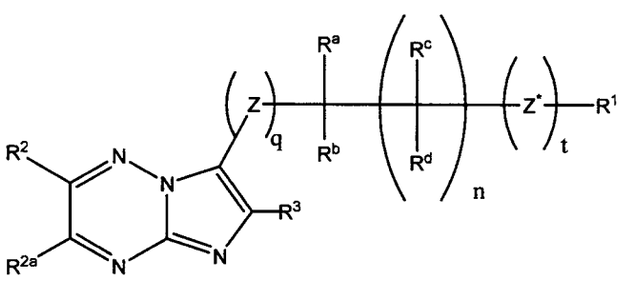
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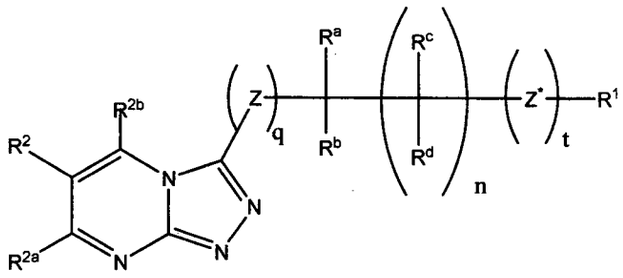
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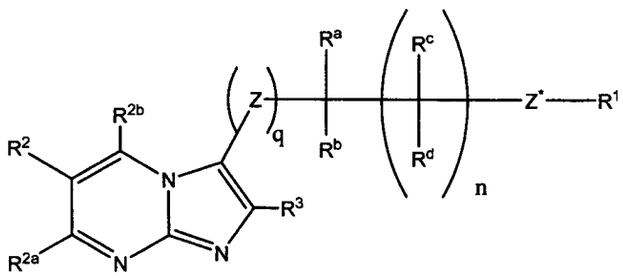
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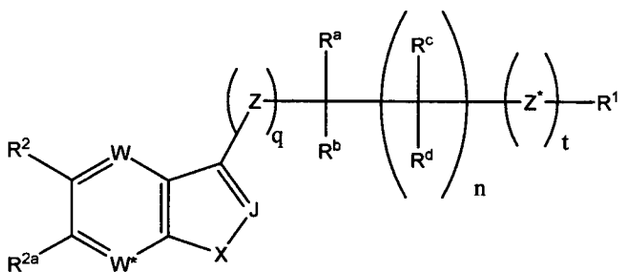
IV



V



VI



VII

enantiómeros, diaestereómeros, sales y solvatos de los mismos donde

J es N o CR^3;

W es CR^{2b};

W* es N o CR^{2b};

X es O o S;

Z y Z* son independientemente –O–, $–S(O)_v–$, o $–NR^5–$;

R^a, R^b, R^c y R^d son cada uno independientemente H, halo, alquilo, alquenilo, alquinilo, haloalquilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, $–NO_2$, –CN, $–NR^5R^{5a}$, $–OR^4$, $–C(=O)R^4$, $–C(=O)OR^4$; $–C(=O)NR^5R^{5a}$, $–N(R^5)C(=O)NR^5R^{5a}$, $–OC(=O)NR^5R^{5a}$, $–S(O)_vR^4$, $–S(O)_2NR^5R^{5a}$, $–N(R^5)SO_2R^4$ cualquiera de los cuales puede estar opcionalmente independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia;

o R^a y R^b conjuntamente con el átomo de carbono al cual están unidos pueden combinarse para formar un anillo cicloalquilo de 3–10 miembros, un anillo cicloalquenilo de 3–10 miembros, o un anillo heterociclo, cada uno de los cuales puede estar opcionalmente sustituido con uno o más grupos R^{10} según lo permita la valencia.;

o R^c y R^d conjuntamente con el átomo de carbono al cual están unidos pueden combinarse para formar un anillo cicloalquilo de 3–10 miembros, un anillo cicloalquenilo de 3–10

miembros, o un anillo heterociclo, cada uno de los cuales puede estar opcionalmente sustituido con uno o más grupos R^{10} según lo permita la valencia.;

o R^a y/o R^b pueden combinarse con cualquier R^c o R^d para formar un anillo cicloalquilo de 3–8 miembros parcialmente o completamente saturado o un anillo heterociclo, cualquiera de los cuales puede estar opcionalmente sustituido con uno o más grupos R^{10} según lo permita la valencia;

o R^a y R^b pueden combinarse para formar un grupo carbonilo;

o R^c y R^d unidos al mismo átomo de carbono pueden combinarse para formar un grupo carbonilo;

R^1 es arilo, heteroarilo o heterociclo cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia;

R^2 es

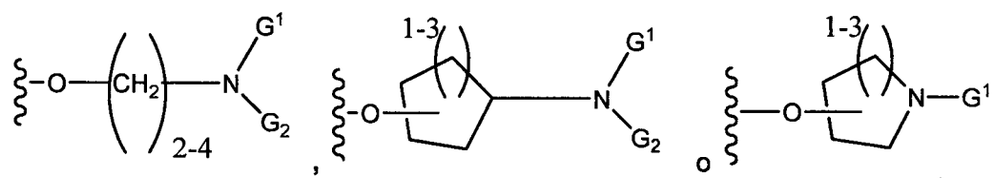
(i) H, halo, ciano, nitro, o

(ii) alquilo, haloalquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilo, $–OR^4$, $–S(O)_vR^4$, $–NR^5R^{5a}$, $–C(=O)R^4$, $–C(=S)R^4$, $–C(=O)OR^4$, $–C(=S)OR^4$, $–C(=O)NR^5R^{5a}$, $–C(=S)NR^5R^{5a}$, $–N(R^5)C(=O)NR^5R^{5a}$, $–N(R^5)C(=S)NR^5R^{5a}$, $–N(R^5)C(=O)R^4$, $–N(R^5)C(=S)R^4$, $–OC(=O)NR^5R^{5a}$, $–OC(=S)NR^5R^{5a}$, $–SO_2NR^5R^{5a}$, $–N(R^5)SO_2R^4$, $–N(R^5)SO_2NR^5R^{5a}$, $–N(R^5)C(=O)OR^4$, $–N(R^5)C(=S)OR^4$, $–N(R^5)SO_2R^4$, cada uno de los cuales puede estar opcionalmente independientemente sustituido com uno o más grupos R^{10} según lo permita la valencia,

con la condición de que en los compuestos de fórmula I cuando W y J son ambos N, R^2 es distinto

(a) $–NR^5R^{5a}$ donde R^5 y R^{5a} son independientemente H, alquilo, haloalquilo, cicloalquilo, alquenilo, alquinilo, arilo, heteroarilo, heterociclo, arilalquilo, heteroarilalquilo, heterocicloalquilo, y cicloalquilalquilo; y

(b) fenilo sustituido con un grupo



donde G^1 y G^2 son independientemente alquilo, cicloalquilo, o G^1 y G^2 conjuntamente con el átomo de nitrógeno al cual están unidos se combinan para formar un anillo heterociclo de 5 a 8 miembros;

R^{2a}, R^{2b} y R^3 están independientemente seleccionados en cada caso de H, halo, ciano, nitro, alquilo, haloalquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilo, $–OR^4$, –

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$S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia;

R^4 está independientemente seleccionado en cada caso de H, alquilo, haloalquilo, cicloalquilo, alquenilo, alquinilo, arilo, heteroarilo, heterociclo, arilalquilo, heteroarilalquilo, heterocicloalquilo, y cicloalquilalquilo, cada uno de los cuales puede estar opcionalmente independientemente sustituido según lo permita la valencia con uno o más grupos R^{10};

R^5 y R^{5a} están en cada caso independientemente seleccionados de H, alquilo, haloalquilo, cicloalquilo, alquenilo, alquinilo, arilo, heteroarilo, heterociclo, arilalquilo, heteroarilalquilo, heterocicloalquilo, y cicloalquilalquilo, cada uno de los cuales puede estar opcionalmente sustituido según lo permita la valencia con uno o más R^{10};

o R^5 y R^{5a} pueden combinarse para formar un anillo heterociclo opcionalmente sustituido con uno o más R^{10};

R^{10} en cada caso es independientemente, halo, ciano, nitro, oxo, alquilo, haloalquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilo, $-(alquileno)_m-OR^4$, $-(alquileno)_m-S(O)_vR^4$, $-(alquileno)_m-NR^5R^{5a}$, $-(alquileno)_m-C(=O)R^4$, $-(alquileno)_m-C(=S)R^4$, $-(alquileno)_m-C(=O)OR^4$, $-(alquileno)_m-OC(=O)R^4$, $-(alquileno)_m-C(=S)OR^4$, $-(alquileno)_m-C(=O)NR^5R^{5a}$, $-(alquileno)_m-C(=S)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=S)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)R^4$, $-(alquileno)_m-N(R^5)C(=S)R^4$, $-(alquileno)_m-OC(=O)NR^5R^{5a}$, $-(alquileno)_m-OC(=S)NR^5R^{5a}$, $-(alquileno)_m-SO_2NR^5R^{5a}$, $-(alquileno)_m-N(R^5)SO_2R^4$, $-(alquileno)_m-N(R^5)SO_2NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)OR^4$, $-(alquileno)_m-N(R^5)C(=S)OR^4$, o $-(alquileno)_m-N(R^5)SO_2R^4$;

donde dichos grupos alquilo, haloalquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilo pueden estar además independientemente sustituidos con uno o más $-(alquileno)_m-OR^4$, $-(alquileno)_m-S(O)_vR^4$, $-(alquileno)_m-NR^5R^{5a}$, $-(alquileno)_m-C(=O)R^4$, $-(alquileno)_m-C(=S)R^4$, $-(alquileno)_m-C(=O)OR^4$, $-(alquileno)_m-OC(=O)R^4$, $-(alquileno)_m-C(=S)OR^4$, $-(alquileno)_m-C(=O)NR^5R^{5a}$, $-(alquileno)_m-C(=S)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=S)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)R^4$, $-(alquileno)_m-N(R^5)C(=S)R^4$, $-(alquileno)_m-OC(=O)NR^5R^{5a}$, $-(alquileno)_m-OC(=S)NR^5R^{5a}$, $-(alquileno)_m-SO_2NR^5R^{5a}$, $-(alquileno)_m-N(R^5)SO_2R^4$, $-(alquileno)_m-N(R^5)SO_2NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)OR^4$, $-(alquileno)_m-N(R^5)C(=S)OR^4$, o $-(alquileno)_m-N(R^5)SO_2R^4$;

y además donde dos grupos R^{10} cualquiera unidos al mismo átomo o unidos a átomos adyacentes pueden combinarse para formar un sistema de anillo de 3 a 8 miembros opcionalmente sustituido;

m es 0 o 1;

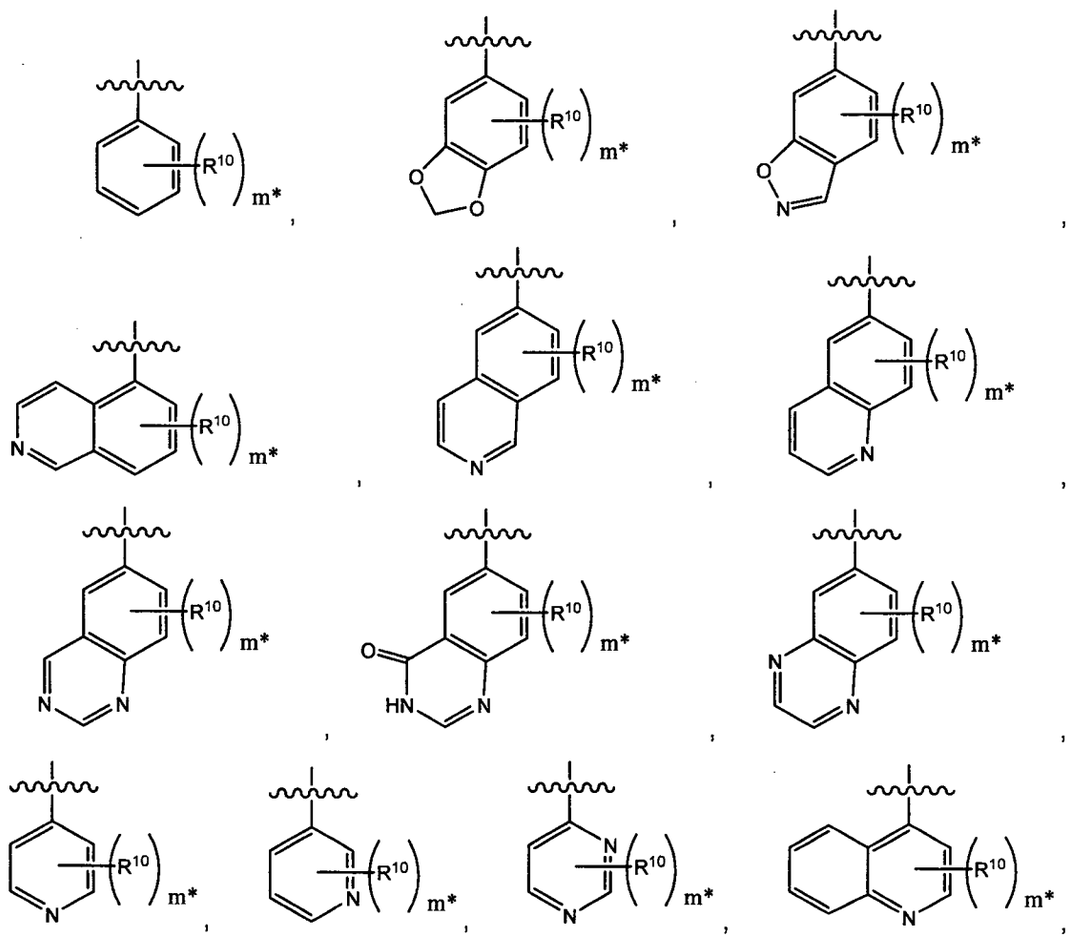
n es 0, 1 o 2;

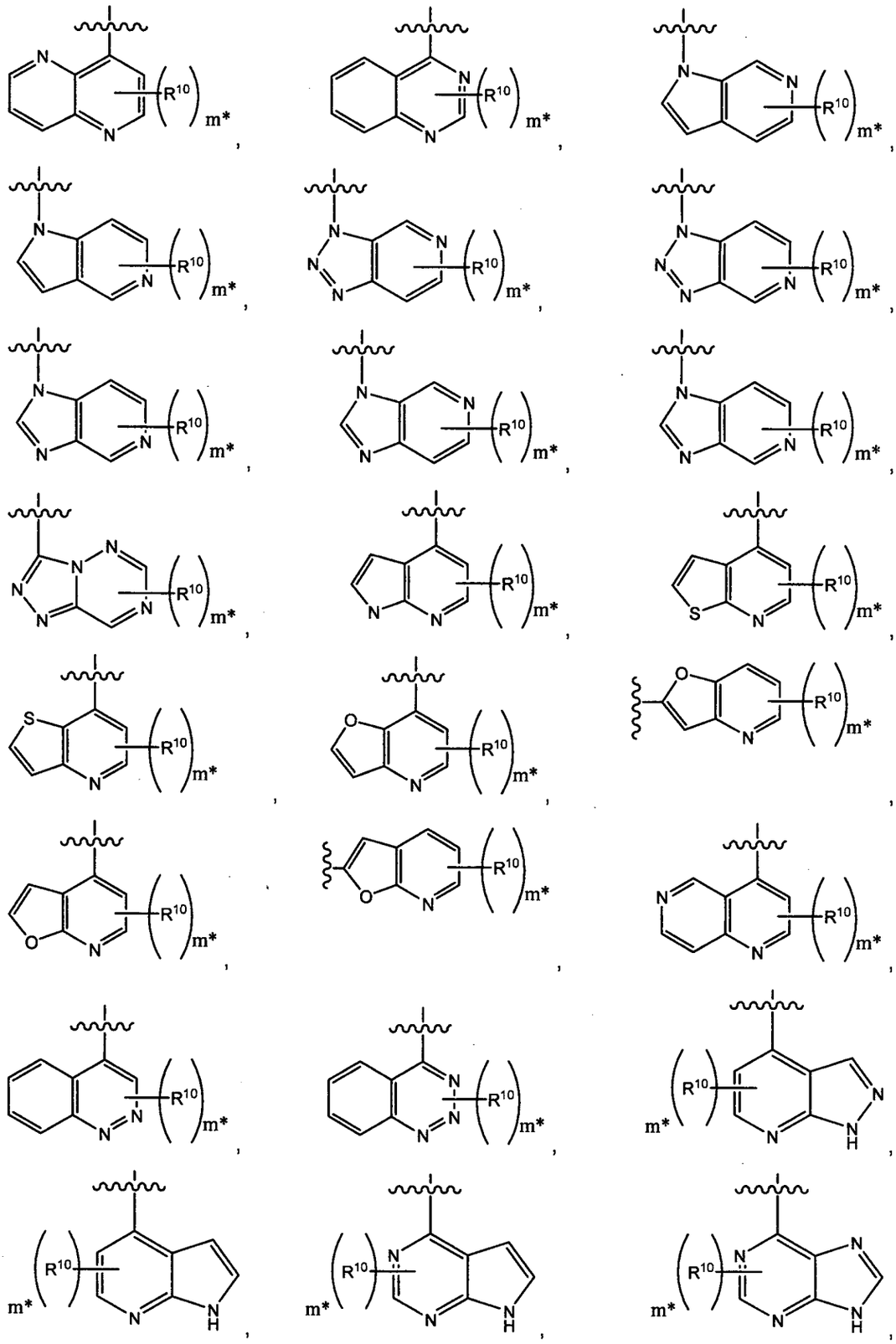
q y t son cada uno independientemente 0 o 1;

v es 0, 1 o 2.

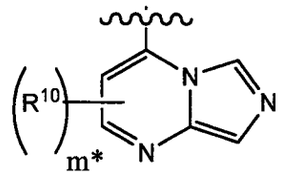
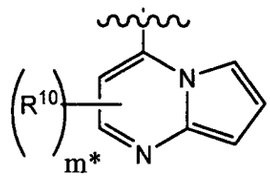
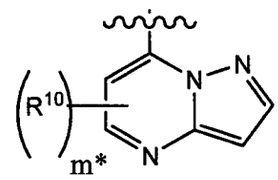
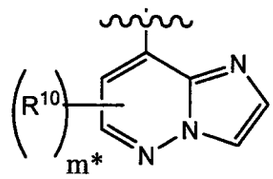
Los compuestos preferidos incluyen compuestos donde R^1 es fenilo, naftilo, benzodioxolilo, benzooxazolilo, benzoisoxazolilo, piridinilo, pirimidinilo, pirazinilo, pirimidinilo, pirazidinilo, isoquinolinilo, quinolinilo, quinazolinilo, quinazolinonilo, quinoxalinilo, naftiridinilo, benzotriazinilo, triazolopiridinilo, triazolopirimidinilo, triazolopiridazinilo, imidazopiridinilo, imidazopirimidinilo, imidazopiridazinilo, pirrolpiridinilo, pirrolpirimidinilo, pirrolpiridazinilo, pirazolpiridinilo, pirazolpirimidinilo, pirazolpiridazinilo, cinolinilo, tienopiridinilo, tienopirimidinilo, tienopiridazinilo, furopiridinilo, furopirimidinilo, furopirazidinilo, benzofuranilo, benzoimidazolilo, indolilo, benzoisoxazolilo, benzotiazolilo, benzoisotiazolilo, piridopirimidinilo, oxazolopiridinilo, tiazolopiridinilo, pirazolpirazinilo, triazolopirazinilo y triazolopiridinilo cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia.

Los grupos R^1 preferidos incluyen



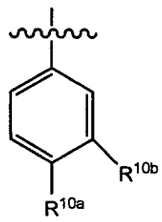
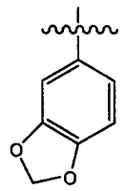
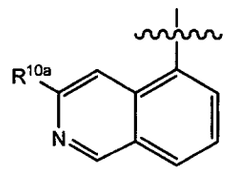
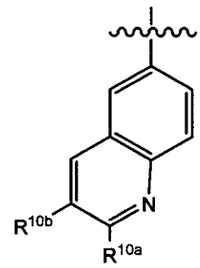
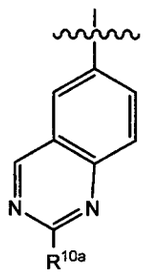
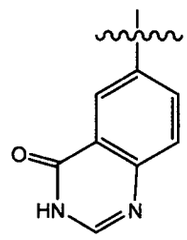
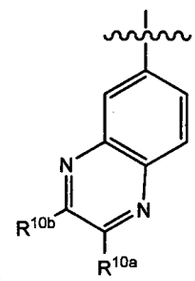
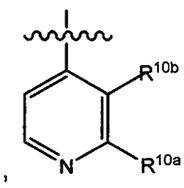
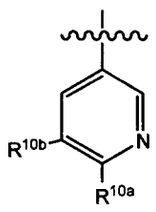
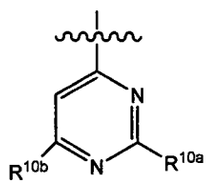
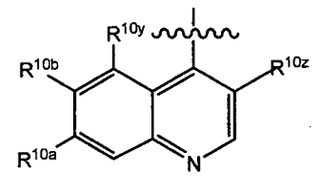
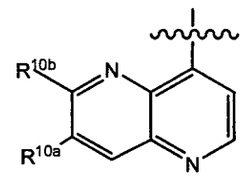
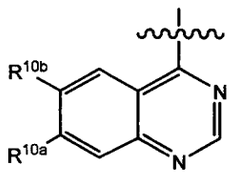
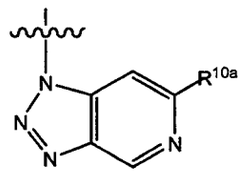
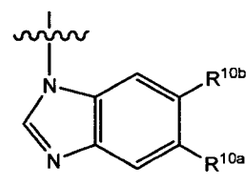
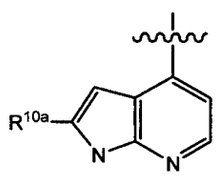
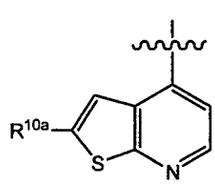
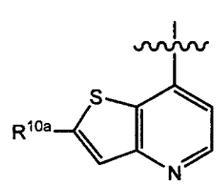
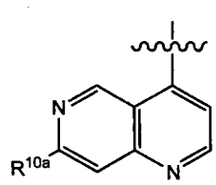
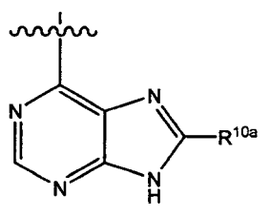


5




y


donde m* es 0, 1, 2, 3, 4, 5 o 6, según lo permita la valencia.

Los grupos R^1 especialmente preferidos incluyen

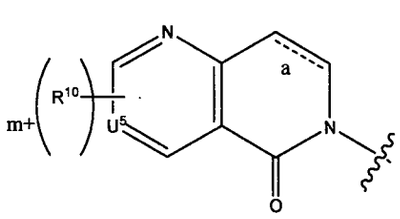



















y


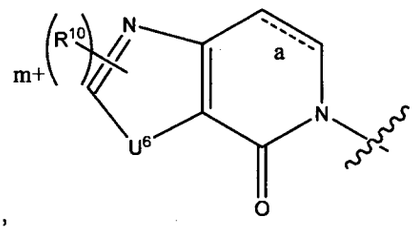
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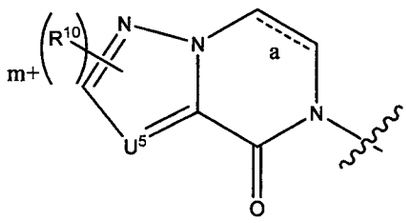
donde R^{10a}, R^{10b}. R^{10y} y R^{10z} son independientemente ausente, halo, ciano, nitro, alquilo, alquenilo, alquinilo, haloalquilo, $-(alquileno)_m-OR^4$, $-(alquileno)_m-NR^5R^{5a}$, $-(alquileno)_m-C(=O)R^4$, $-(alquileno)_m-C(=O)OR^4$, $-(alquileno)_m-OC(=O)R^4$, $-(alquileno)_m-C(=O)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)R^4$, $-(alquileno)_m-OC(=O)NR^5R^{5a}$, o $-(alquileno)_m-N(R^5)C(=O)OR^4$;

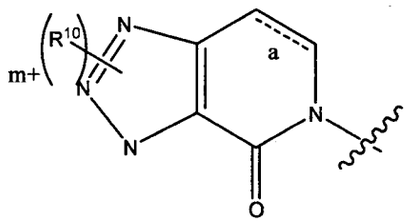
o donde R^{10a} y R^{10b} se combinan para formar un sistema de anillo opcionalmente sustituido de 3 a 8 miembros.

Los grupos R^1 preferidos incluyen además









, o

donde a es un enlace o está ausente;

U^5 es C o N;

U^6 es NH, O o S; y

m+ es 0, 1, 2 o 3 .

Los grupos R^1 más preferidos incluyen restos que están o bien no sustituidas o sustituidas independientemente según lo permita la valencia con uno o más halo, ciano, nitro, alquilo, alquenilo, alquinilo, haloalquilo, $-(alquileno)_m-OR^4$, $-(alquileno)_m-NR^5R^{5a}$, $-(alquileno)_m-C(=O)R^4$, $-(alquileno)_m-C(=O)OR^4$, $-(alquileno)_m-OC(=O)R^4$, $-(alquileno)_m-C(=O)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)R^4$, $-(alquileno)_m-OC(=O)NR^5R^{5a}$, o $-(alquileno)_m-N(R^5)C(=O)OR^4$.

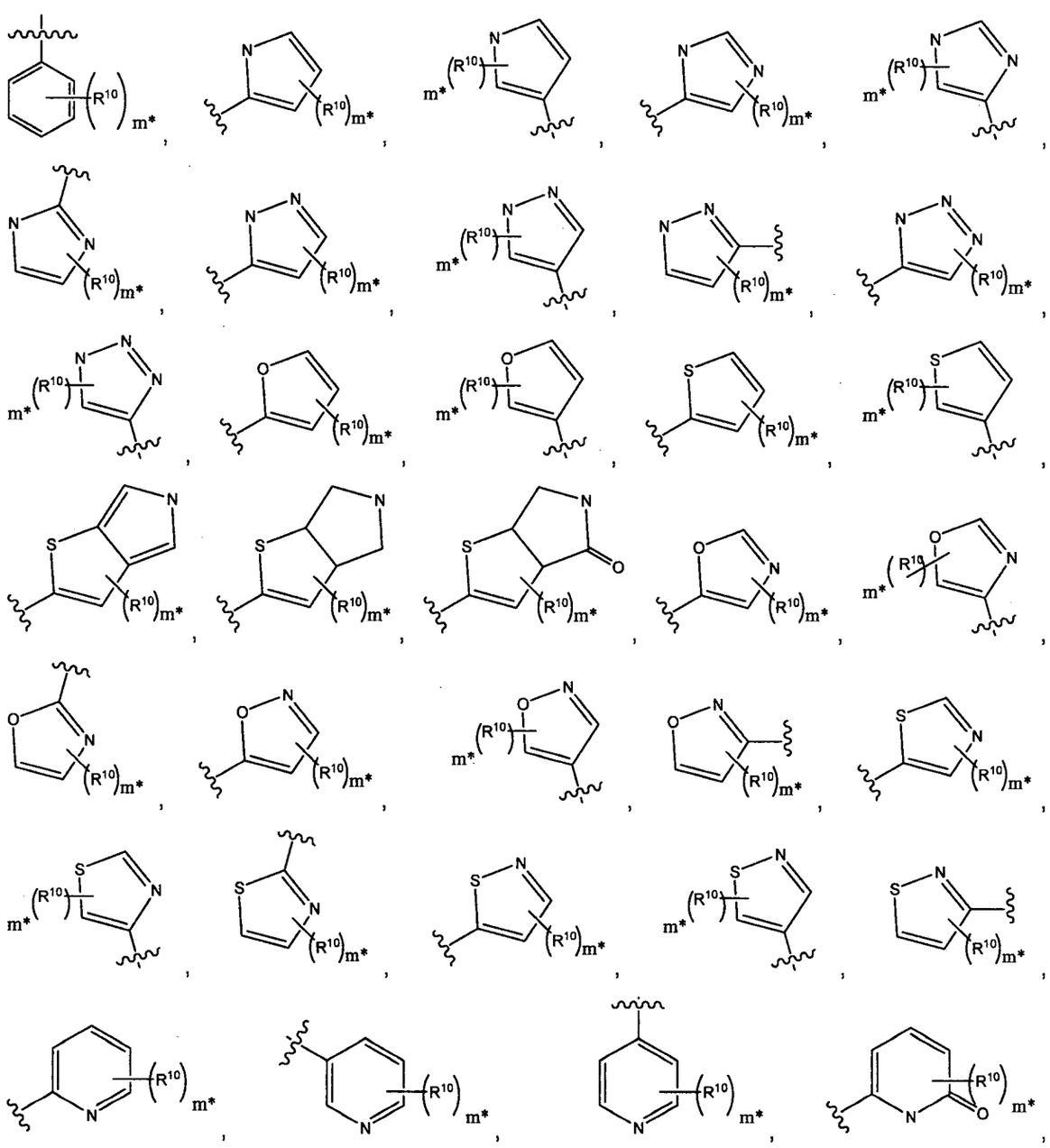
Los compuestos preferidos de la presente invención incluyen además compuestos donde R^2 es H, halo, ciano, alquinilo, $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=O)OR^4$, fenilo, naftilo, pirrolilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo, furanilo, tienilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, piridinilo, tetrahidropiridinilo, piridinonilo, pirazinilo, pirimidinilo, piridazinilo, indolilo, isoindolilo, indolinilo, indolinonilo, isoidolinilo, isoindolinonilo, dihidrobenzofuranilo, dihidroisobenzofuranilo, benzofuranilo, isobenzofuranilo, quinolinilo, isoquinolinilo, quinazolinilo, quinazolinonilo, tetrahidroquinolinilo, tetrahidroisoquinolinilo, dihidroquinolinonilo, dihidroisoquinolinonilo, quinoxalinilo, tetrahidroquinoxalinilo, benzomorfolinilo, dihidrobenzodioxinilo, imidazopiridinilo, naftiridinilo, benzotriazinilo,

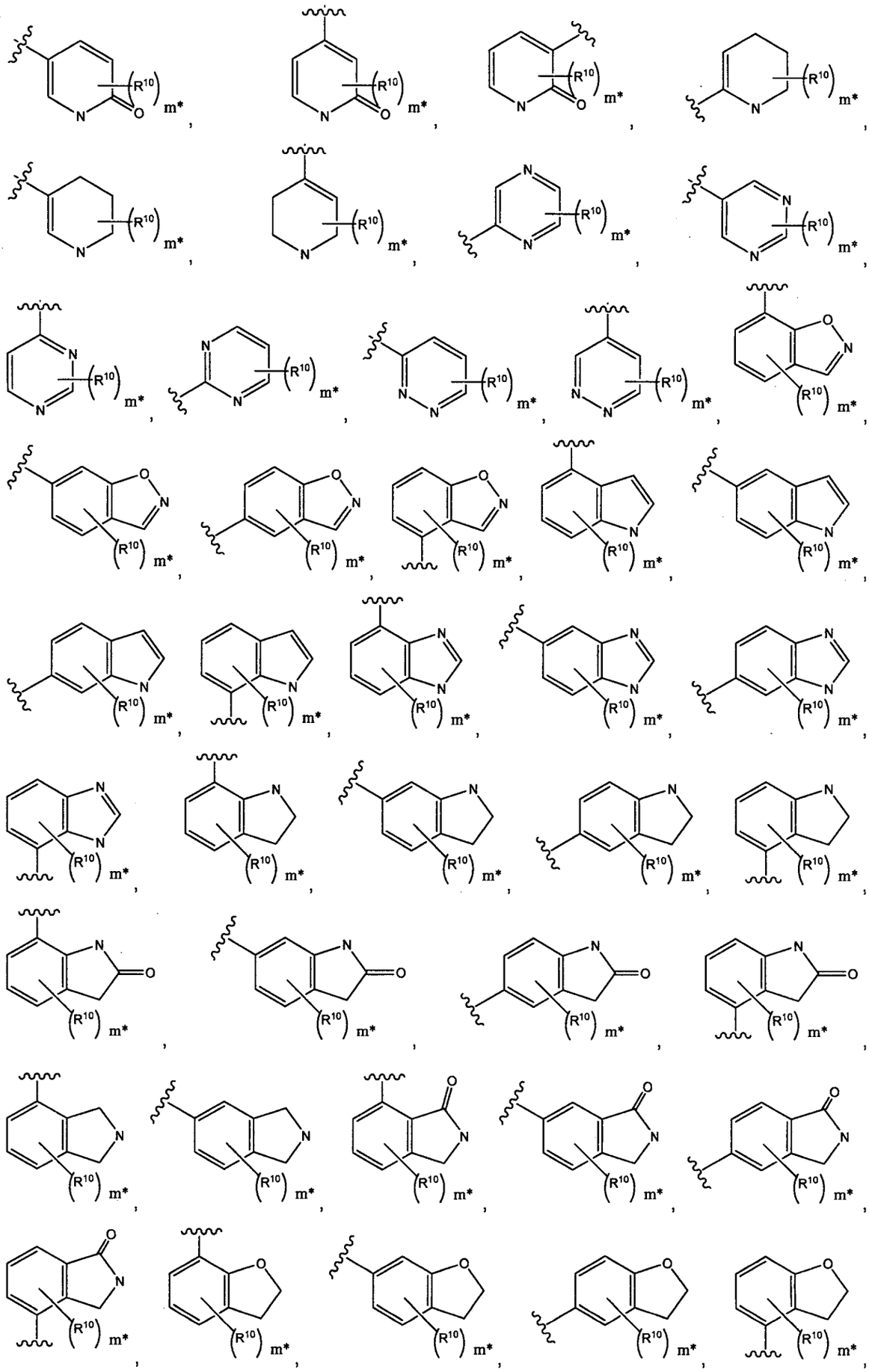
triazolopiridinilo, triazolopirimidinilo, triazolopiridazinilo, imidazopiridinilo, imidazopirimidinilo, imidazopiridazinilo, pirrolpiridinilo, pirrolpirimidinilo, pirrolpiridazinilo, pirazolpiridinilo, pirazolpirimidinilo, pirazolpiridazinilo, cinolinilo, tienopirrolilo, tetrahidrotienopirrolilo, dihidrotienopirrolonilo, tienopiridinilo, tienopirimidinilo, tienopiridazinilo, furopiridinilo, furopirimidinilo, furopirazidinilo, benzofuranilo, benzoimidazolilo, benzoisoxazolilo, benzotiazolilo, o benzoisotiazolilo cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia.

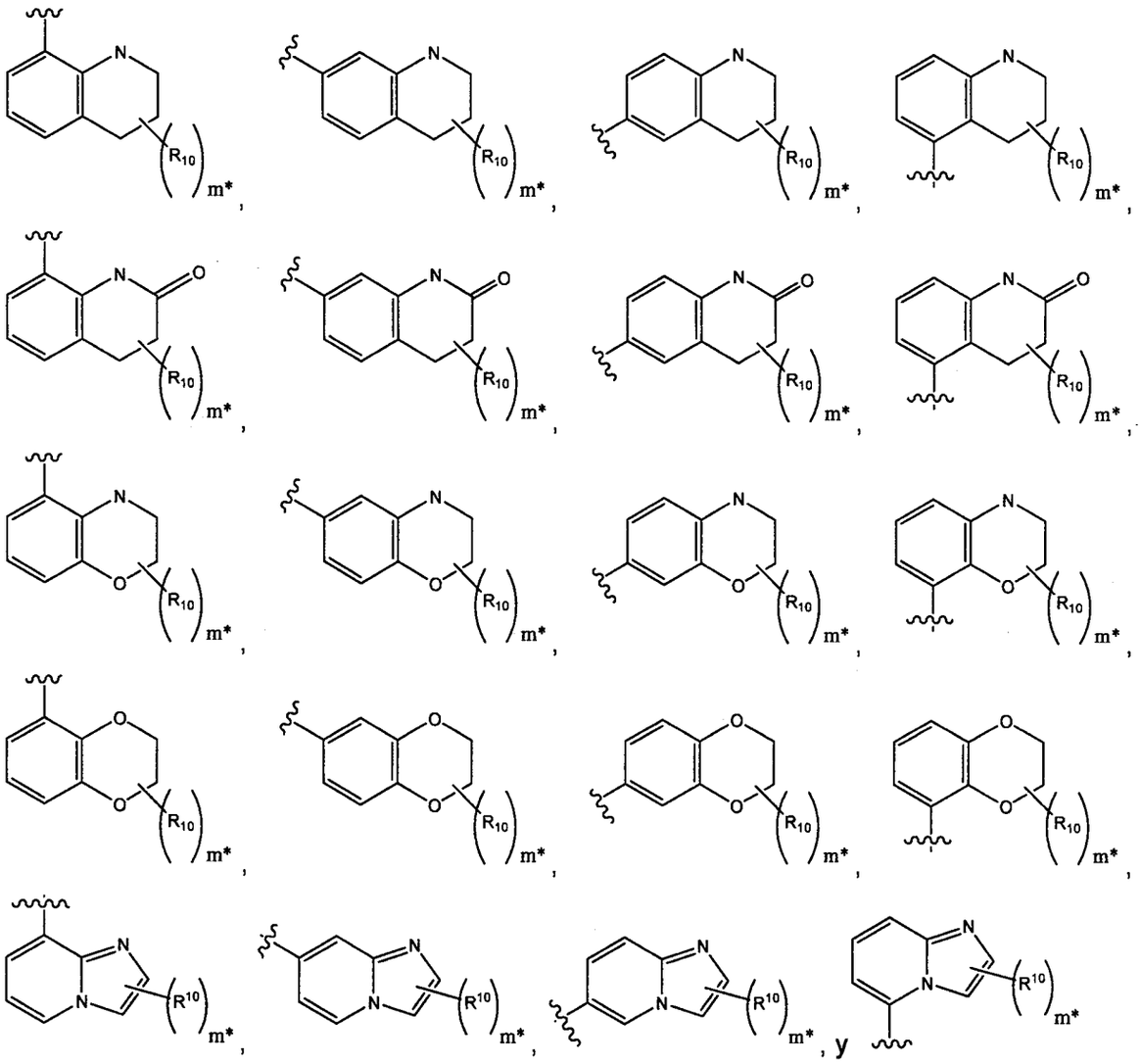
Los grupos R^2 preferidos incluyen

(a) halo, alquinilo, $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$ o $-N(R^5)C(=O)OR^4$ cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia; y

(b) un sistema de anillo arilo, heteroarilo o heterociclo seleccionado de





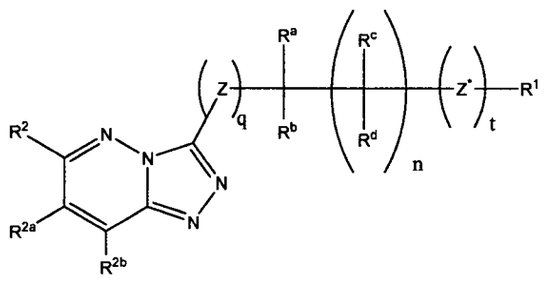


donde m* es 0, 1, 2, 3, 4, 5 o 6, según lo permita la valencia.

Los compuestos preferidos de la presente invención incluyen compuestos que tienen cualquiera o ambos grupos R^1 preferidos y grupos R^2 preferidos, solos o en cualquier combinación de los mismos.

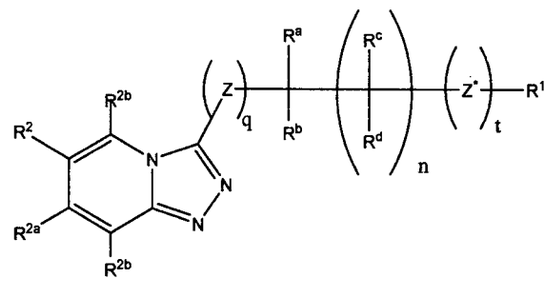
Los compuestos de la presente invención incluyen compuestos donde los grupos R^a, R^b, R^c y R^d son independientemente hidrógeno, alquilo (especialmente metilo) y halógeno (especialmente flúor).

Los compuestos preferidos dentro del alcance de las fórmulas I y II incluyen compuestos de las siguientes fórmulas IA, IB, IC, ID y IIA

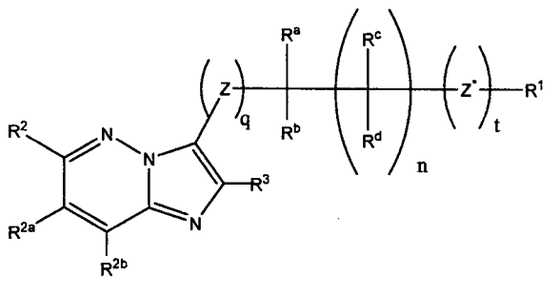


IA

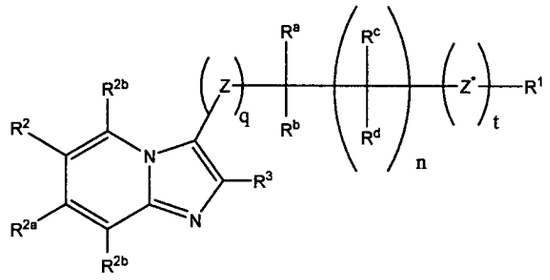
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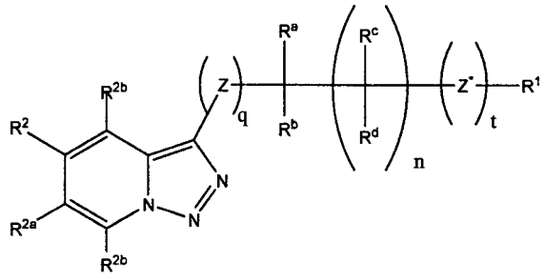
IB



IC



ID

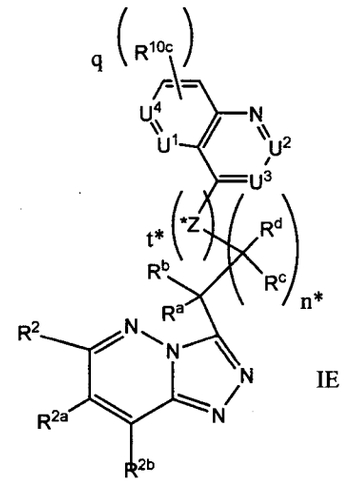


IIA

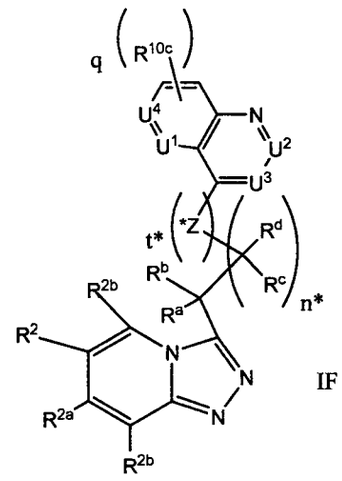
enantiómeros, diaestereómeros, sales y solvatos de los mismos, donde las variables R^a, R^b, R^c, R^d, R^1, R^2, R^{2a}, R^{2b}, R^3, Z, Z*, n, q y t son tal como previamente se han definido anteriormente. Los compuestos preferidos de fórmulas IA, IB, IC, ID y IIA incluyen compuestos que tienen cualquiera de los grupos R^1 y R^2 preferidos, solos o en cualquier combinación de los mismos.

Los compuestos preferidos dentro del alcance de las fórmulas I y II incluyen también compuestos que tienen las siguientes fórmulas IE, IF, IIB y IIC

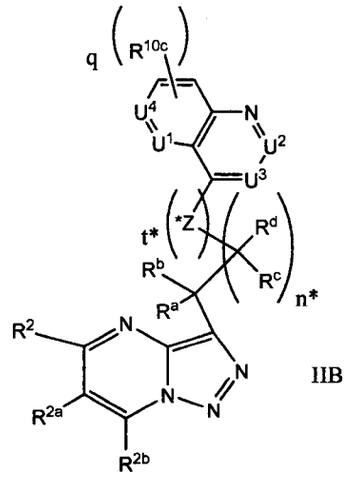
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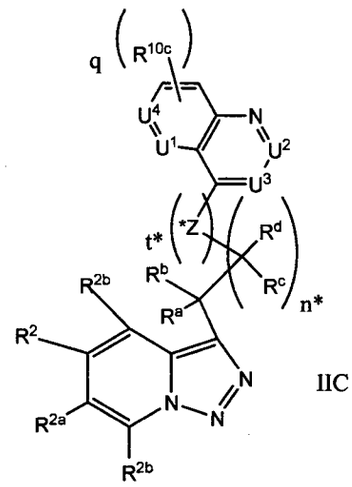
IE



IF



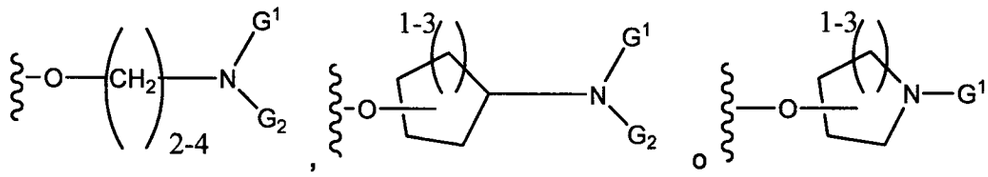
IIB



IIC

enantiómeros, diastereómeros, sales y solvatos de los mismos

donde las variables R^a, R^b, R^c, R^d, R^2, R^{2a}, R^{2b}, y Z*, son tal como previamente se han definido antes, con la condición de que en los compuestos de fórmula IE R^2 no es fenilo sustituido con un grupo



donde G^1 y G^2 son independientemente alquilo, cicloalquilo, o G^1 y G^2 conjuntamente con el átomo de nitrógeno al cual están unidos se combinan para formar un anillo heterociclo de 5 a 8 miembros; y además donde

q es 0, 1, 2 o 3;

n* es 0, 1 o 2;

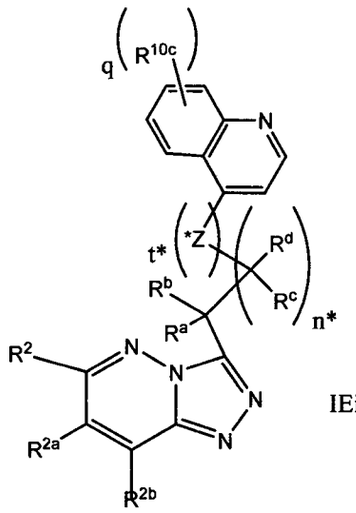
t* es 0 o 1

U^1, U^2, U^3 y U^4 son cada uno independientemente C, o N; y

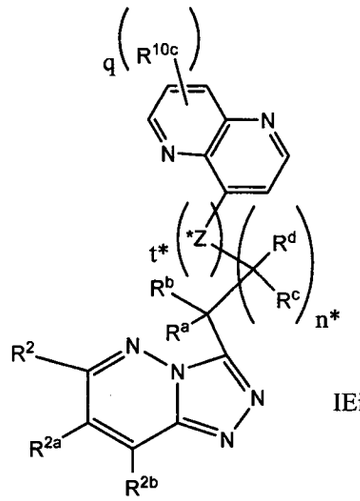
R^{10c} en cada caso está independientemente seleccionado de los grupos enumerados en la definición de R^{10} previamente descrita.

Los compuestos preferidos de fórmulas IE, IF, IIB y IIC incluyen compuestos que tienen cualquiera de los grupos R^2 preferidos descritos anteriormente.

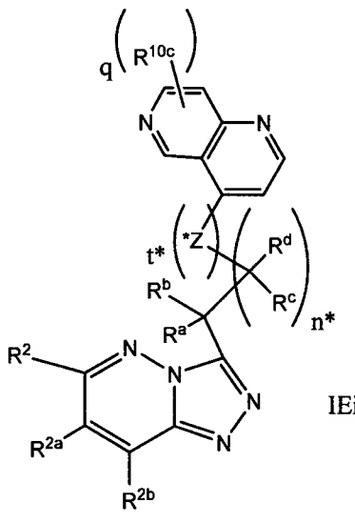
Los compuestos preferidos dentro del alcance de las fórmulas IE y IF incluyen compuestos de las siguientes fórmulas IEi, IEii, IEiii, IEiv, IFi, IFii, IFiii y IFiv



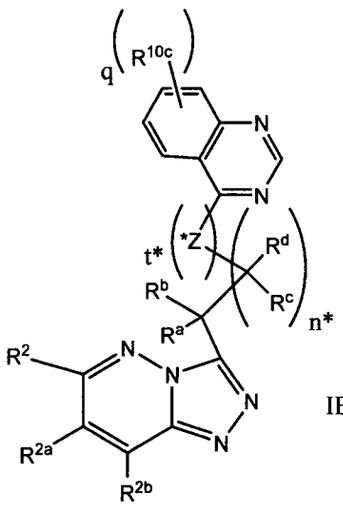
IEi



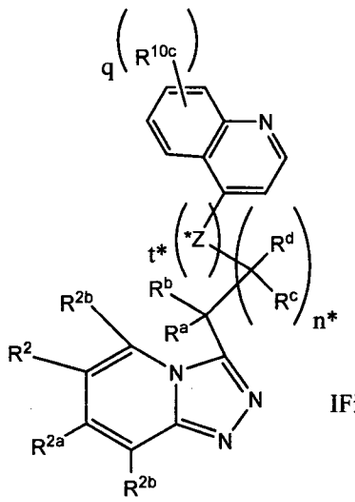
IEii



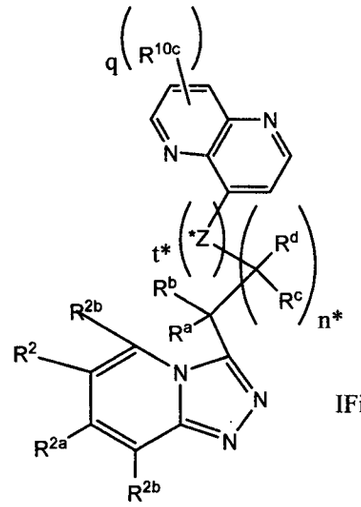
IEiii



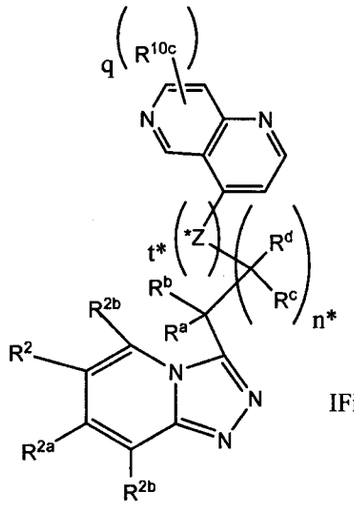
IEiv



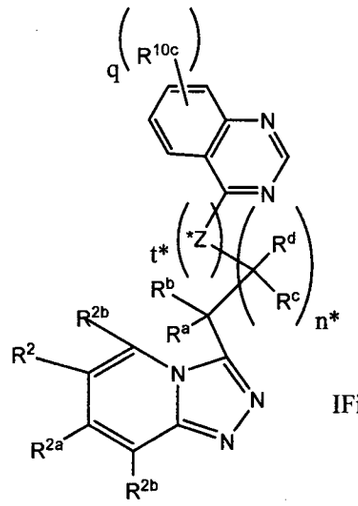
IFi



IFii



IFiii

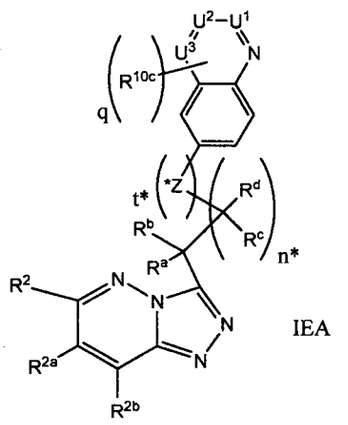


IFiv

y

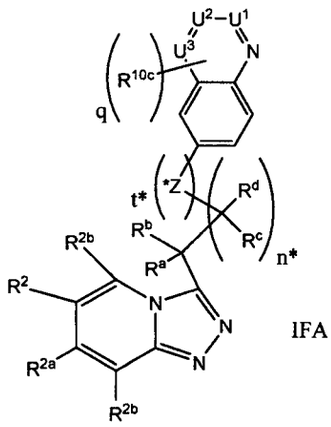
enantiómeros, diaestereómeros, sales y solvatos de los mismos.

Los compuestos preferidos dentro del alcance de la fórmula I incluyen además compuestos de las siguientes fórmulas IEA y IFA



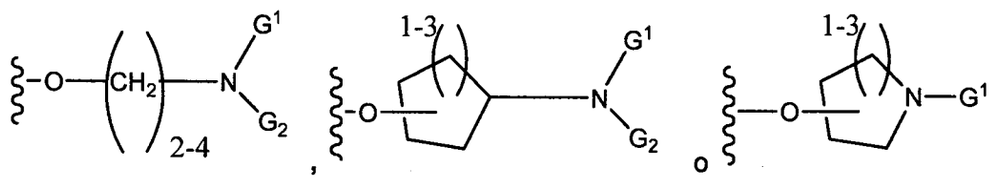
IEA

C00269



IFA

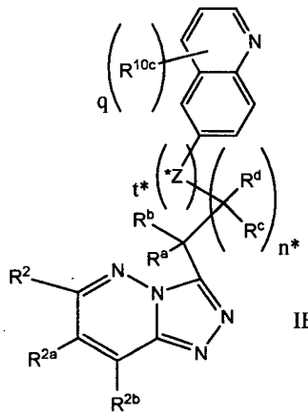
enantiómeros, diastereómeros, sales y solvatos del mismo donde las variables R^a, R^b, R^c, R^d, R^2, R^{2a}, R^{2b}, R^{10c}, U^1, U^2, U^3, Z*, n*, q, y t* son tal como se han definido previamente con la condición de que en los compuestos de fórmula IEA R^2 no es fenilo sustituido con un grupo



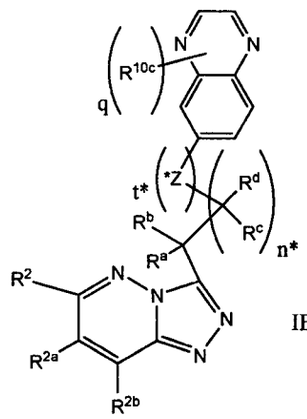
donde G^1 y G^2 son independientemente alquilo, cicloalquilo, o G^1 y G^2 conjuntamente con el átomo de nitrógeno al cual están unidos se combinan para formar un anillo heterociclo de 5 a 8 miembros. Los compuestos preferidos de las fórmulas IEA y IFA incluyen los compuestos que tienen cualquiera de los grupos R^2 preferidos descritos anteriormente.

Los compuestos preferidos de fórmulas IEA y IFA incluyen compuestos de fórmulas IEAi, IEAii, IEAiii, IFAi, IFAii y IFAiii

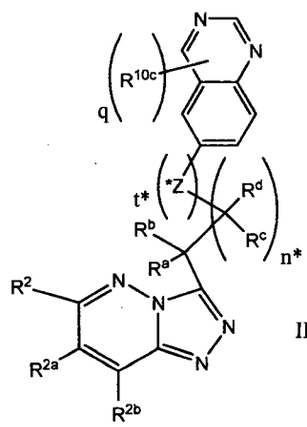
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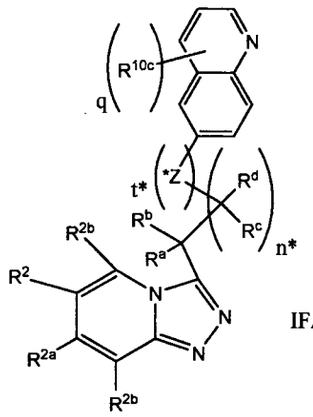
IEAi



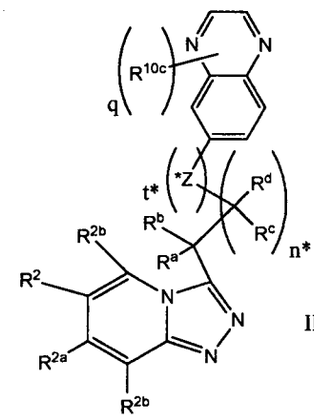
IEAii



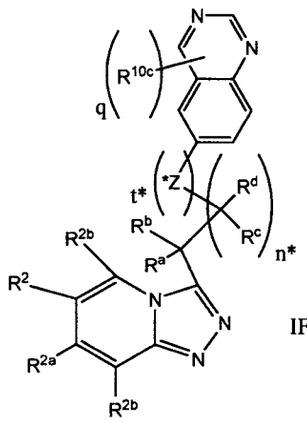
IEAiii



IFAi



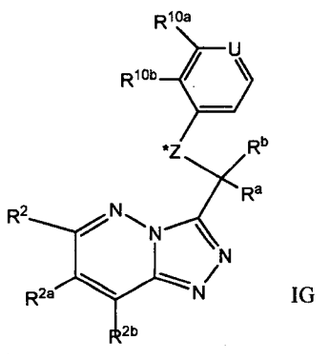
IFAii



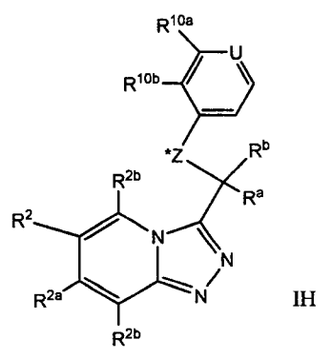
IFAiii

enantiómeros, diaestereómeros, sales y solvatos de los mismos.

Los compuestos preferidos dentro del alcance de la fórmula I incluyen además compuestos de la siguiente fórmula IG o IH

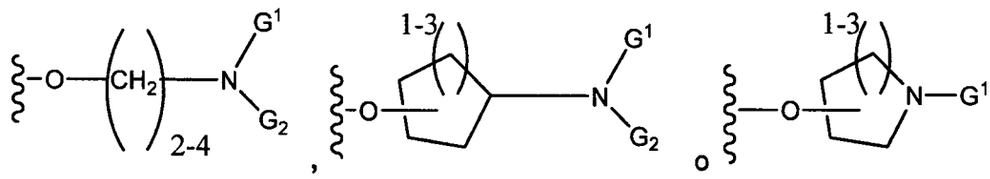


IG



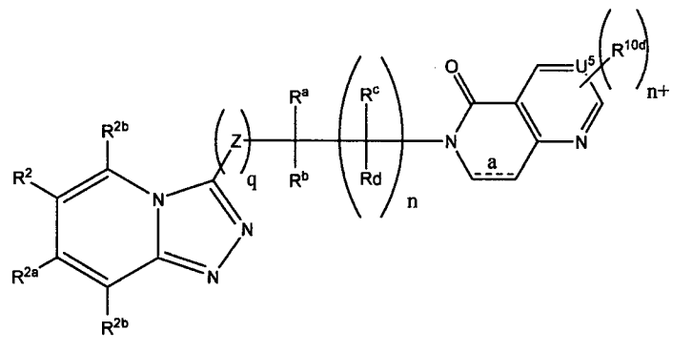
IH

donde U es CR^{10c} o N, y las variables R^a, R^b, R^2, R^{2a}, R^{2b}, R^{10a}, R^{10b}, R^{10c}, y Z*, son tal como se han definido previamente antes; con la condición de que en los compuestos de fórmula IG R^2 no es fenilo sustituido con un grupo

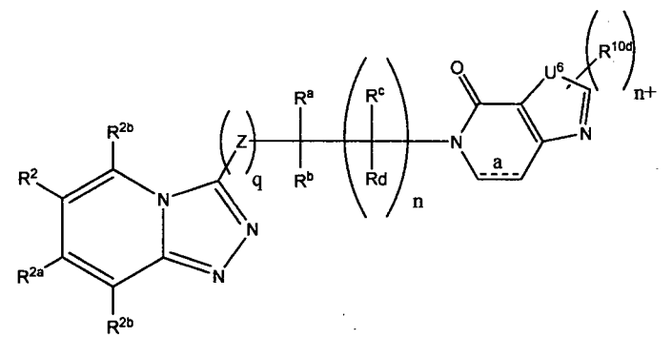


donde G^1 y G^2 son independientemente alquilo, cicloalquilo, o G^1 y G^2 conjuntamente con el átomo de nitrógeno al cual están unidos se combinan para formar un anillo heterocilo de 5 a 8 miembros. Los compuestos preferidos de fórmulas IG y IH incluyen compuestos que tienen cualquiera de los grupos R^2 preferidos descritos anteriormente.

Los compuestos preferidos dentro del alcance de la fórmula I incluyen además compuestos de las siguientes fórmulas IJ o IK



IJ



IK

donde a es un enlace o está ausente; U^5 es C o N; U^6 es NH, O o S; y m+ es 0, 1, 2 o 3. Los compuestos preferidos de fórmulas IJ y IK incluyen compuestos que tienen cualquiera de los grupos R^2 preferidos descritos anteriormente.

Los compuestos preferidos de la presente invención incluyen los compuestos ejemplificados aquí.

La invención se refiere también a composiciones farmacéuticas que contienen los compuestos anteriores, conjuntamente con un portador o vehículo farmacéuticamente aceptable.

La invención se refiere también a un método de tratamiento de cáncer en un sujeto usando los compuestos anteriores.

La invención se refiere también a un método de reducción del tamaño de un tumor en un sujeto usando los compuestos anteriores.

La invención se refiere también a un método de reducción de metástasis de un tumor en un sujeto, usando los compuestos anteriores.

La invención se refiere también a un método de tratamiento de trastornos medidados por HGF en un sujeto usando los compuestos anteriores.

INDICACIONES

Los compuestos de la presente invención serían útiles para, pero sin limitados a la prevención o tratamiento de enfermedades relacionadas con angiogénesis. Los compuestos de la invención tienen actividad inhibitoria c–Met. Los compuestos de la invención son útiles en terapia como agentes antineoplásicos o para minimizar los efectos nocivos de HGF.

Los compuestos de la invención serían útiles para el tratamiento de neoplasia incluyendo cáncer y metástasis, incluyendo, pero sin limitarlos a: carcinoma tal como cáncer de vejiga, de mama, colon, riñón, hígado, pulmón (incluyendo cáncer de células pequeñas de pulmón), esófago, vesícula biliar, ovario, páncreas, estómago, cuello uterino, tiroides, próstata, y piel (incluyendo carcinoma de células escamosas); tumores hematopoyéticos de linaje linfoide (incluyendo leucemia, leucemia linfocítica aguda, leucemia linfoblástica aguda, linfoma de células B, linfoma de células T, linfoma de Hodgkin, linfoma no Hodgkiniano, linfoma tricoleucocítico y linfoma de Burkett); tumores hematopoyéticos de linaje mieloide (incluyendo leucemias mielógenas aguda y crónica, síndrome mielodisplásico y leucemia promielocítica); tumores de origen mesenquimal (incluyendo fibrosarcoma y rabdomiosarcoma, y otros sarcomas, por ejemplo, tejidos blandos y hueso); tumores del sistema nervioso periférico y central (incluyendo astrocitoma, neuroblastoma, glioma y schwannomas); y otros tumores (incluyendo melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentoso, queratocantoma, cáncer folicular tiroideo y sarcoma de Kaposi).

Preferiblemente, los compuestos son útiles para el tratamiento de neoplasia seleccionada de cáncer de pulmón, cáncer de colon y cáncer de mama.

Los compuestos serán también útiles para el tratamiento de trastornos oftalmológicos tales como injerto de tejido corneal, neovascularización ocular, neovascularización retinal incluyendo neovascularización seguida de daño o infección, retinopatía diabética, fibroplasia retrolental y glaucoma neovascular; isquemia retinal; hemorragia vítrea, enfermedades ulcerativas tales como úlcera gástrica; patológica, pero no maligna, trastornos tales como hemangiomas, incluyendo hemangiomas infantiles, angiofibroma de nasofaringe y necrosis avascular del hueso; y trastornos del sistema reproductor femenino tal como endometriosis. Los compuestos son también útiles para el tratamiento de edema, y trastornos de hiperpermeabilidad vascular.

Los compuestos de la invención son útiles en terapia de enfermedades proliferativas. Estos compuestos pueden ser útiles para el tratamiento de una enfermedad reumatoidea o reumática inflamatoria, especialmente de manifestaciones en el aparato locomotor, tal como

varias enfermedades reumatoideas inflamatorias, especialmente poliartritis crónica incluyendo artritis reumatoidea, artritis juvenil o artropatía psoriásica; síndrome paraneoplásico o enfermedades de inflamaciones inducidas por tumor, derrames efusiones turbias, colagenosis, tal como Lupus eritematoso sistémico, poli–miositis, dermato–miositis, esclerodermia sistémica o colagenosis mixta; artritis post–infecciosa (en el que no puede hallarse un organismo patógeno vivo, o en la parte del cuerpo afectada), espondiloartritis seronegativa, tal como espondilitis anquilosante; vasculitis, sarcoidosis, o artrosis; o cualquier combinación de los mismos. Un ejemplo de un trastorno relacionado con inflamación es (a) inflamación sinovial, por ejemplo, sinovitis, incluyendo cualquiera de las formas particulares de sinovitis, en particular sinovitis bursal y sinovitis purulenta, en la medida que no esté inducida por cristales. Dicha inflamación sinovial puede por ejemplo, ser consecuencia de o estar asociada con enfermedades, por ejemplo, artritis, por ejemplo, osteoartritis, artritis reumatoidea o artritis deformante. La presente invención se también aplicable al tratamiento sistémico de inflamación, por ejemplo, trastornos o enfermedades inflamatorias, de las articulaciones o aparato locomotor en la región de la inserción de tendones y vainas del tendón. Dicha inflamación puede ser, por ejemplo, consecuencia de o asociada con enfermedad o además (en un sentido más amplio de la invención) con intervención quirúrgica incluyendo, en particular, trastornos tales como inserción endopática, síndrome miofacial y tendomiosis. La presente invención se aplica además especialmente al tratamiento de inflamación, por ejemplo, trastorno o enfermedad inflamatoria, de tejido conjuntivo, incluyendo dermatomiositis y miositis.

Estos compuestos pueden usarse como agentes activos contra enfermedades tales como artritis, ateroesclerosis, psoriasis, hemangiomas, angiogénesis miocárdica, colaterales coronarias y cerebrales, angiogénesis isquémica límbica, curación de heridas, enfermedades relacionadas con úlcera péptica Helicobacter, fracturas, linfadenitis regional, rubeosis, glaucoma neovascular y retinopatias tales como aquellas asociadas con retinopatía diabética o degeneración macular. Además, algunos de estos compuestos pueden ser usados como agentes activos contra tumores sólidos, ascitis maligna, cánceres hematopoyéticos y trastornos hiperproliferativos tales como hiperplasia tiroidea (especialmente enfermedad de Grave) y quistes (tal como hipervascularidad de estroma de ovario, característica de síndrome de poliquistosis ovárica (síndrome de Stein–Leventhal)) ya que dichas enfermedades requieren una proliferación de células de vasos sanguíneos para su crecimiento y/o metástasis.

Además, algunos de estos compuestos pueden ser usados como agentes activos contra quemaduras, enfermedad crónica de pulmón, accidente cerebro–vascular, pólipos, anafilaxis, inflamación alérgica crónica, síndrome de hiperestimulación de ovario, edema cerebral asociado con tumor cerebral, edema pulmonar o cerebral inducido por altura, trauma o hipoxia, edema ocular y macular, ascitis, y otras enfermedades donde la hiperpermeabilidad vascular, derrames, exudados, extravasación de proteína o edema es una manifestación de la enfermedad. Los compuestos pueden ser también útiles en el

tratamiento de trastornos en los cuales la extravasación de proteínas produce el depósito de fibrina y matriz extracelular, promoviendo la proliferación estromal (por ejemplo, fibrosis, cirrosis y síndrome del túnel carpiano).

Los compuestos de la presente invención son también útiles en el tratamiento de úlceras incluyendo úlceras bacteriana, fungal, úlcera de Mooren y colitis ulcerativa.

Los compuestos de la presente invención son también útiles en el tratamiento de trastornos en los cuales ocurre angiogénesis no deseada, edema, o deposición estromal en infecciones virales tales como Herpes simplex, Herpes Zoster, SIDA, sarcoma de Kaposi, infecciones protozoales y toxoplasmosis, seguidas de trauma, radiación, accidentes cerebro–vasculares, endometriosis, síndrome de hiperestimulación de ovario, lupus sistémico, sarcoidosis, sinovitis, enfermedad de Crohn, anemia celular falciforme, enfermedad de Lyme, pénfigo, enfermedad de Paget, síndrome de hiperviscosidad, enfermedad de Osler–Weber–Rendu, inflamación crónica, enfermedad pulmonar oclusiva crónica, asma, y enfermedad reumática o reumatoidea inflamatoria. Los compuestos son también útiles en la reducción de grasa subcutánea y para el tratamiento de la obesidad.

Los compuestos de la presente invención son también útiles en el tratamiento de trastornos oculares tales como edema macular y ocular, enfermedad neovascular ocular, escleritis, queratotomia radial, uveitis, vitritis, miopia, fosas ópticas, desprendimiento retinal crónico, complicaciones post–láser, glaucoma, conjuntivitis, enfermedad de Stargardt y enfermedad de Eales además de retinopatía y degeneración macular.

Los compuestos de la presente invención son también útiles en el tratamiento de trastornos cardiovasculares tales como ateroesclerosis, restenosis, arterioesclerosis, oclusión vascular y enfermedad obstructiva de la carótida.

Los compuestos de la presente invención son también útiles en el tratamiento de indicios relacionadas con cáncer tales como tumores sólidos, sarcomas (especialmente sarcoma de Ewing y osteosarcoma), retinoblastoma, rabdomiosarcomas, neuroblastoma, enfermedades hematopoyéticas, incluyendo leucemia y linfoma, tumor inducido por derrames pleurales o pericardiales, y ascitis malignas.

Los compuestos de la presente invención son también útiles en el tratamiento de trastornos diabéticos tales como retinopatía diabética y microangiopatía.

Los compuestos de la presente invención son también útiles en la reducción del flujo sanguíneo en un tumor en un sujeto.

Los compuestos de la presente invención son también útiles en la reducción de metástasis de un tumor en un sujeto.

Los compuestos de esta invención pueden también actuar como inhibidores de otras proteín quinasas, por ejemplo, tie–2, lck, src, fgf, c–Met, ron, ckit y ret, y por lo tanto ser eficaces en el tratamiento de enfermedades asociadas con otras proteín quinasas.

Además de ser útiles en el tratamiento de seres humanos, estos compuestos son también útiles para tratamiento veterinario en animales domésticos, animales exóticos y

animales de granja, incluyendo mamíferos, roedores y similares. Los animales más preferidos incluyen caballos, perros y gatos.

Tal como se usa aquí, los compuestos de la presente invención incluyen los derivados farmacéuticamente aceptables de los mismos.

Cuando se usa la forma plural para compuestos, sales y similares, tiene el mismo significado también para un compuesto, sal y similar, en forma singular.

DEFINICIONES

"Angiogénesis" se define como cualquier alteración de un lecho vascular existente o a la formación de nueva vasculatura que beneficia la perfusión del tejido. Esto incluye, formación de nuevos vasos mediante el brote de células endoteliales existentes en los vasos sanguíneos o remodelación de vasos existentes para alterar el tamaño, la madurez, las propiedades de dirección o fluidez del tejido.

Tal como se usa aquí, "HGF" se refiere al factor de crecimiento/ factor de dispersión de hepatocitos. Esto incluye al factor de crecimiento/ factor de dispersión de hepatocitos purificado, fragmentos del factor de crecimiento/ factor de dispersión de hepatocitos, fragmentos sintetizados químicamente del factor de crecimiento/ factor de dispersión de hepatocitos, derivados o versiones mutadas del factor de crecimiento/ factor de dispersión de hepatocitos y proteínas de fusión que comprenden el factor de crecimiento/ factor de dispersión y otra proteína. "HGF" tal como se usa aquí incluye también al factor de crecimiento/ factor de dispersión de hepatocitos, aislado de especies distintas de las del ser humano.

Tal como se usa aquí, "c–Met" se refiere al receptor para HGF. Esto incluye al receptor purificado, a fragmentos del receptor, fragmentos del receptor sintetizados químicamente, derivados o versiones mutadas del receptor, y proteínas de fusión que comprenden al receptor y otra proteína. "c–Met" tal como se usa aquí incluye también al receptor HGF aislado de una especie distinta de la del ser humano.

Tal como se usan aquí, los términos "factor de crecimiento de hepatocitos" y "HGF" se refieren a un factor de crecimiento que tiene típicamente una estructura con seis dominios (dominios finger, Kringle 1, Kringle 2, Kringle 3, Kringel 4 y serina proteasa). Los fragmento de HGF constituyen HGF con unos pocos dominios y variantes de HGF que pueden tener algunos de los dominios de HGF repetidos; ambos están incluidos si es que aún retienen su respectiva capacidad de unirse a un receptor HGF. Los términos "factor de crecimiento de hepatocitos" y "HGF" incluyen factor de crecimiento de hepatocitos de seres humanos ("HGFhu") y cualquier especie de mamífero no humano y en particular HGF de rata. Los términos que se usan aquí incluyen formas madura, pre–pro y pro purificadas a partir de una fuente natural, sintetizadas químicamente o producidas recombinantemente. El HGF humano está codificado en la secuencia de ADNc publicada por Miyazawa et al. (1989), supra, o Nakamura et al. (1989), supra. La secuencia descrita por Miyazawa et al. y Nakamura et al.

difiere en 14 amino ácidos. La razón de las diferencia no es enteramente clara; polimorfismo o artefactos de clonación están entre las posibilidades. Ambas secuencias están abarcadas específicamente por los términos anteriores. Se comprenderá que existen variaciones alélicas naturales que pueden ocurrir entre individuos, tal como se ha demostrado en una o más diferencias de amino ácido en la secuencia de amino ácido de cada individuo. Los términos "factor de crecimiento de hepatocitos" y "HGF" incluyen específicamente el delta 5 HGFhu descrito por Seki et al., supra.

Los términos "receptor HGF" y "c–Met" cuando se usan aquí se refieren a un receptor celular para HGF, que incluye típicamente un dominio extracelular, un dominio de transmembrana y un dominio intracelular, así como también variantes y fragmentos de los mismos que retienen la capacidad de unirse a HGF. Los términos "receptor HGF" y "c–Met" incluyen la molécula polipeptídica que comprende la secuencia natural de amino ácido de longitud total codificada por el gen conocido variadamente como p190.sup.MET. La presente definición abarca específicamente formas solubles del receptor HGF, y del receptor HGF de fuentes naturales, producido sintéticamente in vitro u obtenido por manipulación genética que incluye métodos de tecnología de ADN recombinante. Las variantes o fragmentos del receptor HGF, comparten preferiblemente por lo menos aproximadamente 65% de homología de secuencia y más preferiblemente por lo menos aproximadamente 75% de homología de secuencia con cualquier dominio de la secuencia de amino ácido de c–Met humano, publicada en Rodrigues et al., Mol. Cell. Biol., 11:2962–2970 (1991); Park et al., Proc. Natl. Acad. Sci., 84:6379–6383 (1987); o Ponzetto et al., Oncogene, 6:553–559 (1991).

Los términos "agonista" and "agonístico" cuando se usan aquí se refieren a o describen una molécula que es capaz de inducir, promover o realzar sustancialmente, directa o indirectamente, la actividad biológica de HGF o la activación del receptor HGF.

Los términos "cáncer" y "canceroso" cuando se usan aquí se refieren o describen el estado fisiológico en los mamíferos, el cual se manifiesta típicamente por el crecimiento desrregulado de células. Ejemplos de cáncer incluyen, pero no están limitados a carcinoma, linfoma, sarcoma, blastoma y leucemia. Ejemplos más particulares de dichos cánceres incluyen carcinoma de células escamosas, cáncer de pulmón, cáncer pancreático, cáncer de cuello uterino, cáncer de vesícula, hepatoma, cáncer de mama, carcinoma de colon y cáncer de cráneo y cuello. Aunque el término "cáncer" tal como se usa aquí no está limitado a ninguna forma específica de la enfermedad, se cree que los métodos de la invención serán particularmente eficaces para cánceres que van acompañados de niveles incrementados de HGF o expresión de c–Met en el mamífero.

Los términos "tratar," "tratamiento," y "terapia" tal como se usan aquí, se refieren a terapia curativa, terapia profiláctica, y terapia preventiva.

El término "mamífero" tal como se usa aquí, se refiere a cualquier mamífero clasificado como un mamífero, incluyendo seres humanos, vacas, caballos, perros y gatos. En una realización preferida de la invención, el mamífero es un ser humano.

Dados los niveles elevados de c–Met y HGF que se observan en hipertensión, arteriosclerosis, infarto de miocardio, y artritis reumatoidea, los ligandos de ácido nucleico servirán como agentes terapéuticos útiles para estas enfermedades.

El término "tratamiento" incluye tratamiento terapéutico así como también tratamiento profiláctico (ya sea para prevenir la aparición de trastornos o para demorar la aparición de una etapa pre—clínicamente evidente de trastornos en individuos).

Un "derivado farmacéuticamente aceptable " denota cualquier sal, éster o compuesto de esta invención, o cualquier otro compuesto que por administración a un paciente es capaz de proveer (directa o indirectamente) un compuesto de esta invención, o un metabolito o residuo del mismo, caracterizado por la capacidad de inhibir angiogénesis.

La frase "terapéuticamente eficaz " se da para calificar la cantidad de cada agente, que logrará el objetivo de proporcionar una mejora en la gravedad y frecuencia de incidencia de la enfermedad, en el tratamiento de cada agente por sí mismo, evitando los efectos colaterales adversos asociados típicamente con terapias alternativas. Por ejemplo los agentes terapéuticos neoplásicos eficaces prolongan la supervivencia del paciente, inhiben la proliferación rápida del crecimiento de células asociado con el neoplasma o efectúan una regresión del neoplasma.

El término "H" denota un átomo de hidrógeno únicamente. Este radical puede estar unido, por ejemplo, a un átomo de oxígeno para formar un radical hidroxilo.

Cuando se usa el término "alquilo", solo o dentro de otros términos, tales como "haloalquilo" y "alquilamino", se abarcan radicales lineales o ramificados que tienen uno hasta aproximadamente doce átomos de carbono. Radicales alquilo más preferidos son los radicales "alquilo inferior" que tienen uno hasta aproximadamente seis átomos de carbono. Ejemplos de dichos radicales incluyen metilo, etilo, n–propilo, isopropilo, n–butilo, isobutilo, *sec*–butilo, *ter*–butilo, pentilo, isoamilo, hexilo y similares. Son aún más preferidos los radicales alquilo inferior que tienen uno o dos átomos de carbono. El término "alquilenilo" abarca radicales alquilo divalentes puenteados tales como metilenilo y etilenilo. El término "alquilo inferior sustituido con R^2" no incluye una porción "acetal".

El término "alquenilo" abarca radicales lineales o ramificados que tienen por lo menos un enlace doble de carbono a carbono de dos hasta aproximadamente doce átomos de carbono. Los radicales alquenilo más preferidos son los radicales "alquenilo inferior" que tienen de dos hasta aproximadamente seis átomos de carbono. Los radicales alquenilo inferior más preferidos son los radicales que tienen dos hasta aproximadamente cuatro átomos de carbono. Ejemplos de radicales alquenilo incluyen etenilo, propenilo, alilo, propenilo, butenilo y 4–metilbutenilo. Los términos "alquenilo" y "alquenilo inferior", abarcan radicales que tienen orientaciones "cis" y "trans", o alternativamente, orientaciones "E" y "Z".

El término "alquinilo" denota radicales lineales o ramificados que tienen por lo menos un enlace triple de carbono a carbono y tienen dos hasta aproximadamente doce átomos de carbono. Los radicales alquinilo más preferidos son los radicales "alquinilo inferior" que tienen dos hasta aproximadamente seis átomos de carbono. Son más preferidos los

radicales alquinilo inferior que tienen dos hasta aproximadamente cuatro átomos de carbono. Ejemplos de dichos radicales incluyen propargilo, butinilo, y similares.

Los radicales alquilo, alquilenilo, alquenilo y alquinilo pueden estar opcionalmente sustituidos con uno o más grupos funcionales tales como halo, hidroxi, nitro, amino, ciano, haloalquilo, arilo, heteroarilo, heterociclo y similares.

El término "halo" se refiere a halógeno, tal como átomos de fluor, cloro, bromo o yodo.

El término "haloalquilo" abarca radicales en los cuales uno cualquiera o más de los átomos de carbono del alquilo están sustituidos con halo tal como se ha definido anteriormente. Están abarcados específicamente los radicales monohaloalquilo, dihaloalquilo y polihaloalquilo incluyendo perhaloalquilo. Un radical monohaloalquilo, para dar un ejemplo, puede tener un átomo de yodo, bromo, cloro o fluor dentro del radical. Los radicales dihalo y polihaloalquilo pueden tener dos o más de los mismos átomos de halógeno o una combinación de radicales halo diferentes. "Haloalquilo inferior" abarca radicales que tienen 1–6 átomos de carbono. Son aún más preferidos los radicales haloalquilo que tienen uno a tres átomos de carbono. Ejemplos de radicales haloalquilo incluyen fluormetilo, difluormetilo, trifluormetilo, clorometilo, diclorometilo, triclorometilo, pentafluoretilo, heptafluorpropilo, difluorclorometilo, diclorofluormetilo, difluoretilo, difluorpropilo, dicloroetilo y dicloropropilo. "Perfluoralquilo" significa radicales alquilo que tienen todos los átomos de hidrógeno reemplazados con átomos de fluor. Ejemplos incluyen trifluormetilo y pentafluoretilo.

El término "hidroxialquilo" abarca radicales alquilo lineales o ramificados que tienen uno hasta aproximadamente diez átomos de carbono, cualquiera de los cuales puede ser sustituido con uno o más radicales hidroxilo. Los radicales hidroxialquilo más preferidos son los radicales "hidroxialquilo inferior" que tienen de uno a seis átomos de carbono y uno o más radicales hidroxilo. Ejemplos de dichos radicales incluyen hidroximetilo, hidroxietilo, hidroxipropilo, hidroxibutilo e hidroxihexilo. Son aún más preferidos los radicales hidroxialquilo que tienen uno a tres átomos de carbono.

El término "alcoxi" abarca radicales lineales o ramificados, que contienen oxi, teniendo cada uno de ellos porciones alquilo de uno hasta aproximadamente diez átomos de carbono. Radicales alcoxi más preferidos son los radicales "alcoxi inferior" que tienen desde uno a seis átomos de carbono. Ejemplos de dichos radicales incluyen metoxi, etoxi, propoxi, butoxi y *ter*–butoxi. Son aún más preferidos los radicales alcoxi inferior que tienen de uno hasta tres átomos de carbono. Los radicales alcoxi pueden estar adicionalmente sustituidos con uno o más átomos de halógeno, tales como fluor, cloro o bromo, para proveer radicales "haloalcoxi". Son aún más preferidos los radicales haloalcoxi que tienen desde uno hasta tres átomos de carbono. Ejemplos de dichos radicales incluyen fluormetoxi, clorometoxi, trifluormetoxi, trifluoretoxi, fluoretoxi y fluorpropoxi.

El término "arilo", solo o en combinación, significa un sistema aromático carbocíclico que contiene uno o dos anillos, donde dichos anillos pueden estar unidos conjuntamente de manera fusionada. El término "arilo" abarca radicales aromáticos tales como fenilo, naftilo,

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indenilo, tetrahidronaftilo, e indanilo. El arilo más preferido es fenilo. Dicho grupo "arilo" puede tener 1 o más sustituyentes tales como alquilo inferior, hidroxilo, halo, haloalquilo, nitro, ciano, alcoxi, alquilamino inferior, y similares. Fenilo sustituido con –O–CH_2–O– forma el sustituyente aril benzodioxolilo.

El término "heterociclilo" (o "heterociclo") abarca radicales de anillos, saturados y parcialmente saturados, que contienen heteroátomos, donde los heteroátomos pueden estar seleccionados entre nitrógeno, azufre y oxígeno. No incluye anillos que contienen porciones –O–O–,–O–S– o –S–S–. Dicho grupo "heterociclilo" puede tener 1 a 3 sustituyentes tales como hidroxilo, Boc, halo, haloalquilo, ciano, alquilo inferior, aralquilo inferior, oxo, alcoxi inferior, amino, alquilamino inferior, y similares.

Ejemplos de radicales heterocíclicos saturados incluyen grupos heteromonocíclicos saturados de 3 a 6 miembros que contienen de 1 a 4 átomos de nitrógeno [por ejemplo pirrolidinilo, imidazolidinilo, piperidinilo, pirrolinilo, piperazinilo]; un grupo heteromonocíclico de 3 a 6 miembros que contiene de 1 a 2 átomos de oxígeno y 1 a 3 átomos de nitrógeno [por ejemplo morfolinilo]; un grupo heteromonocíclico saturado, de 3 a 6 miembros que contiene 1 a 2 átomos de azufre y 1 a 3 átomos de nitrógeno [por ejemplo, tiazolidinilo]. Ejemplos de radicales heterociclilo parcialmente saturados incluyen dihidrotienilo, dihdropiranilo, dihidrofurilo, dihdrotiazolilo, y similares.

Ejemplos particulares de heterociclilo saturado y parcialmente saturado incluyen pirrolidinilo, imidazolidinilo, piperidinilo, pirrolinilo, pirazolidinilo, piperazinilo, morfolinilo, tetrahidropiranilo, tiazolidinilo, dihidrotienilo, 2,3–dihidro–benzo[1,4]dioxanilo, indolinilo, isoindolinilo, dihidrobenzotienilo, dihidrobenzofurilo, isocromanilo, cromanilo, 1,2–dihidroquinolilo, 1,2,3,4–tetrahidro–isoquinolilo, 1,2,3,4–tetrahidro–quinolilo, 2,3,4,4a,9,9a–hexahdro–1H–3–aza–fluorenilo, 5,6,7–trihidro–1,2,4–triazolo[3,4–a]isoquinolilo, 3,4–dihidro–2H–benzo[1,4]oxazinilo, benzo[1,4]dioxanilo, 2,3–dihidro–1H–1λ'–benzo[d]isotiazol–6–ilo, dihidropiranilo, dihidrofurilo y dihidrotiazolilo, y similares.

El término heterociclilo, (o heterociclo) abarca también radicales donde los radicales heterocíclicos son fusionados/ condensados con radicales arilo: un grupo heterocíclico insaturado, condensado que contiene 1 a 5 átomos de nitrógeno, por ejemplo, indolilo, isoindolilo, indolizinilo, benzimidazolilo, quinolilo, isoquinolilo, indazolilo, benzotriazolilo, tetrazolopiridazinilo [por ejemplo, tetrazol [1,5–b]piridazinilo]; un grupo heterocíclico insaturado, condensado que contiene 1 a 2 átomos de oxígeno y 1 a 3 átomos de nitrógeno [por ejemplo, benzoxazolilo, benzoxadiazolilo]; un grupo heterocíclico condensado insaturado que contienen 1 a 2 átomos de azufre y 1 a 3 átomos de nitrógeno [por ejemplo, benzotiazolilo, benzotiadiazolilo]; y un grupo heterocíclico saturado, parcialmente insaturado e insaturado condensado que contiene 1 a 2 átomos de oxígeno o azufre [por ejemplo benzofurilo, benzotienilo, 2,3–dihidro–benzo[1,4]dioxinilo y dihidrobenzofurilo].

El término "heteroarilo" denota sistemas de anillo arilo que contienen uno o más heteroátomos seleccionados del grupo O, N y S, donde los átomos de nitrógeno y azufre del anillo, están opcionalmente oxidados y los átomos de nitrógeno están opcionalmente

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cuaternizados. Ejemplos de éstos, incluyen un grupo heteromonociclilo insaturado de 5 a 6 miembros, que contiene 1 a 4 átomos de nitrógeno, por ejemplo, pirrolilo, imidazolilo, pirazolilo, 2–piridilo, 3–piridilo, 4–piridilo, pirimidilo, pirazinilo, piridazinilo, triazolilo [por ejemlo, 4H–1,2,4–triazolilo, 1H–1,2,3–triazolilo, 2H–1,2,3–triazolilo]; un grupo heteromonocíclico insaturado de 5 a 6 miembros, que contiene un átomo de oxígeno, por ejemplo, piranilo, 2–furilo, 3–furilo, etc.; un grupo heteromonocíclico de 5 a 6 miembros que contienen un átomo de azufre, por ejemplo 2–tienilo, 3–tienilo, etc.; un grupo heteromonocíclico insaturado de 5 a 6 miembros que contiene 1 a 2 átomos de oxígeno y 1 a 3 átomos de nitrógeno, por ejemplo, oxazolilo, isoxazolilo, oxadiazolilo [por ejemplo, 1,2,4–oxadiazolilo, 1,3,4–oxadiazolilo, 1,2,5–oxadiazolilo]; un grupo heteromonocíclico que contiene 1 a 2 átomos de azufre y 1 a 3 átomos de nitrógeno, por ejemplo, tiazolilo, tiadiazolilo [por ejemplo 1,2,4–tiadiazolilo, 1,3,4–tiadiazolilo, 1,2,5–tiadiazolilo].

El término "sulfonilo", usado solo o ligado a otros términos, tales como alquilsulfonilo, denota respectivamente radicales divalentes $–SO_2–$.

Los términos "sulfamilo," "aminosulfonilo" y "sulfonamidilo," denotan un radical sulfonilo sustituido con un radical amina, que forma una sulfonamida ($–SO_2NH_2$).

El término "alquilaminosulfonilo" incluye "N–alquilaminosulfonilo" donde los radicales sulfamilo están sustituidos independientemente con uno o dos radicales alquilo. Los radicales alquilaminosulfonilo más preferidos son los radicales "alquilaminosulfonilo inferior" que tienen uno a seis átomos de carbono. Se prefieren aún más los radicales alquilaminosulfonilo inferior que tienen uno a tres átomos de carbono. Ejemplos de dichos radicales alquilaminosulfonilo inferior incluyen N–metilaminosulfonilo, y N–etilaminosulfonilo.

Los términos "carboxi" o "carboxilo", usados solos o con otros términos, tales como "carboxialquilo", denotan $–CO_2H$.

El término "carbonilo", usado solo o con otros términos, tales como "aminocarbonilo", denota –(C=O)–.

El término "aminocarbonilo" denota un grupo amida de fórmula $–C(=O)NH_2$.

Los términos "N–alquilaminocarbonilo" y "N,N–dialquilaminocarbonilo" denotan radicales aminocarbonilo independientemente sustituidos con uno o dos radicales alquilo, respectivamente. Más preferido es "alquilaminocarbonilo inferior" que tiene radicales alquilo inferior tal como se describió anteriormente, unidos a un radical aminocarbonilo.

Los términos "N–arilaminocarbonilo" y "N–alquil–N–arilaminocarbonilo" denoten radicales aminocarbonilo sustituidos, respectivamente, con un radical arilo, o un radical alquilo y uno arilo.

Los términos "heterociclilalquilenilo" y "heterociclilalquilo" abarcan radicales alquilo heterocíclico– sustituídos. Los radicales heterociclilalquilo más preferidos son radicales "heteroarilalquilo de 5– o 6– miembros" que tienen porciones alquilo de uno a seis átomos de carbono y un radical heteroarilo de 5 o 6 miembros. Son aún más preferidos los radicales heteroarilalquilenilo que tienen porciones alquilo de uno a tres átomos de carbono. Ejemplos de éstos incluyen radicales tales como piridilmetilo y tienilmetilo.

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El término "aralquilo" abarca radicales alquilo arilo–sustituidos. Los radicales aralquilo preferidos son radicales "aralquilo inferior" que tiene radicales arilo unidos a radicales alquilo que tienen uno a seis átomos de carbono. Son aún más preferidos "fenilalquilenilo" unido a porciones alquilo que tienen uno a tres átomos de carbono. Ejemplos de dichos radicales incluyen bencilo, difenilmetilo y feniletilo. El arilo en dicho aralquilo puede estar adicionalmente sustituido con halo, alquilo, alcoxi, haloalquilo y haloalcoxi.

El término "alquiltio" abarca radicales contienen un radical alquilo lineal o ramificado, de uno a diez átomos de carbono, unido a un átomo de azufre divalente. Son aún más preferidos los radicales alquiltio inferior que tienen de uno a tres átomos de carbono. Un ejemplo de "alquiltio" es metiltio, (CH_3S–).

El término "haloalquiltio" abarca radicales que contienen un radical haloalquilo, de uno a diez átomos de carbono, unido a un átomo de azufre divalente. Son aún más preferidos los radicales haloalquiltio inferior que tienen uno a tres átomos de carbono. Un ejemplo de "haloalquiltio" es trifluormetiltio.

El término "alquilamino" abarca "N–alquilamino" y "N,N–dialquilamino" donde los grupos están independientemente sustituidos con un radical alquilo y con dos radicales alquilo, respectivamente. Radicales alquilamino más preferidos son radicales "alquilamino inferior" que tienen uno o dos radicales alquilo de uno a seis átomos de carbono, unidos a un átomo de nitrógeno. Son aun más preferidos los radicales alquilamino inferior que tienen uno a tres átomos de carbono. Radicales alquilamino apropiados pueden ser mono o dialquilamino, tales como N–metilamino, N–etilamino, N,N–dimetilamino, N,N–dietilamino y similares.

El término "arilamino" denota grupos amino, que han sido sustituidos con uno o dos radicales arilo, tales como N–fenilamino. Los radicales arilamino pueden estar adicionalmente sustituidos en la porción de anillo arilo del radical.

El término "heteroarilamino" denota grupos amino que han sido sustituidos con uno o dos radicales heteroarilo, tal como N–tienilamino. Los radicales "heteroarilamino" pueden estar además sustituidos en la porción de anillo heteroarilo del radical.

El término "aralquilamino" denota grupos amino que han sido sustituidos con uno o dos radicales aralquilo. Los más preferidos son radicales fenil–alquilamino C_1–C_3, tales como N–bencilamino. Los radicales aralquilamino pueden estar además sustituidos en la porción de anillo, arilo.

Los términos "N–alquil–N–arilamino" y "N–aralquil–N–alquilamino" denotan grupos amino, que han sido sustituidos independientemente con un radical aralquilo y uno alquilo, o un radical arilo y uno alquilo, respectivamente, para un grupo amino.

El término "aminoalquilo" abarca radicales alquilo lineales o ramificados que tienen uno hasta aproximadamente diez átomos de carbono, donde cualquiera de los cuales puede estar sustituido con uno o más radicales amino. Los radicales aminoalquilo más preferidos son radicales "aminoalquilo inferior" que tienen uno a seis átomos de carbono y uno o más radicales amino. Ejemplos de dichos radicales incluyen aminometilo, aminoetilo,

aminopropilo, aminobutilo y aminohexilo. Son aún más preferidos los radicales aminoalquilo inferior que tienen uno a tres átomos de carbono.

El término "alquilaminoalquilo" abarca radicales alquilo sustituidos con radicales alquilamino. Radicales alquilaminoalquilo más preferidos son los radicales "alquilaminoalquilo inferior" que tienen radicales alquilo de uno a seis átomos de carbono. Son aún más preferidos los radicales alquilaminoalquilo inferior que tienen radicales alquilo de uno a tres átomos de carbono. Radicales alquilaminoalquilo apropiados pueden ser mono o dialquilo sustituidos, tales como N–metilaminometilo, N,N–dimetil–aminoetilo, N,N–dietilaminometilo y similares.

El término "alquilaminoalcoxi" abarca radicales alcoxi sustituidos con radicales alquilamino. Radicales alquilaminoalcoxi más preferidos son los radicales "alquilaminoalcoxi inferior" que tienen radicales alcoxi de uno a seis átomos de carbono. Son aún más preferidos los radicales alquilaminoalcoxi inferior que tienen radicales alquilo de uno a tres átomos de carbono. Radicales alquilaminoalcoxi apropiados pueden ser mono o dialquilo sustituidos, tales como N–metilaminoetoxi, N,N–dimetilaminoetoxi, N,N–dietilaminoetoxi y similares.

El término "alquilaminoalcoxialcoxi" abarca radicales alcoxi sustituidos con radicales alquilaminoalcoxi. Radicales alquilaminoalcoxialcoxi más preferidos son radicales "alquilaminoalcoxialcoxi inferior" que tienen radicales alcoxi de uno a seis átomos de carbono. Son aún más preferidos los radicales alquilaminoalcoxialcoxi inferior que tienen radicales alquilo de uno a tres átomos de carbono. Radicales alquilaminoalcoxialcoxi apropiados pueden ser mono o dalquilo–sustituidos, tales como N–metilaminometoxietoxi, N–metilaminoetoxietoxi, N,N–dimetilaminoetoxietoxi, N,N–dietilaminometoximetoxi y similares.

El término "carboxialquilo" abarca radicales alquilo lineales o ramificados que tienen uno hasta aproximadamente diez átomos de carbono cualquiera de los cuales puede estar sustituido con uno o más radicales carboxi. Radicales carboxialquilo más preferidos son radicales "carboxialquilo inferior" que tienen uno a seis átomos de carbono y un radical carboxi. Ejemplos de dichos radicales incluyen carboximetilo, carboxipropilo, y similares. Son aún más preferidos los radicales carboxialquilo que tienen uno a tres grupos CH_2.

El término "halosulfonilo" abarca radicales sulfonilo sustituidos con un radical halógeno. Ejemplos de dichos radicales halosulfonilo incluyen clorosulfonilo y fluorsulfonilo.

El término "ariltio" abarca radicales arilo de seis a diez átomos de carbono, unidos a un átomo de azufre divalente. Un ejemplo de "ariltio" es feniltio.

El término "aralquiltio" abarca radicales aralquilo tal como está descrito anteriormente, unidos a un átomo de azufre divalente. Son más preferidos los radicales fenil–alquiltio C_1–C_3. Un ejemplo de "aralquiltio" es benciltio.

El término "ariloxi" abarca radicales arilo opcionalmente sustituidos, tal como se han definido anteriormente, unidos a un átomo de oxígeno. Ejemplos de dichos radicales incluyen fenoxi.

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El término "aralcoxi" abarca radicales aralquilo que contienen oxi unidos a través de un átomo de oxígeno a otros radicales. Radicales aralcoxi más preferidos son radicales "aralcoxi inferior" que tienen radicales fenilo opcionalmente sustituidos unidos a un radical alcoxi inferior tal como está descrito anteriormente.

El término "heteroariloxi" abarca radicales heteroarilo opcionalmente sustituidos, tal como se definió anteriormente, unidos a un átomo de oxígeno.

El término "heteroarilalcoxi" abarca radicales heteroarilalquilo que contienen oxi, unidos a través de un átomo de oxígeno a otros radicales. Radicales heteroarilalcoxi más preferidos son radicales "heteroarilalcoxi inferior" que tienen radicales heteroarilo opcionalmente sustituidos unidos a un radical alcoxi inferior tal como está descrito anteriormente.

El término "cicloalquilo" incluye grupos carbocíclicos saturados. Grupos cicloalquilo preferidos incluyen anillos C_3–C_6. Compuestos más preferidos incluyen ciclopentilo, ciclopropilo, y ciclohexilo.

El término "cicloalquilalquilo" abarca radicales cicloalquil–alquilo sustituidos. Radicales cicloalquilalquilo preferidos son radicales "cicloalquilalquilo inferior" que tienen radicales cicloalquilo unidos a radicales alquilo que tienen uno a seis átomos de carbono. Es aún más preferido "cicloalquilalquilo de 5–6 miembros" unidos a porciones alquilo que tienen uno a tres átomos de carbono. Ejemplos de dichos radicales incluyen ciclohexilmetilo. El cicloalquilo en dichos radicales puede estar adicionalmente sustituido con halo, alquilo, alcoxi e hidroxi.

El término "cicloalquenilo" incluye grupos carbocíclicos que tienen uno o más enlaces de carbono a carbono, incluyendo compuestos "cicloalquildienilo". Grupos cicloalquenilo preferidos incluyen anillos C_3–C_6. Compuestos más preferidos incluyen, por ejemplo, ciclopentenilo, ciclopentadienilo, ciclohexenilo y cicloheptadienilo.

El término "que comprende" significa que tiene un final abierto, que incluye al componente indicado pero que no excluye otros elementos.

Los términos "Fórmulas I, II, III, IV, V, VI y VII" solos o en combinación incluyen cualquier sub–fórmula.

Los compuestos de la invención están dotados de actividad inhibidora de c–Met.

La presente invención comprende también el uso de un compuesto de la invención o una sal farmacéuticamente aceptable del mismo, en la manufactura de un medicamento para el tratamiento de una enfermedad intermediada por angiogénesis aguda o crónica, incluyendo aquellas descritas previamente. Los compuestos de la presente invención son útiles en la manufactura de un medicamento anti–cáncer. Los compuestos de la presente invención son también útiles en la manufactura de un medicamento para atenuar o prevenir trastornos a través de la inhibición de c–Met.

La presente invención comprende una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de la presente invención, en asociación con por lo menos un portador, un coadyuvante o un diluyente farmacéuticamente aceptable.

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La presente invención comprende también un método para tratar trastornos relacionados con angiogénesis en un sujeto que tiene o que es susceptible de tener dicho trastorno, donde dicho método comprende tratar al sujeto con una cantidad terapéuticamente eficaz de un compuesto de la presente invención.

COMBINACIONES

Si bien los compuestos de la invención pueden administrarse como único agente farmacéuticamente activo, también pueden usarse en combinación con uno o más compuestos de la invención u otros agentes. Cuando se administran como una combinación los agentes terapéuticos pueden formularse como composiciones separadas que se administran al mismo tiempo o consecutivamente en tiempos diferentes, o los agentes terapéuticos pueden administrarse como composición única

La frase "co–terapia" (o terapia de combinación"), al definir el uso de un compuesto de la presente invención y otro agente farmacéutico, pretende abarcar la administración de cada agente de manera consecutiva en un régimen que proporcionará efectos beneficiosos de la droga de combinación y pretende también abarcar la co–administración de estos agentes en una manera sustancialmente simultánea, tal como en una sola cápsula que tiene una relación fijada de estos agentes activos, o en cápsulas múltiples, separadas para cada agente.

Específicamente la administración de los compuestos de la presente invención puede efectuarse conjuntamente con terapias adicionales conocidas por los expertos en la materia de prevención o tratamiento de neoplasia, tal como con terapia de radiación o con agentes citostáticos o citotóxicos.

Si se formulan como dosis fija, dichos productos de combinación emplean los compuestos de esta invención dentro de los rangos de dosificación aceptados. Los compuestos de la presente invención pueden administrarse también consecutivamente con agentes anticáncer o citotóxicos conocidos, cuando una formulación de combinación es inapropiada. La invención no está limitada a la secuencia de administración; los compuestos de la invención pueden administrarse antes de, simultáneamente con, o después de la administración del agente anticáncer o citotóxico conocido. Corrientemente, el tratamiento convencional de los tumores primarios consiste en escisión quirúrgica, ya sea por radiación o por quimioterapia administrada por IV. El régimen de quimioterapia típica consiste en cualquier agente alquilante de ADN, agentes intercaladores de ADN, inhibidores de CDLK, o venenos microtubulares. Las dosis de quimioterapia usadas, están justo por debajo de la dosis máxima tolerada y por lo tanto las toxicidades limitativas de dosis incluyen típicamente, náuseas, vómitos, diarrea, pérdida de cabello, neutropenia y similares.

Hay grandes cantidades disponibles de agentes antineoplásicos en uso comercial, que están en evaluación clínica y en desarrollo pre–clínico que se podrían seleccionar para el tratamiento de neoplasia mediante la quimioterapia con drogas de combinación. Dichos agentes antineoplásicos entran en varias categorías principales, es decir, agentes de tipo

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antibiótico, agentes alquilantes, agentes antimetabolito, agentes hormonales, agentes inmunológicos, agentes de tipo interferón y una categoría de agentes misceláneos.

Una primera familia de agentes antineoplásicos que pueden usarse en combinación con los compuestos de la presente invención, consiste en agentes antineoplásicos inhibidores, de tipo antimetabolito/ timidilato sintasa. Agentes antineoplásicos antimetabolito apropiados pueden seleccionarse entre, pero sin limitarse al grupo que consiste de 5–FU–fibrinógeno, ácido acantifólico, aminotiadiazol, brequinar sodio, carmofur, Ciba–Geigy CGP–30694, ciclopentil citosina, citarabina fosfato estearato, conjugados de citarabina, Lilly DATHF, Merrel Dow DDFC, dezaguanina, dideoxicitidina, dideoxiguanosina, didox, Yoshitomi DMDC, doxifluridina, Wellcome EHNA, Merck & Co. EX–015, fazarabini, floxuridina, fosfato de fludarabina, 5–fluoruracilo, N–(2'–furanidil)–5–fluoruracilo, Daiichi Seiyaku FO–152, isopropil pirrolizina, Lilly LY–188011, Lilly LY–264618, metobenzaprim, metotrexato, Wellcome MZPES, norspermidina, NCI NSC–127716, NCI NSC–264880, NCI NSC–39661, NCI NSC–612567, Warner–Lambert PALA, pentostatina, piritrexim, plicamicina, Asahi Chemical PL–AC, Takeda TAC–788, tioguanina, tiazofurina, Erbamont TIF, trimetrexato, inhibidores de tirosin quinasa, Taiho UFT y uricitina.

Una segunda familia de agentes antineoplásicos que pueden usarse en combinación con los compuestos de la presente invención, consiste en agentes antineoplásicos de tipo alquilante. Pueden seleccionarse agentes antineoplásicos de tipo alquilante apropiados entre, pero sin limitarlos al grupo que consiste en Shionogi 254–S, análogos de aldo–fosfamida, altretamina, anaxirona, Boehringer Mannheim BBR–2207, bestrabucil, budotitano, Wakunaga CA–102, carboplatina, carmustina, Chinoin–139, Chinoin–153, clorambucil, cisplatina, ciclofosfamida, American Cyanamid CL–286558, Sanofi CY–233, ciplatato, Degussa D–19–384, Sumimoto DACHP(Myr)2, difenilespiromustina, diplatino citostático, derivados de distamicina Erba, Chugai DWA–2114R, ITI E09, elmustina, Erbamont FCE–24517, estramustina fosfato de sodio, fotemustina, Unimed G–6–M, Chinoin GYKI–17230, hepsul–fam, ifosfamida, iproplatina, lomustine, mafosfamida, mitolactol, Nippon Kayaku NK–121, NCI NSC–264395, NCI NSC–342215, oxaliplatina, Upjohn PCNU, prednimustina, Proter PTT–119, ranimustina, semustina, SmithKline SK&F–101772, Yakult Honsha SN–22, espiromus–tina, Tanabe Seiyaku TA–077, tauromustina, temozolomida, teroxirona, tetraplatin y trimelamol.

Una tercera familia de agentes antineoplásicos que pueden usarse en combinación con los compuestos de la presente invención, consiste en agentes antineoplásicos de tipo antibiótico. Pueden seleccionarse agentes antineoplásicos de tipo antibiótico apropiados entre, pero sin limitarlo al grupo que consiste en Taiho 4181–A, aclarubicina, actinomicina D, actinoplanona, Erbamont ADR–456, derivado de aeroplisinina, Ajinomoto AN–201–II, Ajinomoto AN–3, Nippon Soda anisomicinas, antraciclina, azino–micin–A, bisucaberina, Bristol–Myers BL–6859, Bristol–Myers BMY–25067, Bristol–Myers BMY–25551, Bristol–Myers BMY–26605, Bristol–Myers BMY–27557, Bristol–Myers BMY–28438, sulfato de bleomicina, briostatin–1, Taiho C–1027, caliquemicina, cromoximicina, dactinomicina,

daunorubicina, Quiowa Hakko DC–102, Quiowa Hakko DC–79, Quiowa Hakko DC–88A, Quiowa Hakko DC89–A1, Quiowa Hakko DC92–B, ditrisarubicina B, Shionogi DOB–41, doxorubicina, doxorubicina–fibrinógeno, elsamicin–A, epirubicina, erbstatina, esorubicina, esperamicin–A1, esperamicin–Alb, Erbamont FCE–21954, Fujisawa FK–973, fostriecina, Fujisawa FR–900482, glidobactina, gregatin–A, grincamicina, herbimicina, idarubicina, illudinas, kazusamicina, kesarirhodinas, Quiowa Hakko KM–5539, Kirin Brewery KRN–8602, Quiowa Hakko KT–5432, Quiowa Hakko KT–5594, Quiowa Hakko KT–6149, American Cyanamid LL–D49194, Meiji Seika ME 2303, menogaril, mitomicina, mitoxantrona, SmithKline M–TAG, neoenactina, Nippon Kayaku NK–313, Nippon Kayaku NKT–01, SRI International NSC–357704, oxalisina, oxaunomicina, peplomicina, pilatina, pirarubicina, porotramicina, pirindanicina A, Tobishi RA–I, rapamicina, rizoxina, rodorubicina, sibanomicina, siwenmicina, Sumitomo SM–5887, Snow Brand SN–706, Snow Brand SN–07, sorangicin–A, esparsomicina, SS Pharmaceutical SS–21020, SS Pharmaceutical SS–7313B, SS Pharmaceutical SS–9816B, estefimicina B, Taiho 4181–2, talisomicina, Takeda TAN–868A, terpentecina, trazina, tricrozarina A, Upjohn U–73975, Quiowa Hakko UCN–10028A, Fujisawa WF–3405, Yoshitomi Y–25024 y zorubicina.

Una cuarta familia de agentes antineoplásicos que pueden usarse en combinación con compuestos de la presente invención consiste en una familia miscelánea de agentes antineoplásicos, que incluyen agentes de interacción con tubulina, inhibidores de topoisomerasa II, inhibidores de topoisomerasa I y agentes hormonales seleccionados entre, pero sin limitarlos al grupo que consiste en α–caroteno, α–difluormetil–arginina, acitretina, Biotec AD–5, Quiorin AHC–52, alstonina, amonafida, anfetinilo, amsacrina, Angiostat, ankinomicina, anti–neoplaston A10, antineoplaston A2, antineoplaston A3, antineoplaston A5, antineoplaston AS2–1, Henkel APD, glicinato de afidicolina, asparaginasa, Avarol, bacarina, batraciclina, benfluron, benzotript, Ipsen–Beaufour BIM–23015, bisantreno, Bristol–Myers BMY–40481, Vestar boron–10, bromofosfamida, Wellcome BW–502, Wellcome BW–773, caracemida, clorhidrato de carmetizol, Ajinomoto CDAF, clorsulfaquinoxalona, Chemes CHX–2053, Chemex CHX–100, Warner–Lambert CI–921, Warner–Lambert CI–937, Warner–Lambert CI–941, Warner–Lambert CI–958, clanfenur, claviridenona, ICN compuesto 1259, ICN compuesto 4711, Contracan, Yakult Honsha CPT–11, crisnatol, curaderm, citocalasina B, citarabina, citocitina, Merz D–609, DABIS maleato, dacarbazina, dateliptinio, didemnina–B, éter de dihematoporfirina, dihidrolenperona, dinalina, distamicina, Toyo Pharmar DM–341, Toyo Pharmar DM–75, Daiichi Seiyaku DN–9693, docetaxel eliprabina, acetato de eliptinio, Tsumura EPMTC, los epotilones, ergotamina, etoposida, etretinato, fenretinida, Fujisawa FR–57704, nitrato de galio, genkwadafnina, Chugai GLA–43, Glaxo GR–63178, grifolan NMF–5N, hexadecil fosfocolina, Green Cross HO–221, homoharringtonina, hidroxiurea, BTG ICRF–187, ilmofosina, isoglutamina, isotretinoin, Otsuka JI–36, Ramot K–477, Otsuak K–76COONa, Kureha Chemical K–AM, MECT Corp KI–8110, American Cyanamid L–623, leukoregulina, lonidamina, Lundbeck LU–23–112, Lilly LY–186641, NCI (US) MAP, maricina,

Merrel Dow MDL–27048, Medco MEDR–340, merbarona, derivados de merocianlna, metilanilino acridina, Molecular Genetics MGI–136, minactivina, mitonafida, mitoquidona mopidamol, motretinida, Zenyaku Kogyo MST–16, N–(retinoil)amino ácidos, Nisshin Flour Milling N–021, deshidroalaninas N–aciladas, nafazatrom, Taisho NCU–190, derivado nocodazol, Normosang, NCI NSC–145813, NCI NSC–361456, NCI NSC–604782, NCI NSC–95580, ocreotida, Ono ONO–112, oquizanocina, Akzo Org–10172, paclitaxel, pancratistatina, pazelliptina, Warner–Lambert PD–111707, Warner–Lambert PD–115934, Warner–Lambert PD–131141, Pierre Fabre PE–1001, ICRT péptido D, piroxantrona, polihematoporfirina, ácido polipreico, Efamol porforina, probimano, procarbazina, proglumida, Invitron proteasa nexina I, Tobishi RA–700, razoxana, Sapporo Breweries RBS, restrictina–P, reteliptina, ácido retinoico, Rhone–Poulenc RP–49532, Rhone–Poulenc RP–56976, SmithKline SK&F–104864, Sumitomo SM–108, Kuraray SMANCS, SeaPharm SP–10094, espatol, derivados espirociclopropano, espirogermanium, Unimed, SS Pharmaceutical SS–554, estripoldinona, Stypoldione, Suntory SUN 0237, Suntory SUN 2071, superóxido dismutasa, Toyama T–506, Toyama T–680, taxol, Teijin TEI–0303, teniposida, taliblastina, Eastman Kodak TJB–29, tocotrienol, topotecan, Topostin, Teijin TT–82, Quiowa Hakko UCN–01, Quiowa Hakko UCN–1028, ukraina, Eastman Kodak USB–006, sulfato de vinblastina, vincristina, vindesina, vinestramida, vinorelbina, vintriptol, vinzolidina, witanolidas y Yamanouchi YM–534.

Alternativamente, los presentes compuestos pueden usarse también en co–terapias con otros agentes anti–neoplásicos, tales como acemannano, aclarubicina, aldesleukina, alemtuzumab, alitretinoina, altretamina, amifostina, ácido aminolevulínico, amrubicina, amsacrina, anagrelida, anastrozol, ANCER, ancestim, ARGLABIN, trióxido de arsénico, BAM 002 (Novelos), bexaroteno, bicalutamida, broxuridina, capecitabina, celmoleuquina, cetrorelix, cladribina, clotrimazol, ocfosfato de citarabina, DA 3030 (Dong–A), daclizumab, denileucina diftitox, deslorelina, dexrazoxano, dilazep, docetaxel, docosanol, doxercalciferol, doxifluridina, doxorubicina, bromocriptina, carmustina, citarabina, fluoruracilo, HIT diclofenac, interferon alfa, daunorubicina, doxorubicina, tretinoina, edelfosina, edrecolomab, eflornitina, emitefur, epirubicina, epoetina beta, fosfato de etoposida, exemestano, exisulind, fadrozol, filgrastim, finasteride, fosfato de fludarabina, formestano, fotemustina, nitrato de galio, gemcitabina, gemtuzumab zogamicina, combinación de gimeracil/ oteracil/ tegafur, glicopina, goserelina, heptaplatin, gonadotropina coriónica humana, alfa fetoproteína fetal humana, ácido ibandrónico, idarubicina, (imiquimod, interferon alfa, interferon alfa, natural, interferon alfa–2, interferon alfa–2a, interferon alfa–2b, interferon alfa–N1, interferon alfa–n3, interferon alfacon–1, interferon alfa, natural, interferon beta, interferon beta–1a, interferon beta–1b, interferon gamma, natural interferon gamma–1a, interferon gamma–1b, interleucina–1 beta, iobenguana, irinotecan, irsogladina, lanreotida, LC 9018 (Yakult), leflunomida, lenograstim, sulfato de lentinan, letrozol, leucocito alfa interferon, leuprorelina, levamisol + fluoruracilo, liarozol, lobaplatin, lonidamina, lovastatin, masoprocol, melarsoprol, metoclopramida, mifepristona, miltefosina, mirimostim, ARN doble filamento desemparejado, mitoguazona, mitolactol, mitoxantrona, molgramostim, nafarelina, naloxona + pentazocina, nartograstim,

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nedaplatin, nilutamida, noscapina, proteina novedosa estimuladora de eritropoiesis, NSC 631570 octreotida, oprelvekina, osaterona, oxaliplatin, paclitaxel, ácido pamidrónico, pegaspargasa, peginterferon alfa–2b, pentosan polisulfato de sodio, pentostatina, picibanilo, pirarubicina, anticuerpo policlonal antitimocito de conejo, polietilen glicol interferon alfa–2a, porfimer sodio, raloxifeno, raltitrexed, rasburicasa, renio Re 186 etidronato, RII retinamida, rituximab, romurtida, samario (153 Sm) lexidronam, sargramostim, sizofiran, sobuzoxan, sonermina, cloruro de estroncio–89, suramin, tasonermin, tazaroteno, tegafur, temoporfina, temozolomida, teniposida, tetraclorodeca óxido, talidomida, timalfasina, tirotropina alfa, topotecan, toremifeno, tositumomab–yodo131, trastuzumab, treosulfan, tretinoin, trilostano, trimetrexato, triptorelina, alfa tumor necrosis factor alpha, natural, ubenimex, vacuna de cáncer de vesícula, vacuna Maruyama, vacuna de lisado de melanoma, valrubicina, verteporfina, vinorelbina, VIRULIZIN, zinostatin estimalamer, o ácido zoledrónico; abarelix; AE 941 (Aeterna), ambamustina, oligonucleótido antisentido, bcl–2 (Genta), APC 8015 (Dendreon), cetuximab, decitabina, dexaminoglutetimida, diaziquona, EL 532 (Elan), EM 800 (Endorecherche), eniluracil, etanidazol, fenretinida, filgrastim SD01 (Amgen), fulvestrant, galocitabina, gastrina 17 immunógeno, HLA–B7 terapia génica (Vical), factor estimulador de la colonia macrófaga de granulocitos, diclorhidrato de histamina, ibritumomab tiuxetan, ilomastat, IM 862 (Cytran), interleukina–2, iproxifeno, LDI 200 (Milkhaus), leridistim, lintuzumab, CA 125 MAb (Biomira), cáncer MAb (Japan Pharmaceutical Development), HER–2 and Fc MAb (Medarex), 105AD7 idiotípico MAb (CRC Technology), CEA idiotípico MAb (Trilex), LYM–1–yofo 131 MAb (Techniclone), mucin–itrio epitelial polimórfico 90 MAb (Antisoma), marimastat, menogaril, mitumomab, motexafina gadolinio, MX 6 (Galderma), nelarabina, nolatrexed, P 30 proteína, pegvisomant, pemetrexed, porfiromicina, prinomastat, RL 0903 (Shire), rubitecan, satraplatina, fenilacetato de sodio, ácido esparfósico, SRL 172 (SR Pharma), SU 5416 (SUGEN), TA 077 (Tanabe), tetratiomolibdato, taliblastina, trombopoietina, estaño etil etiopurpurina, tirapazamina, vacuna de cáncer (Biomira), vacuna de melanoma (New York University), vacuna de melanoma (Sloan Kettering Institute), vacuna de oncolisado de melanoma (New York Medical College), vacuna de lisados celulares de melanoma viral (Royal Newcastle Hospital), o valspodar.

Alternativamente, los presentes compuestos pueden usarse también en co–terapias con inhibidores de VEGFR que incluyen:

AMG 706 (difosfato de motesanib);

N–(4–clorofenil)–4–(4–piridinilmetil)–1–ftalazinamina;

4–[4–[[[[4–cloro–3–(trifluormetil)fenil]amino]carbonil]amino]fenoxi]–N–metil–2–piridincarboxamida;

N–[2–(dietilamino)etil]–5–[(5–fluor–1,2–dihidro–2–oxo–3H–indol–3–ilideno)metil]–2,4–dimetil–1H–pirrol–3–carboxamida;

3–[(4–bromo–2,6–difluorfenil)metoxi]–5–[[[[4–(1–pirrolidinil) butil]amino]carbonil]amino]–4–isothiazolecarboxamida;

N–(4–bromo–2–fluorfenil)–6–metoxi–7–[(1–metil–4–piperidinil)metoxi]–4–quinazolinamina;

N,N–dimetil–glicina de éster 3–[5,6,7,13–tetrahidro–9–[(1–metiletoxi)metil]–5–oxo–12H–indeno[2,1–a] pirrolo[3,4–c]carbazol–12–il]propilo;

N–[5–[[[5–(1,1–dimetiletil)–2–oxazolil]metil]tio]–2–tiazolil]–4–piperidinecarboxamida;

N–[3–cloro–4–[(3–fluorfenil)metoxi]fenil]–6–[5–[[[2–(metilsulfonil)etil]amino]metil]–2–furanil]–4–quinazolinamina

4–[(4–Metil–1–piperazinil)metil]–N–[4–metil–3–[[4–(3–piridinil)–2–pirimidinil]amino]–fenil]benzamida

N–(3–cloro–4–fluorfenil)–7–metoxi–6–[3–(4–morfolinpl)propoxi]–4–quinazolinamina

N–(3–etinilfenil)–6,7–bis(2–metoxietoxi)–4–quinazolinamina

N–(3–((((2R)–1–metil–2–pirrolidinil)metil)oxi)–5–(trifluormetil)fenil)–2–((3–(1,3–oxazol–5–il)fenil)amino)–3–piridincarboxamida;

2–(((4–fluorfenil)metil)amino)–N–(3–((((2R)–1–metil–2–pirrolidinil)metil)oxi)–5–(trifluormetil)fenil)–3–piridincarboxamida;

N–[3–(Azetidin–3–ilmetoxi)–5–trifluormetil–fenil]–2–(4–fluor–benzilamino)–nicotinamida.

6–fluor–N–(4–(1–metiletil)fenil)–2–((4–piridinilmetil)amino)–3–piridincarboxamida;

2–((4–piridinilmetil)amino)–N–(3–(((2S)–2–pirrolidinylmetil)oxi)–5–(trifluormetil)fenil)–3–piridincarboxamida;

N–(3–(1,1–dimetiletil)–1H–pyrazol–5–il)–2–((4–piridinilmetil)amino)–3–piridincarboxamida;

N–(3,3–dimetil–2,3–dihidro–1–benzofuran–6–il)–2–((4–piridinilmetil)amino)–3–piridincarboxamida;

N–(3–((((2S)–1–metil–2–pirrolidinil)metil)oxi)–5–(trifluormetil)fenil)–2–((4–piridinilmetil)amino)–3–piridincarboxamida;

2–((4–piridinilmetil)amino)–N–(3–((2–(1–pirrolidinil)etil)oxi)–4–(trifluormetil)fenil)–3–piridincarboxamida;

N–(3,3–dimetil–2,3–dihidro–1H–indol–6–il)–2–((4–piridinilmetil)amino)–3–piridincarboxamida;

N–(4–(pentafluoretil)–3–(((2S)–2–pirrolidinylmetil)oxi)fenil)–2–((4–piridinilmetil)amino)–3–piridincarboxamida;

N–(3–((3–azetidinylmetil)oxi)–5–(trifluormetil)fenil)–2–((4–piridinilmetil)amino)–3–piridincarboxamida;

N–(3–(4–piperidiniloxi)–5–(trifluormetil)fenil)–2–((2–(3–piridinil)etil)amino)–3–piridincarboxamida;

N–(4,4–dimetil–1,2,3,4–tetrahidro–isoquinolin–7–il)–2–(1H–indazol–6–ilamino)–nicotinamida;

2–(1H–indazol–6–ilamino)–N–[3–(1–metilpirrolidin–2–ilmetoxi)–5–trifluormetil–fenil]–nicotinamida;

N–[1–(2–dimetilamino–acetil)–3,3–dimetil–2,3–dihidro–1H–indol–6–il]–2–(1H–indazol–6–ilamino)–nicotinamida;

2–(1H–indazol–6–ilamino)–N–[3–(pirrolidin–2–ilmetoxi)–5–trifluormetil–fenil]–nicotinamida;

N–(1–acetil–3,3–dimetil–2,3–dihidro–1H–indol–6–il)–2–(1H–indazol–6–ilamino)–nicotinamida;

N–(4,4–dimetil–1–oxo–1,2,3,4–tetrahidro–isoquinolin–7–il)–2–(1H–indazol–6–ilamino)–nicotinamida;

N–[4–(ter–butil)–3–(3–piperidilpropil)fenil][2–(1H–indazol–6–ilamino)(3–piridil)]carboxamida;

N–[5–(ter–butil)isoxazol–3–il][2–(1H–indazol–6–ilamino)(3–piridil)]carboxamida; y

N–[4–(ter–butil)fenil][2–(1H–indazol–6–ilamino)(3–piridil)]carboxamida.

Otros compuestos descritos en las siguientes patentes y solicitudes de patente pueden usarse en terapia de combinación: US 6,258,812, US 2003/0105091, WO 01/37820, US 6,235,764, WO 01/32651, US 6,630,500, US 6,515,004, US 6,713,485, US 5,521,184, US 5,770,599, US 5,747,498, WO 02/68406, WO 02/66470, WO 02/55501, WO 04/05279, WO 04/07481, WO 04/07458, WO 04/09784, WO 02/59110, WO 99/45009, WO 00/59509, WO 99/61422, US 5,990,141, WO 00/12089 y WO 00/02871.

En algunas realizaciones la terapia de combinaicón comprende una composición de la presente invención in combinación con por lo menos un agente anti–angiogénico. Los agentes incluyen pero no están limitados a composiciones químicas preparadas sintéticamente *in vitro*, anticuerpos, regiones de unión de antígenos, radionuclidos y combinaciones y conjugados de los mismos. Un agente puede ser un agonista, antagonista, modulador alostérico, toxina o, mas generalmente, pueden actuar para inhibir o estimular su diana (por ejemplo activación o inhibición del receptor o enzima), y promover de esta manera la muerte de células o la inhibición del crecimiento celular.

Ejemplos de agentes anti–tumorales incluyen HERCEPTIN™ (trastuzumab), el cual puede usarse para tratar cáncer de mama y otras formas de cáncer, y RITUXAN™ (rituximab), ZEVALIN™ (ibritumomab tiuxetan), y LYMPHOCIDE™ (epratuzumab), los cuales pueden usarse para tratar linfoma no–Hodgkiniano y otras formas de cáncer, GLEEVAC™ que puede usarse para tratar leucemia mieloide crónica y tumores estromales gastrointestinales, y BEXXAR™ (yodo 131 tositumomab) que puede usarse para el tratamiento de linfoma no–Hodgkiniano.

Ejemplos de agentes anti–angiogénicos incluyen ERBITUX™ (IMC–C225), agentes inhibidorees KDR (receptor de dominio quinasa) (por ejemplo, anticuerpos y regiones de unión al antígeno que se unen específicamente al receptor de dominio quinasa), agentes anti–VEGF (por ejemplo, anticuerpos o regiones de unión al antígeno que se unen específicamente a VEGF, o receptores VEGF solubles o una región de unión al ligando de los mismos) tales como AVASTIN™ o VEGF–TRAP™, y agentes receptores anti–VEGF (por ejemplo, anticuerpos o regiones de unión al antígeno que se unen específicamente a los mismos), agentes inhibidores de EGFR (por ejemplo, anticuerpos y regiones de unión al antígeno que se unen específicamente a los mismos)tales como ABX–EGF (panitumumab), IRESSA™ (gefitinib), TARCEVA™ (erlotinib), agentes anti–Ang1 y anti–Ang2 (por ejemplo, anticuerpos o regiones de unión al antígeno que se unen específicamente a los mismos o a sus receptores, por ejemplo Tie2/Tek), y agentes inhibidores de anti–Tie2 (por ejemplo, anticuerpos o regiones de unión al antígeno que se unen específicamente a los mismos). Las composiciones de la presente invención pueden incluir también uno o más agentes (por

ejemplo, anticuerpos, regiones de unión al antígeno, o receptores solubles) que se unen específicamente e inhiben la actividad de los factores de crecimiento, tales como los antagonistas del factor de crecimiento de hepaptocitos (HGF, conocido también como Factor de dispersión), y anticuerpos o regiones de unión al antígeno que se unen especificametne a su receptor "c–met".

Otros agentes anti–angiogénicos incluyen Campath, IL–8, B–FGF, antagonistas de Tek (Ceretti et al., Publicación US No. 2003/0162712; Patente US No. 6,413,932), agentes anti–TWEAK (por ejemplo, anticuerpos o regiones de unión al antígeno que se unen específicamente a los mismos, o antagonistas del receptor soluble TWEAK; ver, Wiley, Patente US No. 6,727,225), dominio de desintegrina ADAM para antagonizar la unión de integrina a sus ligandos (Fanslow et al., Publicación US No. 2002/0042368), que une específicamente el receptor anti–eph y/ o anticuerpos anti–efrina o regiones de unión al antígeno (Patentes US Nos. 5,981,245; 5,728,813; 5,969,110; 6,596,852; 6,232,447; 6,057,124 y miembros de la familia de patentes de éstas), y antagonistas anti–PDGF–BB (por ejemplo, anticuerpos o regiones de unión al antígeno que se unen especificamente) así como también anticuerpos o regiones de unión al antígeno que se unen específicamente a los ligandos PDGF–BB, y agentes inhibidores de quinasa PDGFR (por ejemplo, anticuerpos o regiones de unión al antígeno que se unen específicamente a los mismos).

Agentes anti–angiogénicos/ anti–tumorales adicionales incluyen: SD–7784 (Pfizer, USA); cilengitida.(Merck KGaA, Germany, EPO 770622); pegaptanib octasodio, (Gilead Sciences, USA); Alphastatin, (BioActa, UK); M–PGA, (Celgene, USA, US 5712291); ilomastat, (Arriva, USA, US 5892112); emaxanib, (Pfizer, USA, US 5792783); vatalanib, (Novartis, Switzerland); 2–metoxiestradiol, (EntreMed, USA); TLC ELL–12, (Elan, Ireland); acetato de anecortave, (Alcon, USA); alfa–D148 Mab, (Amgen, USA); CEP–7055,(Cephalon, USA); anti–Vn Mab, (Crucell, Netherlands) DAC:antiangiogénico, (ConjuChem, Canada); Angiocidina, (InKine Pharmaceutical, USA); KM–2550, (Quiowa Hakko, Japan); SU–0879, (Pfizer, USA); CGP–79787, (Novartis, Switzerland, EP 970070); ARGENT technology, (Ariad, USA); YIGSR–Stealth, (Johnson & Johnson, USA); fibrinógeno–fragmento E, (BioActa, UK); inhibidor de angiogénesis, (Trigen, UK); TBC–1635, (Encysive Pharmaceuticals, USA); SC–236, (Pfizer, USA); ABT–567, (Abbott, USA); Metastatina, (EntreMed, USA); inhibidor de angiogénesis, (Tripep, Sweden); maspina, (Sosei, Japan); 2–metoxiestradiol, (Oncology Sciences Corporation, USA); ER–68203–00, (IVAX, USA); Benefin, (Lane Labs, USA); Tz–93, (Tsumura, Japan); TAN–1120, (Takeda, Japan); FR–111142, (Fujisawa, Japan, JP 02233610); factor de plaquetas 4, (RepliGen, USA, EP 407122); antagonista del factor de crecimiento vascular endotelial, (Borean, Denmark); terapia para cáncer, (University of South Carolina, USA); bevacizumab (pINN), (Genentech, USA); inhibidores de angiogénesis, (SUGEN, USA); XL 784, (Exelixis, USA); XL 647, (Exelixis, USA); MAb, alfa5beta3 integrina, segunda generación, (Applied Molecular Evolution, USA and MedImmune, USA); gene therapy, retinopathy, (Oxford BioMedica, UK); clorhidrato de enzastaurina (USAN), (Lilly, USA); CEP 7055, (Cephalon, USA y Sanofi–Synthelabo, France); BC 1, (Genoa Institute of

Cancer Research, Italy); inhibidor de angiogénesis, (Alchemia, Australia); antagonista de VEGF, (Regeneron, USA); rBPI 21 y antiangiogénico derivado de BPI, (XOMA, USA); PI 88, (Progen, Australia); cilengitida (pINN), (Merck KGaA, German; Munich Technical University, Germany, Scripps Clinic and Research Foundation, USA); cetuximab (INN), (Aventis, France); AVE 8062, (Ajinomoto, Japan); AS 1404, (Cancer Research Laboratory, New Zealand); SG 292, (Telios, USA); Endostatina, (Boston Childrens Hospital, USA); ATN 161, (Attenuon, USA); ANGIOSTATIN, (Boston Childrens Hospital, USA); 2–metoxiestradiol, (Boston Childrens Hospital, USA); ZD 6474, (AstraZeneca, UK); ZD 6126, (Angiogene Pharmaceuticals, UK); PPI 2458, (Praecis, USA); AZD 9935, (AstraZeneca, UK); AZD 2171, (AstraZeneca, UK); vatalanib (pINN), (Novartis, Switzerland y Schering AG, Germany); inhibidores de la vía del factor tisular, (EntreMed, USA); pegaptanib (Pinn), (Gilead Sciences, USA); xanthorrhizol, (Yonsei University, South Korea); vacuna, de base génica, VEGF–2, (Scripps Clinic and Research Foundation, USA); SPV5.2, (Supratek, Canada); SDX 103, (University of California at San Diego, USA); PX 478, (ProlX, USA); METASTATIN, (EntreMed, USA); troponina I, (Harvard University, USA); SU 6668, (SUGEN, USA); OXI 4503, (OXiGENE, USA); o–guanidinas, (Dimensional Pharmaceuticals, USA); motuporamina C, (British Columbia University, Canada); CDP 791, (Celltech Group, UK); atiprimod (pINN), (GlaxoSmithKline, UK); E 7820, (Eisai, Japan); CYC 381, (Harvard University, USA); AE 941, (Aeterna, Canada); vacuna, angiogénesis, (EntreMed, USA); inhibidor de activador de plasminógeno uriquinasa, (Dendreon, USA); oglufanida (pINN), (Melmotte, USA); inhibidores de HIF–1alfa, (Xenova, UK); CEP 5214, (Cephalon, USA); BAY RES 2622, (Bayer, Germany); Angiocidina, (InKine, USA); A6, (Angstrom, USA); KR 31372, (Korea Research Institute of Chemical Technology, South Korea); GW 2286, (GlaxoSmithKline, UK); EHT 0101, (ExonHit, France); CP 868596, (Pfizer, USA); CP 564959, (OSI, USA); CP 547632, (Pfizer, USA); 786034, (GlaxoSmithKline, UK); KRN 633, (Kirin Brewery, Japan); sistema de liberación de drogas, intraocular, 2–metoxiestradiol, (EntreMed, USA); anginex, (Maastricht University, Netherlands, and Minnesota University, USA); ABT 510, (Abbott, USA); AAL 993, (Novartis, Switzerland); VEGI, (ProteomTech, USA); inhibidores de factor alfa de necrosis tumoral, (National Institute on Aging, USA); SU 11248, (Pfizer, USA and SUGEN USA); ABT 518, (Abbott, USA); YH16, (Yantai Rongchang, China); S–3APG , (Boston Childrens Hospital, USA and EntreMed, USA); MAb, KDR, (ImClone Systems, USA); MAb, alfa5 beta1, (Protein Design, USA); inhibidor de quinasa KDR, (Celltech Group, UK, and Johnson & Johnson, USA); GFB 116, (South Florida University, USA and Yale University, USA); CS 706, (Sanquio, Japan); prodroga combretastatina A4, (Arizona State University, USA); condroitinasa AC, (IBEX, Canada); BAY RES 2690, (Bayer, Germany); AGM 1470, (Harvard University, USA, Takeda, Japan, and TAP, USA); AG 13925, (Agouron, USA); Tetraciomolibdato, (University of Michigan, USA); GCS 100, (Wayne State University, USA) CV 247, (Ivy Medical, UK); CKD 732, (Chong Kun Dang, South Korea); MAb, factor de crecimiento vascular endotelial, (Xenova, UK); irsogladina (INN), (Nippon Shinyaku, Japan); RG 13577, (Aventis, France); WX 360, (Wilex, Germany); esqualamina (pINN), (Genaera,

USA); RPI 4610, (Sirna, USA); terapia de cáncer, (Marinova, Australia); inhibidores de heparanasa, (InSight, Israel); KL 3106, (Kolon, South Korea); Honokiol, (Emory University, USA); ZK CDK, (Schering AG, Germany); ZK Angio, (Schering AG, Germany); ZK 229561, (Novartis, Switzerland, and Schering AG, Germany); XMP 300, (XOMA, USA); VGA 1102, (Taisho, Japan); moduladors del receptor VEGF, (Pharmacopeia, USA); antagonistas de VE–caderin–2, (ImClone Systems, USA); Vasostatina, (National Institutes of Health, USA);vaccine, Flk–1, (ImClone Systems, USA); TZ 93, (Tsumura, Japan); TumStatin, (Beth Israel Hospital, USA); FLT 1 soluble truncado (receptor 1 del factor de crecimiento endotelial), (Merck & Co, USA); ligandos Tie–2, (Regeneron, USA); e, inhibidor de trombospondina, (Allegheny Health, Education and Research Foundation, USA).

Alternativamente, los presentes compuestos pueden usarse también en co–terapias con otros agentes anti–neoplásicos, tales como antagonistas de VEGF, otros inhibidores de quinasa que incluyen los inhibidores de p38, inhibidores de KDR, inhibidores de EGF e inhibidores de CDK, inhibidores de TNF, inhibidores de metalomatriz proteasas (MMP), inhibidores de COX–2 que incluyen celecoxib, NSAID's, o inhibidores de $\alpha_v\beta_3$.

La presente invención comprende procedimientos para la preparación de un compuesto de Fórmula I, II, III, IV, V, VI y VII.

Asimismo, se incluyen en la familia de compuestos de la presente, sales farmacéuticamente aceptables y solvatos de las mismas. El termino "sales farmacéuticamente aceptables" abarca sales que se usan comúnmente para formar sales de metales alcalinos y para formar sales de adición de ácidos libres o bases libres. La naturaleza de la sal no es crítica, con la condición de que sea farmacéuticamente aceptable. Sales de adición de ácido farmaceuticamente aceptables apropiadas, de la presente invención, pueden prepararse a partir de un ácido inorgánico o de un ácido orgánico. Ejemplos de dichos ácidos inorgánicos son ácido clorhidrico, bromhídrico, yodhidrico, nítrico, carbónico, sulfúrico y fosfórico.

Ácidos orgánicos apropiados pueden seleccionarse entre clases de ácidos orgánicos alifáticos, cicloalifáticos, aromáticos, arilalifáticos, heterocíclicos, carboxílicos y sulfónicos, ejemplo de los cuales son ácido fórmico, acético, adípico, butírico, propiónico, succínico, glicólico, glucónico, láctico, málico, tartárico, cítrico, ascórbico, glucurónico, maleico, fumárico, pirúvico, aspártico, glutámico, benzoico, antranílico, mesílico, 4–hidroxibenzoico, fenilacético, mandélico, embónico (pamoico), metansulfónico, etansulfónico, etandisulfónico, benzenesulfónico, pantoténico, 2–hidroxietansulfónico, toluensulfónico, sulfanílico, ciclohexilaminosulfónico, alcanfórico, alcanforsulfónico, diglucónico, ciclopentanpropiónico, dodecilsulfónico, glucoheptanoico, glicerofosfónico, heptanoico, hexanoico, 2–hidroxi–etnesulfónico, nicotínico, 2–napftalensulfónico, oxálico, pamoico, pectínico, persulfúrico, 2–fenilpropiónico, pícrico, piválico propiónico, succínico, tartárico, tiociánico, mesílico, undecanoico, esteárico, algénico, β–hidroxibutírico, salicílico, galactárico y galacturónico. Sales de adición de base farmacéuticamente aceptables apropiadas de los compuestos de la

presente invención incluyen sales metálicas, tales como sales preparadas a partir de aluminio, calcio, litio, magnesio, potasio, sodio y zinc, o sales preparadas a partir de bases orgánicas que incluyen aminas primarias, secundarias y terciarias, aminas sustituidas que incluyen aminas cíclicas, tales como cafeína, arginina, dietilamina, N–etil piperidina, histidina, glucamina, isopropilamina, lisina, morfolina, N–etil morfolina, piperazina, piperidina, trietilamina, trimetilamina. Todas estas sales pueden prepararse por medios convencionales a partir del compuesto correspondiente de la invención mediante la reacción, por ejemplo del ácido o base apropiados con el compuesto de la presente invención. Cuando están presentes un grupo básico y un ácido en la misma molécula, un compuesto de la presente invención puede formar también sales internas.

PROCEDIMIENTOS GENERALES DE SÍNTESIS

Los compuestos de la invención pueden sintetizarse de acuerdo con los procedimientos generales descritos en la WO 08/008539 (cuya totalidad se incorpora aquí como referencia) así como también aquellos ilustrados en los compuestos que se dan como ejemplo que se describen a continuación.

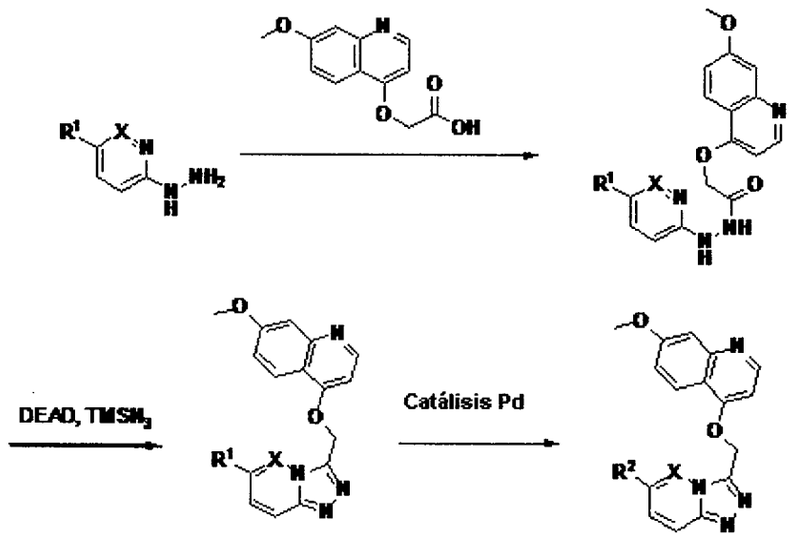
Las abreviaturas siguientes se usan a través de toda la memoria:

HOAc	–	ácido acético
MeCN, CH_3CN	–	acetonitrilo
NH_3	–	amoníaco
NH_4Cl	–	cloruro de amonio
Ar	–	argon
HBTA	–	Hexafluorfosfato de O–benzotriazol–1–il–N,N,N',N'–tetrametiluronio
HATU	–	Hexafluorfosfato de O–(7–azabenzotriazol–1–il)–N,N,N',N'–tetrametiluronio
PyBop	–	Hexafluorfosfato de benzotriazol–1–il–oxi–tripirrolidino–fosfonio
$Pd_2(dba)_3$	–	bis(dibencilidenacetona) paladio
BINAP	–	2,2'–bis(difenilfosfino)–1,1'–binaftilo
TEAC	–	carbonato de bis(tetra–etilamonio)
BBr_3	–	tribromuro de boro
BSA	–	albúmina de suero bovino
Br_2	–	bromo
BOC	–	butiloxicarbonilo
Cs_2CO_3	–	carbonato de cesio
$CHCl_3$	–	cloroformo
$CDCl_3$	–	cloroformo deuterizado
Cu	–	cobre
CuI	–	yoduro de cobre (I)
Et_2O	–	éter dietílico

	DBU	–	1,8–diazabiciclo[5.4.0]undec–7–eno
	DIBAL	–	hidruro de diisobutilaluminio
	DIAD	–	azodicarboxilato de diisopropilo
	DIEA	–	diisopropiletilamina
	DMF	–	dimetilformamida
	DMAP	–	4–dimetilaminopiridina
	DMSO	–	sulfóxido de dimetilo
	EDC, EDCI	–	clorhidrato de 1–(3–dimetilamino propil) –3–etilcarbodimida
	dppa	–	difenilfosforil azida
	EtOAc	–	acetato de etilo
	FBS	–	suero fetal bovino
	g	–	gramo
	h	–	hora
	HBr	–	ácido bromhídrico
	HCl	–	ácido clorhídrico
	HOBt	–	hidrato de 1–hidroxibenzotriazol
	H_2	–	hidrógeno
	H_2O_2	–	peróxido de hidrógeno
	Fe	–	hierro
	LiHMDS	–	bis(trimetilsilil)–amida de litio
	LDA	–	diisopropilamida de litio
	MCPBA	–	ácido *meta*–cloroperbenzoico
	$MgSO_4$	–	sulfato de magnesio
	MeOH, CH_3OH	–	metanol
	MeI	–	yoduro de metilo
	CH_2Cl_2, DCM	–	cloruro de metileno
	NMP	–	N–metilpirrolidinona
	ML, ml	–	mililitro
	N_2	–	nitrógeno
	Pd/C	–	paladio sobre carbono
	$Pd(OAc)_2$	–	acetato de paladio
	$Pd(OH)_2$	–	hidróxido de paladio
	$Pd(PPh_3)_4$	–	tetrakis trifenilfosfina de paladio
	$Pd(dppf)Cl_2$	–	1,1–bis(difenilfosfino)ferroceno paladio
	PBS	–	solución salina regulada con fosfato
	$POCl_3$	–	oxicloruro fosforoso
	K_2CO_3	–	carbonato de potasio.
	KOH	–	hidróxido de potasio
	RT	–	temperatura ambiente
	$NaHCO_3$	–	bicarbonato de sodio

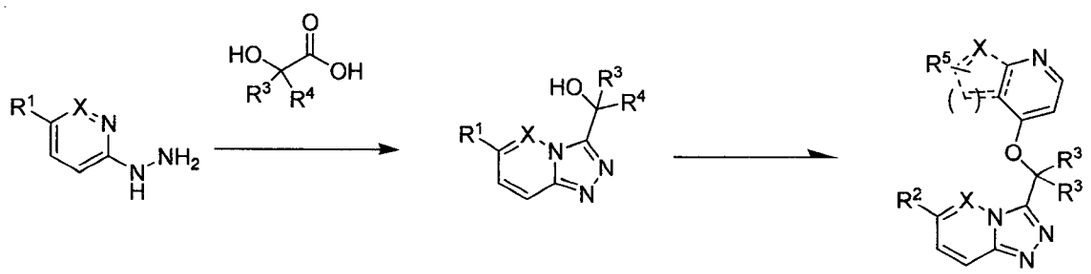
	$NaBH_4$	–	borohidruro de sodio
	$NaBH_3CN$	–	cianoborohidruro de sodio
	NaOtBu	–	ter–butóxido de sodio
	NaOH	–	hidróxido de sodio
5	$NaClO_2$	–	clorito de sodio
	NaCl	–	cloruro de sodio
	$NaHPO_4$	–	bifosfato de sodio
	NaH	–	hidruro de sodio
	NaI	–	yoduro de sodio
10	Na_2SO_4	–	sulfato de sodio
	TBTU	–	O–benzotriazol–1–yl–N,N,N',N'–tetrametiluronio tetrafluorborato
	THF	–	tetrahidrofurano
	Et_3N, TEA	–	trietilamina
	TFA	–	ácido trifluoracético
15	$P(t\text{–bu})_3$	–	tri(ter–butil)fosfina
	H_2O	–	agua

Método General A

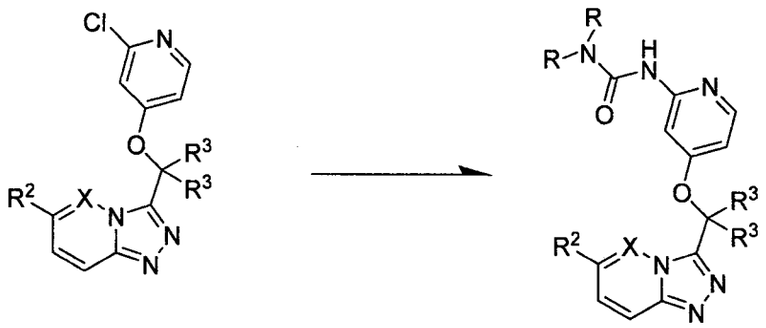


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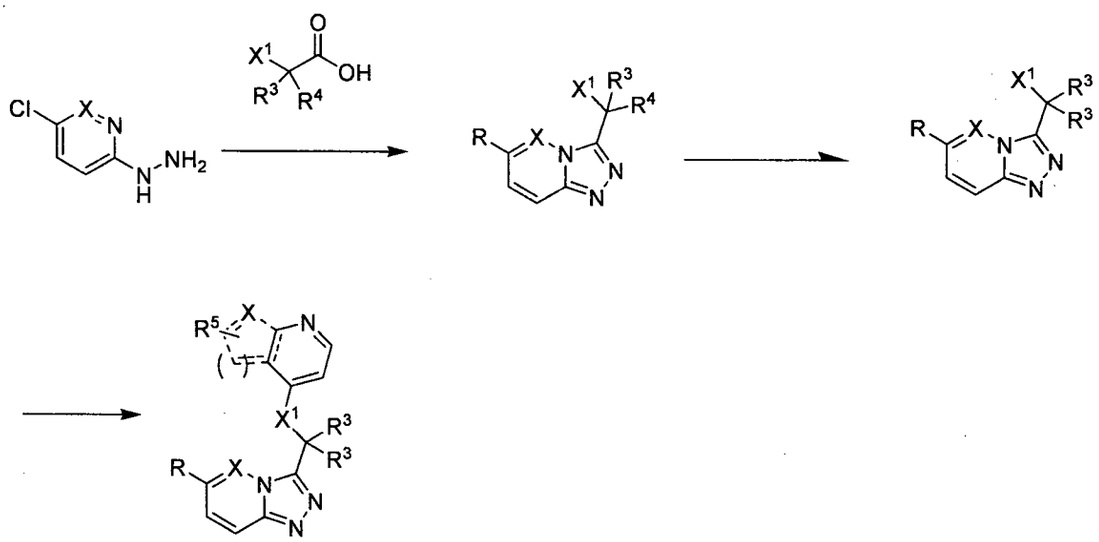
Método General B



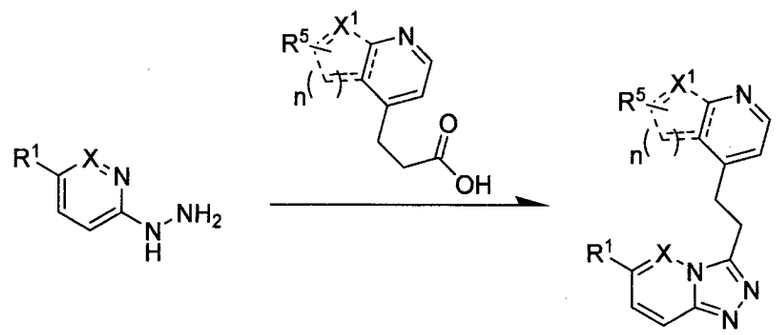
Método General C



Método General D



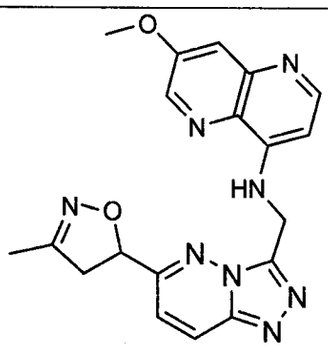
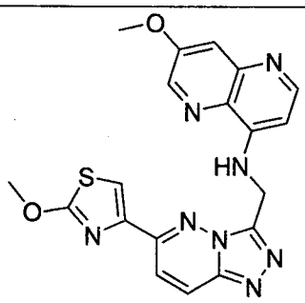
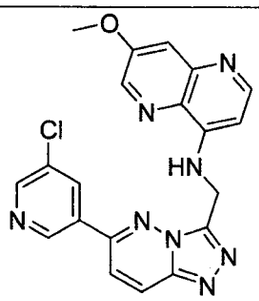
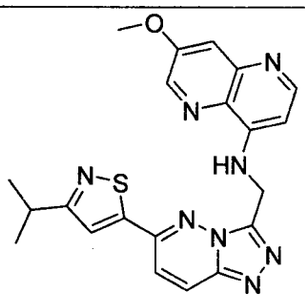
Método General E

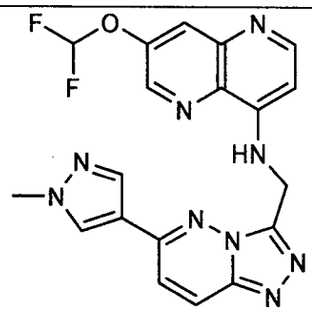
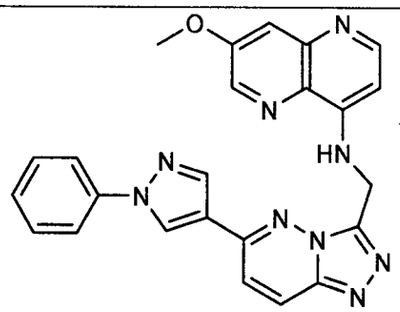
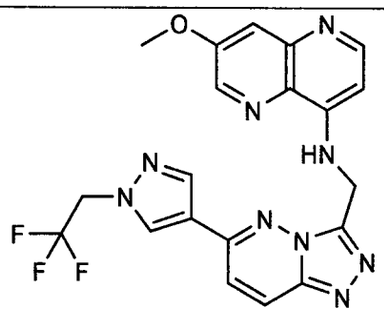
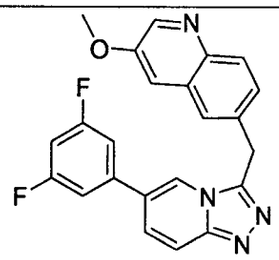
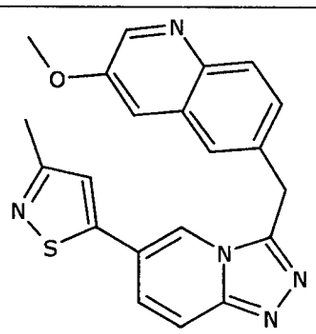


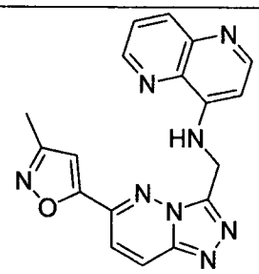
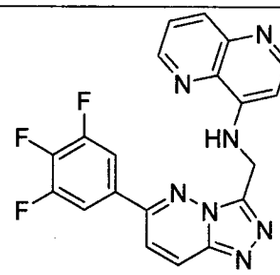
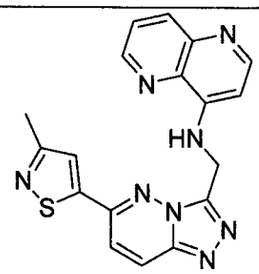
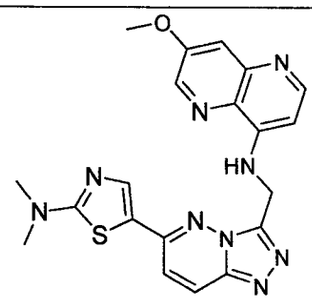
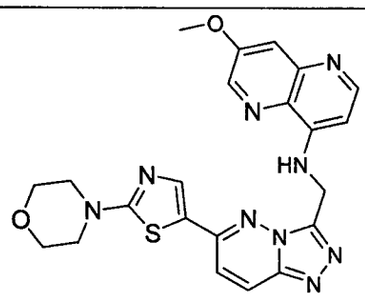
Ejemplos 1–343

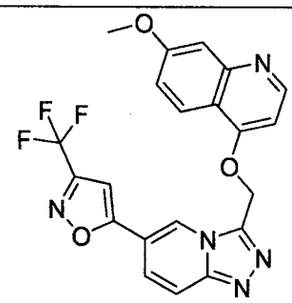
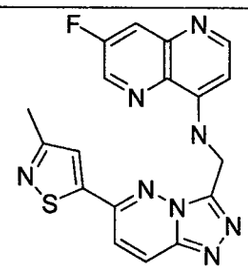
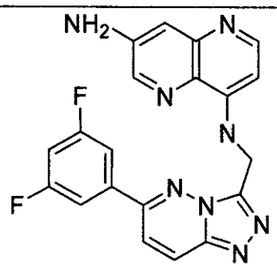
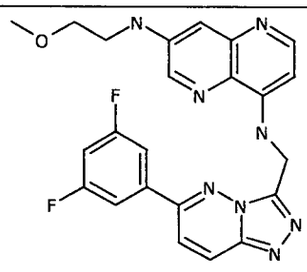
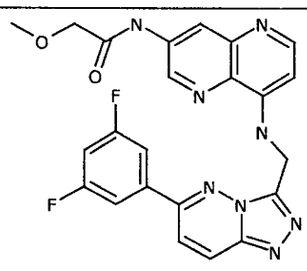
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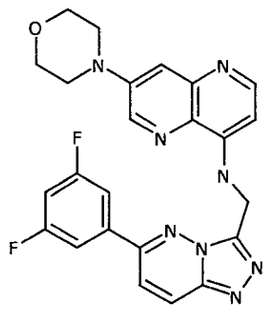
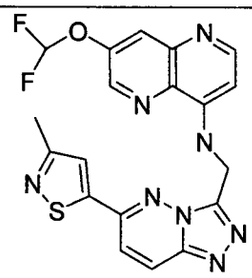
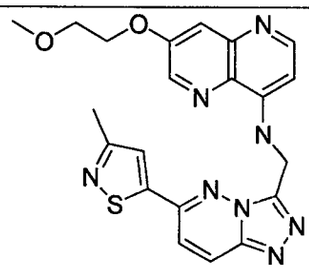
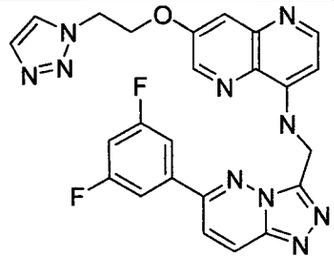
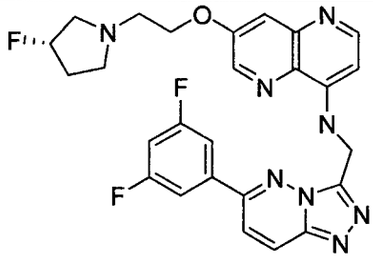
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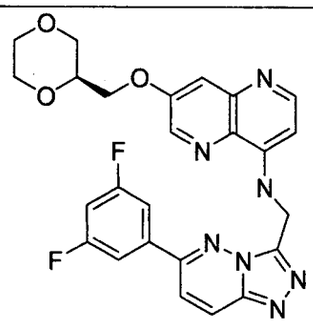
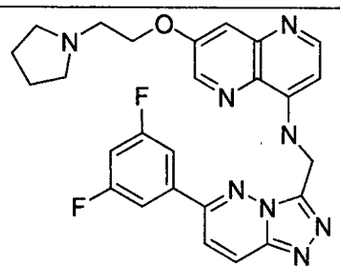
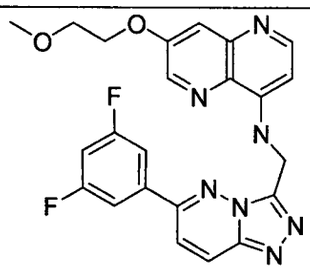
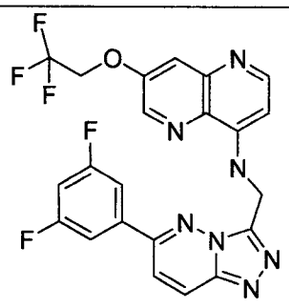
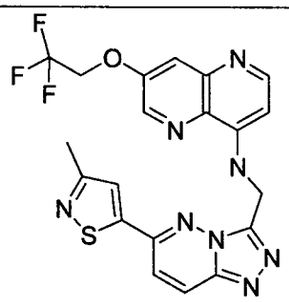
Ej.	Estructura	PM	Masa Hallada	Método General
344		390	391	D
345		420	421	D
346		418	419	D
347		432	433	D

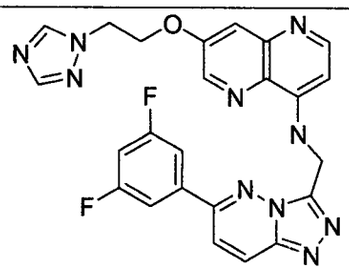
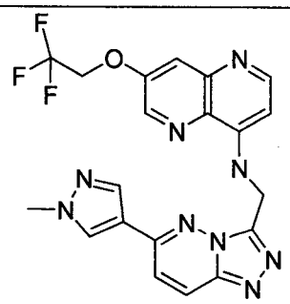
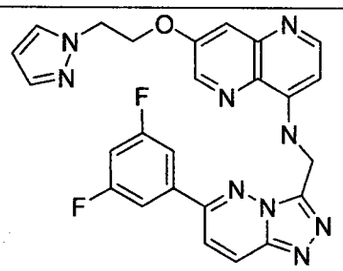
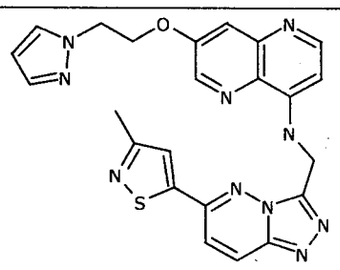
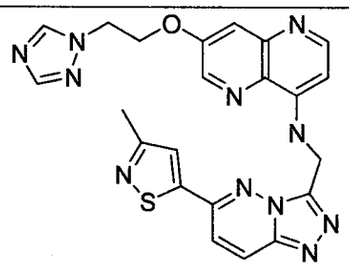
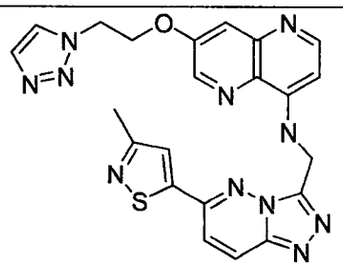
Ej.	Estructura	PM	Masa Hallada	Método General
348		423	424	D
349		449	450	D
350		455	456	D
351		402	403	A
352		387	388	A

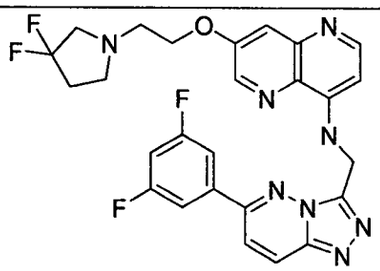
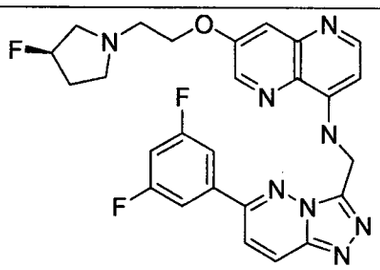
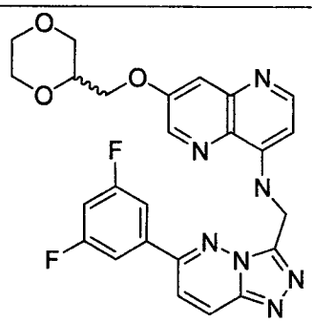
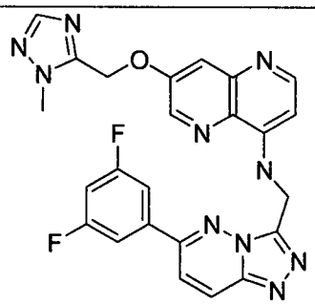
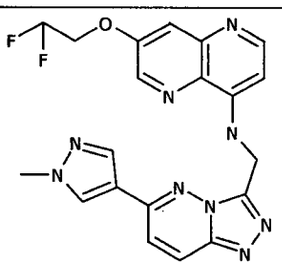
Ej.	Estructura	PM	Masa Hallada	Método General
353		358	359	D
354		407	408	D
355		374	375	D
356		433	434	D
357		475	476	D

Ej.	Estructura	PM	Masa Hallada	Método General
358		441	442	A
359		392	393	D
360		404	405	D
361		462	463	D
362		476	477	D

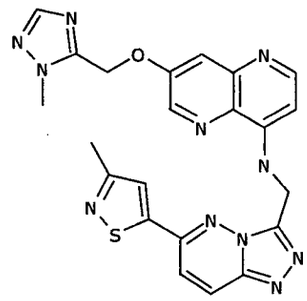
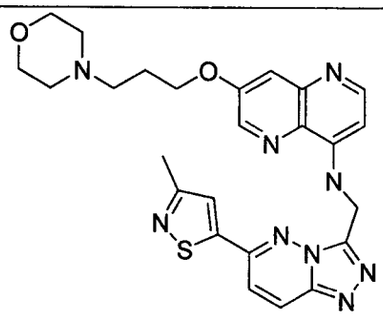
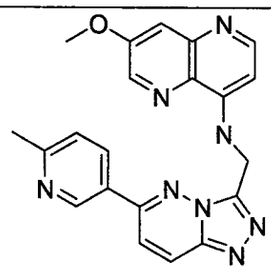
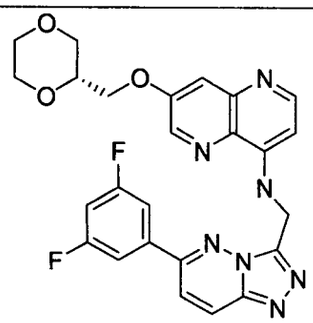
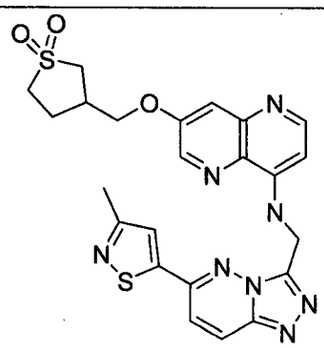
Ej.	Estructura	PM	Masa Hallada	Método General
363		474	475	D
364		440	441	D
365		448	449	D
366		500	501	D
367		520	521	D

Ej.	Estructura	PM	Masa Hallada	Método General
368		505	506	D
369		502	503	D
370		463	464	D
371		487	488	D
372		472	473	D

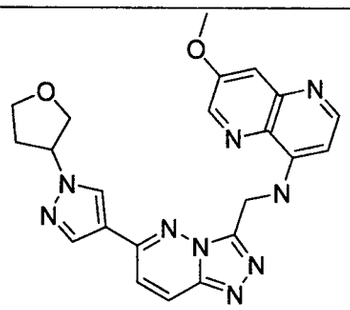
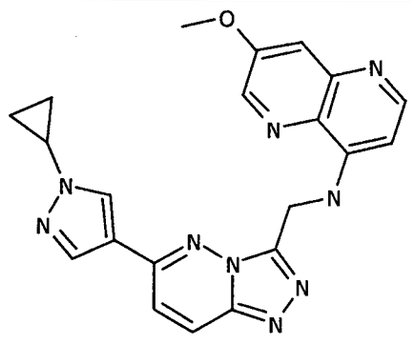
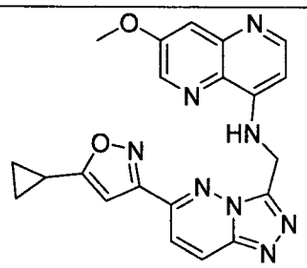
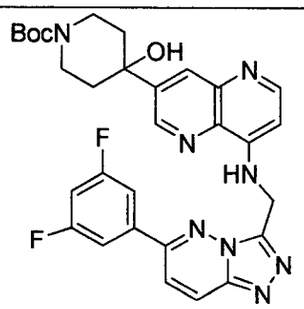
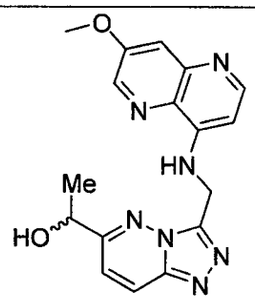
Ej.	Estructura	PM	Masa Hallada	Método General
373		500	501	D
374		455	456	D
375		499	500	D
376		484	485	D
377		485	486	D
378		485	485	D

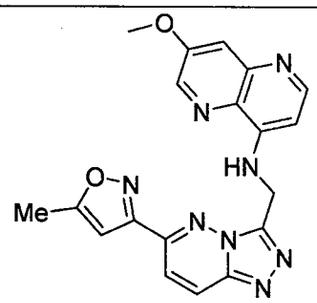
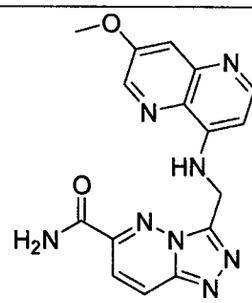
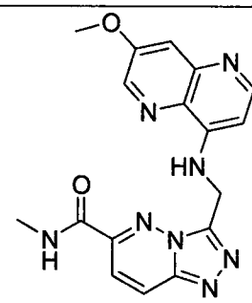
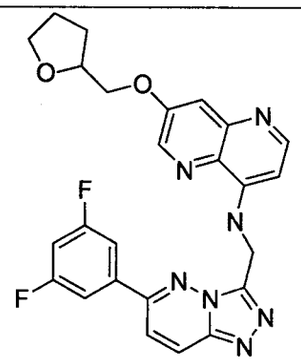
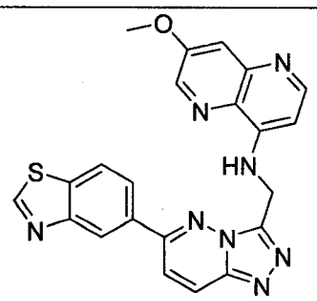
Ej.	Estructura	PM	Masa Hallada	Método General
379		538	539	D
380		520	521	D
381		505	506	D
382		500	501	D
383		437	438	D

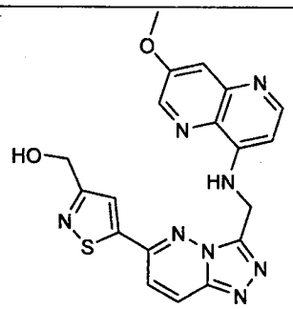
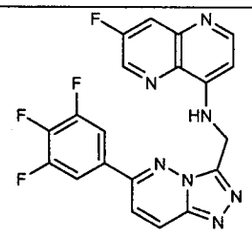
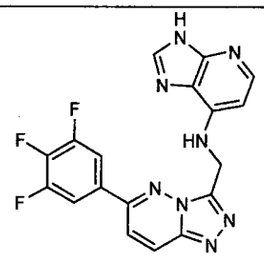
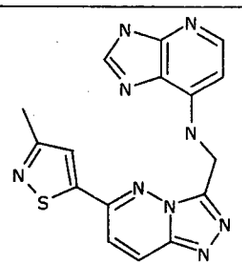
000308

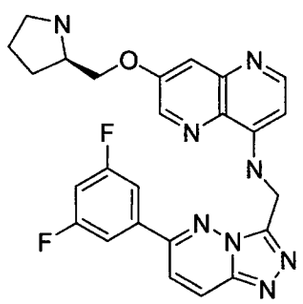
Ej.	Estructura	PM	Masa Hallada	Método General
384		485	486	D
385		517	518	D
386		398	399	D
387		505	506	D
388		522	523	D

000309

Ej.	Estructura	PM	Masa Hallada	Método General
389		443	444	D
390		413	414	D
391		414	415	D
392		488	489	D
393		351	352	D

Ej.	Estructura	PM	Masa Hallada	Método General
394		388	388	D
395		350	351	D
396		364	365	D
397		489	490	D
398		440	441	D

Ej.	Estructura	PM	Masa Hallada	Método General
399		420	421	D
400		425	426	D
401		396	397	D
402		363	364	D



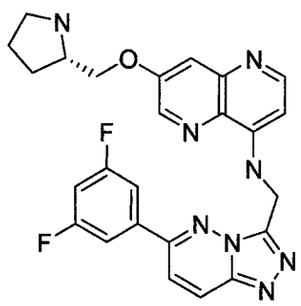
000312

Ejemplo 403

(R)–N–((6–(3,5–difluorfenil)–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)–7–(pirrolidin–2–ilmetoxi)–1,5–naftiridin–4–amina

a) Se preparó 2–((8–((6–(3,5–difluorfenil)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilamino)–1,5–naftiridin–3–iloxi)metil)pirrolidin–1–carboxilato de (R)–ter–butilo de acuerdo con el método D.

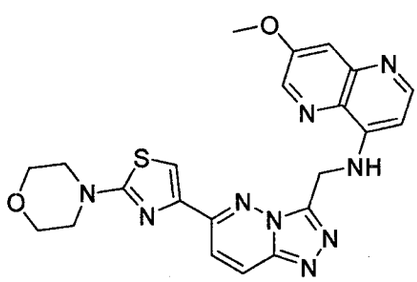
b) (R)–N–((6–(3,5–difluorfenil)–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)–7–(pirrolidin–2–ilmetoxi)–1,5–naftiridin–4–amina . Se preparó el compuesto del título a partir de 2–((8–((6–(3,5–difluorfenil)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilamino)–1,5–naftiridin–3–iloxi)metil)pirrolidin–1–carboxilato de (R)–ter–butilo siguiendo el procedimiento usado para preparar 7–metoxi–4–((6–(6–(piperazin–1–il)piridin–3–il)–[1,2,4]triazol[4,3–b]piridazin–3–il)metoxi)quinolina. *m/z*: 489 (M+H). Calc. para $C_{25}H_{22}F_2N_8O$ – 488.



Ejemplo 404

(S)–N–((6–(3,5–difluorfenil)–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)–7–(pirrolidin–2–ilmetoxi)–1,5–naftiridin–4–amina

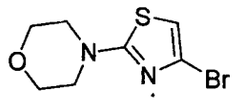
Se preparó el compuesto del título de la misma manera que (R)–N–((6–(3,5–difluorfenil)–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)–7–(pirrolidin–2–ilmetoxi)–1,5–naftiridin–4–amina . *m/z*: 489 (M+H). Calc. para $C_{25}H_{22}F_2N_8O$ – 488.



Ejemplo 405

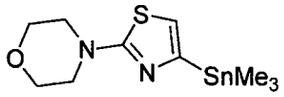
7–metoxi–*N*–((6–(2–morfolinotiazol–4–il)–[1,2,4]triazol[4,3–*b*]piridazin–3–il)metil)–1,5–naftiridin–4–amina

1) 4–(4–bromotiazol–2–il)morfolina



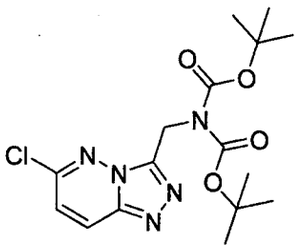
A un frasco para microondas se agregó *N,N*–diisopropiletilamina (0,86 ml, 4,9 mmol), 2,4–dibromotiazol (1.00 g, 4.1 mmol), y morfolina (0.43 ml, 4.9 mmol) en EtOH (4 mL). La mezcla se calentó bajo irradiación de microondas a 140 °C durante 35 minutos. La mezcla de reacción se concentró al vacío. El material crudo se disolvió en un mínimo de DCM/MeOH y se purificó a través de MPLC (eluyendo con 0–30% EtOAc en hexanos) para proporcionar 4–(4–bromotiazol–2–il)morfolina (0.700 g, 68% de rendimiento) en forma de un sólido blanco.

2) 4–(4–(trimetilestanil)tiazol–2–il)morfolina



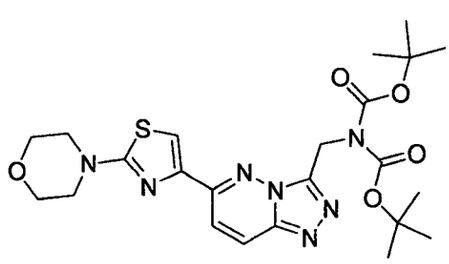
Se preparó en un método similar a 3–metil–5–trimetilestanil) isotiazol.

3) (6–cloro–[1,2,4]triazol[4,3–*b*]piridazin–3–il)metilcarbamato de bis–ter–butilo



Se agregó dicarbonato de di–ter–butilo (24.42 g, 111.9 mmol) bajo agitación, a una suspensión de (6–cloro–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo (10.58 g, 37.3 mmol) en acetonitrilo (200 mL) a 0°C seguido de 4–dimetilaminopiridina (4.556 g, 37.3 mmol). Se continuó la agitación a 0°C durante ~10 min y luego se removió el baño de enfriamiento y se continuó la agitación a temperatura ambiente durante la noche. La mezcla de reacción se concentró al vacío, se diluyó con EtOAc y se lavó con agua. Se secó la capa orgánica sobre $MgSO_4$, se filtró y se concentró al vacío. La purificación a través de MPLC (EtOAc/MeOH: 100/0 a 90/10) proporcionó el compuesto del título (14,3 g, 37,3 mmoles, 100% de rendimiento).

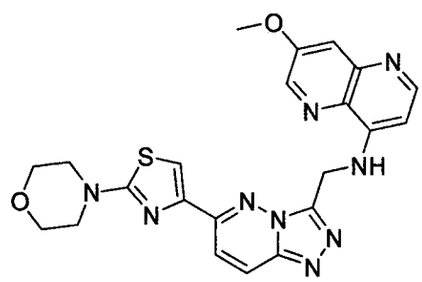
4) (6–(2–morfolinotiazol–4–il)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de di–ter–butilo



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A un recipiente de presión purgado con argón se agregó acetato de paladio (II) (0.0029 g, 0.013 mmol), Xantphos (0.015 g, 0.026 mmol) y (6–cloro–[1,2,4]triazol[4,3–*b*]piridazin–3–il)metilcarbamato de bis–ter–butilo (0.100 g, 0.26 mmol) en 1,4–dioxano (0.17 M, 1.5 mL). Se agregaron 4–(4–(trimetilstanilo)tiazol–2–il)morfolina (0.13 g, 0.39 mmol) y agua desgasificada (0.0094 ml, 0.52 mmol), una vez más purgando el frasco con argón. La mezcla de reacción se agitó a 100 °C durante 4h hasta completar el consumo del material de partida. La mezcla de reacción se concentró al vacío. Se disolvió el material crudo en un mínimo de EtOAc y se purificó a través de MPLC (eluyendo con 100% EtOAc). Se obtuvo (6–(2–morfolinotiazol–4–il)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de di–ter–butilo (0.086 g, 64% de rendimiento) en forma de un sólido. El material crudo se mantuvo sin purificación adicional.

5) <u>7–metoxi–*N*–((6–(2–morfolinotiazol–4–il)–[1,2,4]triazol[4,3–*b*]piridazin–3–il)metil)–1,5–naftiridin–4–amina</u>

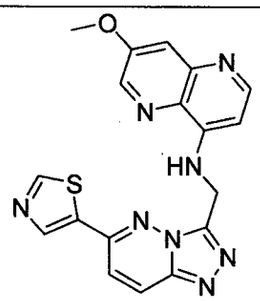
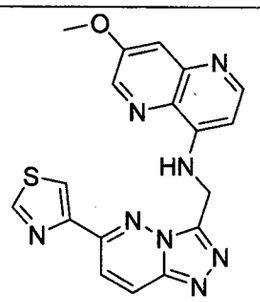


A un frasco para microondas se agregó (6–(2–morfolinotiazol–4–il)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de di–ter–butilo (0.086 g, 0.17 mmol) y 8–cloro–3–metoxi–1,5–naftiridina (0.036 g, 0.18 mmol) en 2–butanol (1.0 mL). El frasco se selló y calentó bajo irradiación microondas a 120 °C durante 6 h. La reacción se concentró al vacío. Se disolvió el material crudo en amoníaco 2M en metanol y se purificó a través de MPLC (eluyendo con 0–10% 1% NH_4OH/ en DCM). Se obtuvo 7–metoxi–N–((6–(2–morfolinotiazol–4–il)–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)–1,5–naftiridin–4–amina (0.031 g, 39% de rendimiento) en forma de un sólido amarillo. *m/z*: 476.0 (M+H). Calc. para $C_{22}H_{21}N_9O_2S$ – 475.53.

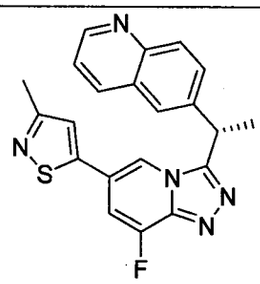
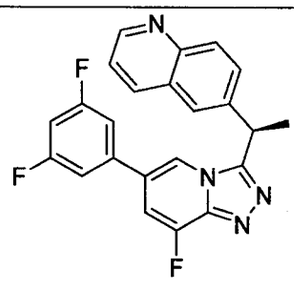
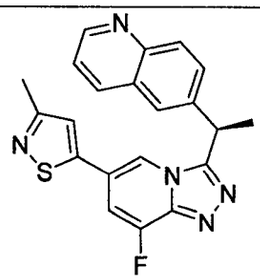
Los siguientes ejemplos de compuestos 406 y 407 se prepararon usando el método para preparar 7–metoxi–*N*–((6–(2–morfolinotiazol–4–il)–[1,2,4]triazol[4,3–*b*]piridazin–3–il)metil)–1,5–naftiridin–4–amina :

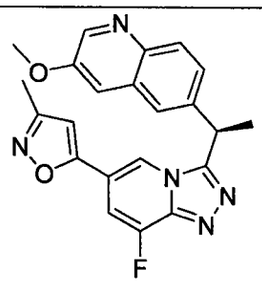
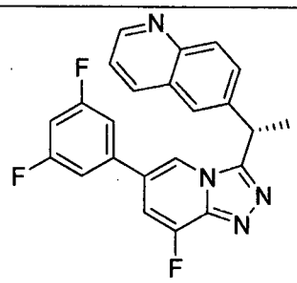
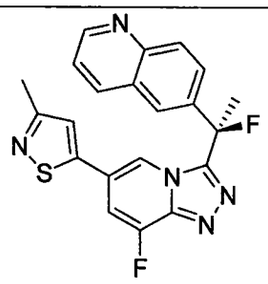
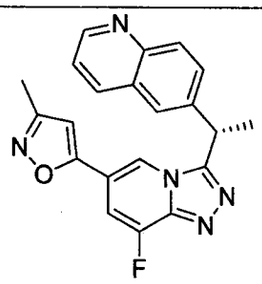
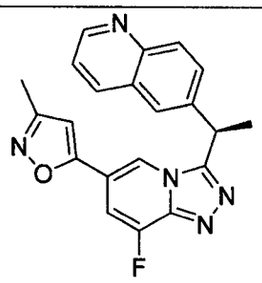
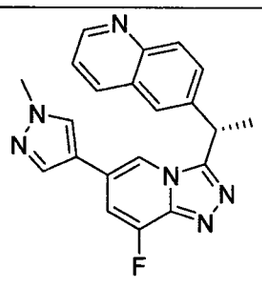
Ej	Estructura	MW	Masa Hallada

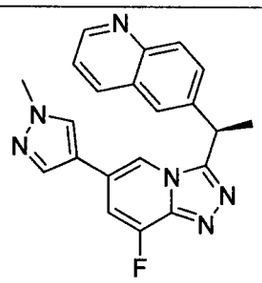
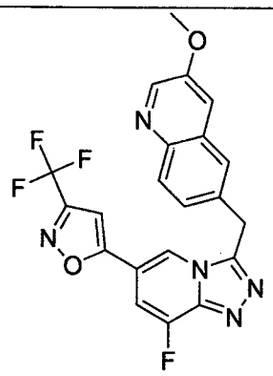
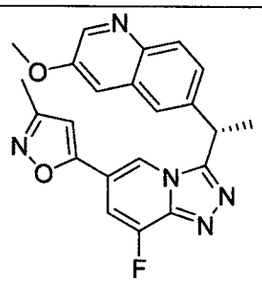
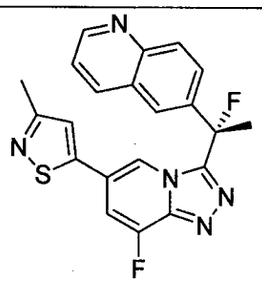
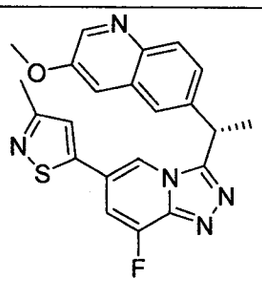
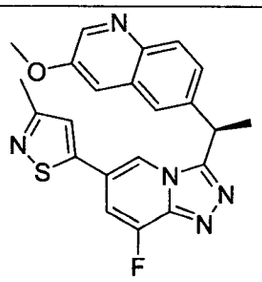
000315

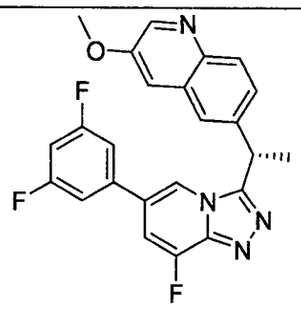
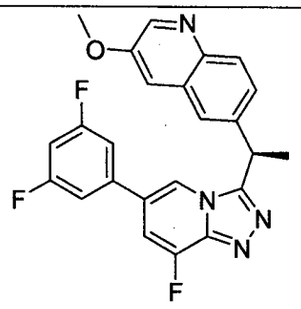
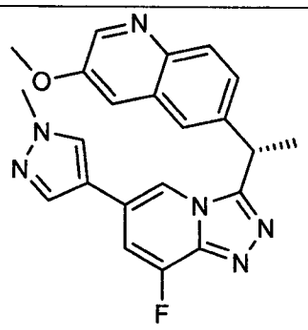
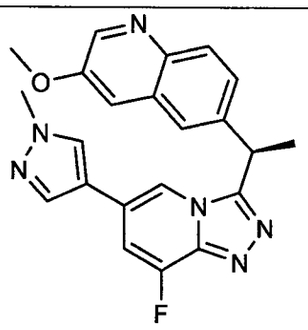
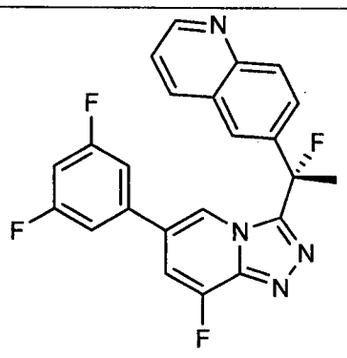
406		390	391
407		390	391

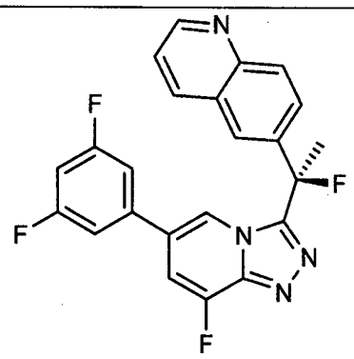
Los siguientes ejemplos de compuestos 408–428 se prepararon usando las etapas 1 y 2 del Método A. Donde es aplicable, el enantiómero se obtuvo a través de SFC:

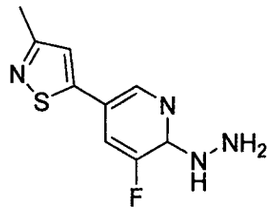
Ej	Estructura	MW	Masa Hallada
408		389	390
409		404	405
410		389	389

411		403	404
412		404	405
413		407	408
414		373	374
415		373	374
416		372	373

417		372	373
418		443	444
419		403	404
420		407	408
421		419	420
422		419	420

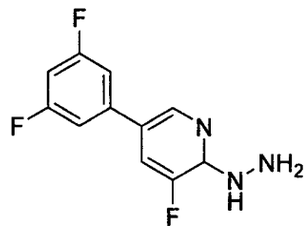
423		434	435
424		434	435
425		402	403
426		402	403
427		422	423

428		422	423



1–(3–fluor–5–(3–metilisotiazol–5–il)piridin–2–il)hidrazina

Se combinaron 5–cloro–2,3–difluorpiridina (0.069 ml, 0.67 mmol), X–Phos (0.045 g, 0.094 mmol) y acetato de paladio (II) (0.011 g, 0.047 mmol) en 1,4–dioxano (0.2 M, 3.4 mL). Al recipiente de reacción se agregó 3–metil–5–(trimetilstanilo)isotiazol (0.53 g, 2.0 mmol) y, después de purgar con argón, la reacción se agitó a 100 °C durante 2h y luego se concentró al vacío. El material crudo se disolvió en un mínimo de DCM y se purificó a través de MPLC (eluyendo primero con 100% de EtOAc seguido por 20% de EtOAc en hexanos –isocrático) para proporcionar 2,3–difluor–5–(3–metilisotiazol–5–il)piridina (0.139 g, 98% de rendimiento) en forma de un sólido amarillo. Se convirtió 2,3–difluor–5–(3–metilisotiazol–5–il)piridina al compuesto del título usando un procedimiento similar a 1–(4–metil–6–fenilpiridazin–3–il)hidrazina.



1–(5–(3,5–difluorfenil)–3–fluorpiridin–2–il)hidrazina

Una mezcla de acetato de paladio (II) (0.0375 g, 0.167 mmol), fosfato de potasio (2.13 g, 10.0 mmol), ácido 3,5–difluorfenilborónico (1.58 g, 10.0 mmol), X–Phos (0.159 g, 0.334 mmol) y 5–cloro–2,3–difluorpiridina (0.347 ml, 3.34 mmol) se diluyó con 1,4–dioxano (0.1M, 33.4 mL) y agua (0.3M, 11.0 mL) y se calentó bajo nitrógeno a 100 °C durante 45 minutos. La reacción se concentró al vacío. El material concentrado se trituró con agua, se filtró y se enjuagó con MeCN. El sólido crudo se extrajo en diclorometano y se filtró sobre un tapón de Celite para eliminar el paladio residual. El material se disolvió en un mínimo de DCM, y se purificó a través de MPLC (eluyendo con 0–10% de EtOAc en hexanos) para proporcionar 5–

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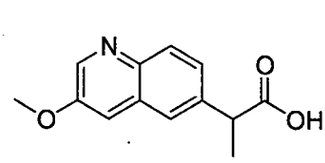
(3,5–difluorfenil)–2,3–difluorpiridina. El material se convirtió a hidrazina en un método similar a este en la síntesis de (*S*)–6–(1–(8–fluor–6–(3–metilisotiazol–5–il)–[1,2,4]triazol[4,3–*a*]piridin–3–il)etil)quinolina.

Se prepararon los siguientes compuestos usando un método similar a 1–(5–(3,5–difluorfenil)–3–fluorpiridin–2–il)hidrazina:

1) 1–(3–fluor–5–(1–metil–1H–pirazol–4–il)piridin–2–il)hidrazina

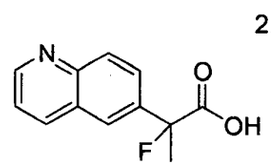
Los siguientes compuestos se prepararon usando un método similar (usando tanto el trimetil– o tributil– estanano) como 1–(3–fluor–5–(3–metilisotiazol–5–il)piridin–2–il)hidrazina:

1–(3–fluor–5–(3–metilisoxazol–5–il)piridin–2–il)hidrazina; y
1–(3–fluor–5–(3–trifluormetilisoxazol–5–il)piridin–2–il)hidrazina.



Clorhidrato de ácido 2–(3–metoxiquinolin–6–il)propanoico

Se disolvió 2–(3–metoxiquinolin–6–il)propanoato de ter–butilo (0.865 g, 3.01 mmol) en EtOAc (0.2M, 15 mL), y HCl (g) (0.0915 ml, 3.01 mmol) se hizo burbujear a través de la solución durante aproximadamente 5 minutos. El recipiente de reacción se selló y la reacción se agitó a temperatura ambiente durante 1,5 h hasta completar. La mezcla de reacción se concentró al vacío para proporcionar clorhidrato de ácido 2–(3–metoxiquinolin–6–il)propanoico (0.805 g, 99.9% de rendimiento) en forma de un sólido naranja.

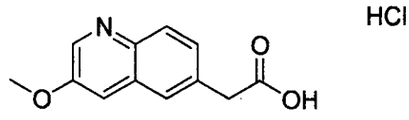


Acido 2–fluor–2–(quinolin–6–il)propanoico

A una solución de 2–(quinolin–6–il)propanoato de metilo (0.868 g, 4.03 mmol) en THF (1.1M, 3.7 mL) a –78 °C se agregó LiHMDS (1M in THF) (5.24 ml, 5.24 mmol). La reacción se agitó a–78 °C durante ~15 minutos, luego a esto se agregó una solución de N–fluorbenzensulfonimida (1.40 g, 4.44 mmol) en THF (1.0M, 4.5 mL). La reacción se dejó calentar a –10 °C durante 2h. La reacción se filtró a través de una almohadilla de Celite, se lavó con EtOAc y el filtrado se concentró luego al vacío. El material concentrado se rediluyó con EtOAc y se lavó con una solución de NH_4Cl saturada. La capa acuosa se extrajo luego

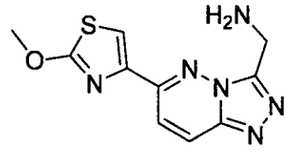
con EtOAc, y las capas orgánicas se secaron sobre $MgSO_4$, se filtraron y se concentraron al vacío. El material crudo se disolvió en un mínimo de DCM y se purificó a través de MPLC (eluyendo con 40% de EtOAc:Hexanos isocrático para proporcionar 2–fluor–2–(quinolin–6–il)propanoato de metilo (0.709 g, 75.4% de rendimiento) en forma de un aceite amarillo.

Para sintetizar el ácido correspondiente, 2–fluor–2–(quinolin–6–il)propanoato de metilo se saponificó en un método similar al del ácido 2–(quinolin–6–il)propanoico.



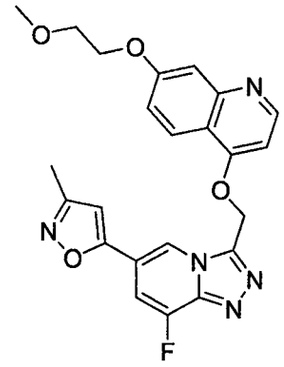
Clorhidrato de ácido 2–(3–metoxiquinolin–6–il)acético

2–(3–metoxiquinolin–6–il)acetato de ter–butilo se saponificó en un método similar a clorhidrato de ácido 2–(3–metoxiquinolin–6–il)propanoico.



(6–(2–metoxitiazol–4–il)–[1,2,4]triazol[4,3–*b*]piridazin–3–il)metanamina

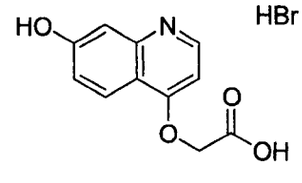
El precursor carbonato de di–ter–butilo ((6–(2–metoxi–4–il)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de di–ter–butilo) se sintetizó en un método similar a (6–(2–morfolinotiazol–4–il)–[1,2,4]triazol[4,3–b]piridazin–3–il)metil di–tert–butil carbamato, usando 2–metoxi–4–(tributilestanilo)tiazol como el organoestanano, seguido de desprotección TFA similar al método descrito para (6–(3–metilisotiazol–5–il)–[1,2,4]triazol[4,3–*b*]piridazin–3–il)metanamina .



Ejemplo 429

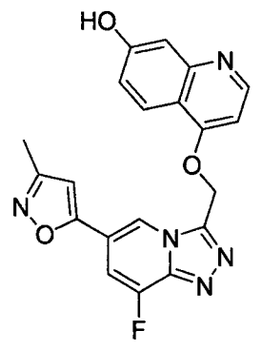
4–((8–fluor–6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–*a*]piridin–3–il)metoxi)–7–(2–metoxietoxi)quinolina

1) Bromhidrato de ácido 2–(7–hidroxiquinolin–4–iloxi)acético



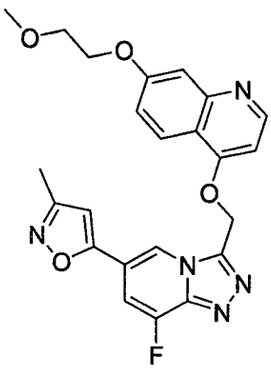
A un frasco de presión se agregó ácido 2–(7–metoxiquinolin–4–iloxi)acético (1.00 g, 4.29 mmol) en DCE (0.6 M, 7 mL). El frasco se enfrió en un baño de hielo y a la solución se agregó BBr_3 (1.62 ml, 17.2 mmol). La reacción se dejó calentar a temperatura ambiente y se agitó durante la noche. Mientras restaba un poco de material de partida, la reacción se detuvo y se diluyó con DCM (se mantuvo bajo cubierta debido al vapor). Se filtraron los sólidos y se secaron sobre alto vacío para proporcionar un sólido crudo marrón claro (~1.8g). El material se usó sin purificación adicional.

2) 4–((8–fluor–6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metoxi)quinolin–7–ol



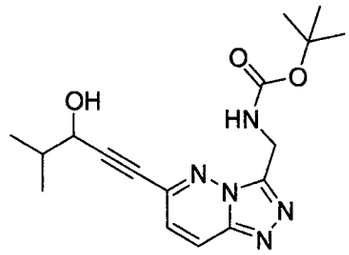
Se preparó el material usando el método general A (con bromhidrato de ácido 2–(7–hidroxiquinolin–4–iloxi)acético y 1–(3–fluor–5–(3–metilisoxazol–5–il)piridin–2–il)hidrazina

3) 4–((8–fluor–6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metoxi)–7–(2–metoxietoxi)quinolina



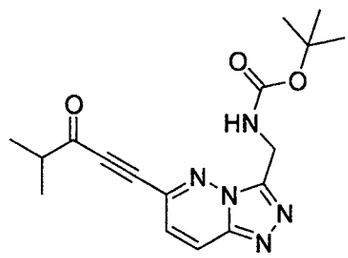
Se combinaron 4–((8–fluor–6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metoxi)quinolin–7–ol (0.110 g, 0.28 mmol), PPh_3 (polímero de sostén: 2.3 mmol/g) (1.2 g, 2.8 mmol) y 2–metoxietanol (0.11 ml, 1.3 mmol) en DCM (11 ml, 0.28 mmol). La mezcla se enfrió a 0 °C, y se agregó por goteo DEAD (0.089 ml, 0.56 mmol). La reacción se removió a partir de un baño de hielo y se agitó a temperatura ambiente durante 1h. El material se diluyó con DCM, y el PS–PPh_3 se filtró y se lavó completamente con DCM. El filtrado se concentró al vacío. El material crudo se disolvió en un mínimo de DCM y se purificó a través de MPLC (eluyendo con 0–100% 90:10:1 DCM:MeOH:NH_4OH en DCM) para proporcionar 4–((8–fluor–6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metoxi)–7–(2–metoxietoxi)quinolina

(0.070 g, 55% de rendimiento) en forma de un sólido blanco. MS (ESI pos. ion) m/z: 450.0 (M+H). Calc. Masa Exacta para $C_{23}H_{20}FN_5O_4$: 449.44



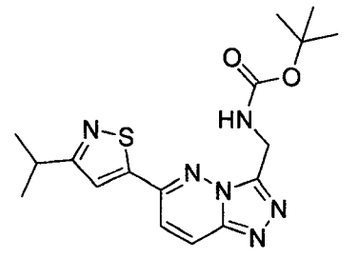
(6–(3–hidroxi–4–metilpent–1–inilo)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo

En un tubo sellado de 15–mL inundado con nitrógeno, se diluyeron (6–cloro–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo (2.00 g, 7.0 mmol), aducto $PdCl_2$(dppf)–CH_2Cl_2 (0.58 g, 0.70 mmol), y yoduro de cobre (I) (0.34 g, 1.8 mmol) en MeCN (70 mL). A la mezcla de reacción se agregó primero 4–metilpent–1–in–3–ol (3.7 ml, 35 mmol), seguido de trietilamina (25 ml, 176 mmol). La reacción se calentó luego a 50 °C durante 7.5 h. El material crudo se disolvió en un mínimo de DCM y se purificó a través de MPLC (dos veces) (eluyendo con 0–10% de MeOH/NH_4OH:DCM) para proporcionar (6–(3–hidroxi–4–metilpent–1–inilo)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo (1.823 g, 75% de rendimiento) en forma de un sólido marrón claro.



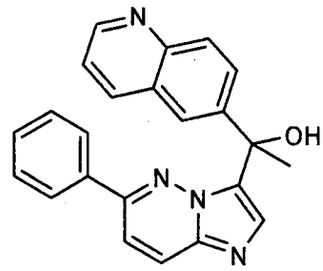
(6–(4–metil–3–oxopent–1–inilo)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo

Se disolvieron (6–(3–hidroxi–4–metilpent–1–inilo)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo (1.82 g, 5.27 mmol) y dióxido de manganeso (activado) (9.16 g, 105 mmol) en DCM (263 mL) y se agitaron a temperatura ambiente durante dos días. Se agregó dióxido de manganeso adicional (activado) (4.58 g, 52.7 mmol) y se agitó continuamente durante la noche. La mezcla de reacción se filtró sobre un tapón de Celite y se lavó con DCM para proporcionar (6–(4–metil–3–oxopent–1–inilo)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo (0.917 g, 50.7% de rendimiento) después de concentración al vacío.



(6–(3–isopropilisotiazol–5–il)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo

Una mezcla acuosa de (6–(4–metil–3–oxopent–1–inilo)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo (0.800 g, 2.33 mmol) y ácido hidroxilamin–O–sulfónico (0.263 g, 2.33 mol) en agua (8.0 mL) y 1,4–dioxano (8.0 mL) se agitó a 0 °C hasta que se observó el completo consumo del material orgánico de partida. La mezcla luego se trató cuidadosamente con bicarbonato de sodio sólido (0.196 g, 2.33 mmol), seguido de tratamiento con hidrosulfuro de sodio acuoso 1.4 M (1.83 ml, 2.56 mmol). La reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con agua (20 mL) y se extrajo con DCM (40 mL), se secó sobre sulfato de sodio, se filtró y se concentró al vacío. El material crudo concentrado se disolvió en un mínimo de DCM y se purificó a través de MPLC (eluyendo con 0–10% MeOH/NH_4OH en DCM) para proporcionar (6–(3–isopropilisotiazol–5–il)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo (0.196 g, 22.5% de rendimiento) con 82% de pureza. MS (ESI pos. ion) m/z: 433.0 (M+H). Calc. Masa Exacta para $C_{21}H_{20}N_8OS$: 432.51.



Ejemplo 430

1–(6–fenilimidazol[1,2–b]piridazin–3–il)–1–(quinolin–6–il)etanol

a) N–metoxi–N–metilquinolin–6–carboxamida

Un frasco RB de 250 mL se cargó con ácido quinolin–6–carboxílico (5.00 g, 28.9 mmol), DCM (100 ml, 1554 mmol), cloruro de oxalilo (3.79 ml, 43.3 mmol), y una pocas gotas de DMF y se agitó a temperatura ambiente durante 2 horas, luego se concentró. El residuo se extrajo en DCM (100 ml, 1554 mmol), se enfrió a 0°C, luego se agregaron lentamente Base de Hunig (17.7 ml, 101 mmol) y clorhidrato de N–metoximetanamina (2.96 g, 30.3 mmol). La mezcla se agitó a temperatura ambiente durante 16 horas (91463–3–1). La mezcla se diluyó con DCM (200 mL), luego se lavó con agua (250 mL), $NaHCO_3$ saturado (250 mL), y salmuera (250 mL). La capa orgánica se secó con $MgSO_4$, se filtró y se concentró para proporcionar un aceite marrón, que se purificó mediante MPLC eluyendo con 2–6% de MeOH/DCM para proporcionar N–metoxi–N–metilquinolin–6–carboxamida (5.943 g, 95.2% de rendimiento) en forma de un aceite marrón.

b) 1–(quinolin–6–il)etanona

Un frasco RB de 250 mL se cargó con N–metoxi–N–metilquinolin–6–carboxamida (5.943 g, 27.5 mmol) y THF (100 ml, 1220 mmol), luego se enfrió a 0 C. Se agregó por goteo bromuro de metilmagnesio (18.3 ml, 55.0 mmol) y la mezcla se dejó calentar a temperatura ambiente y se agitó durante 3 horas. La reacción no se completó, por lo tanto se agregó MeMgBr adicional (3 mL) y la mezcla se agitó durante la noche. La mezcla luego se neutralizó usando HCl 2N y la capa acuosa se extrajo con DCM (200 mL x 2) y EtOAc (200 mL x 2). La capa orgánica se secó con $MgSO_4$, se filtró y se concentró para proporcionar un aceite amarillo. La capa acuosa contenía un poco de producto, entonces la capa se concentró y luego se filtró a través de una columna de fase inversa C_{18}, eluyendo primero con agua que con MeOH. La capa MeOH se concentró para proporcionar un aceite amarillo que se combinó con el aceite amarillo de la capa orgánica. Las porciones combinadas se purificaron mediante MPLC eluyendo con un gradiente de 2–6% de MeOH/DCM. Se aisló 1–(quinolin–6–il)etanona (4.074 g, 86.6% de rendimiento) en forma de un aceite amarillo que se solidificó por reposo.

c) Bromhidrato de 2–bromo–1–(quinolin–6–il)etanona

Un frasco RB de 250 mL se cargó con 1–(quinolin–6–il)etanona (3.82 g, 22.3 mmol) y 30% de HBr/AcOH (45.0 ml). Se agregó lentamente bromo (1.14 ml, 22.1 mmol). Esto se agitó a temperatura ambiente durante 4 horas, en este momento se observó la conversión total del producto (con una pequeña cantidad de producto secundario dibrominado). La mezcla de reacción se filtró y el sólido se lavó con Et_2O para proporcionar bromhidrato de 2–bromo–1–(quinolin–6–il)etanona (5.6359 g, 76.3% de rendimiento). El compuesto se usó en la etapa siguiente sin purificación adicional.

d) (E)–N'–(6–cloropiridazin–3–il)–N,N–dimetilformamidina

Un frasco RB de 500 mL se cargó con 6–cloropiridazin–3–amina (10.0 g, 77.2 mmol) y dimetoxi–N,N–dimetilmetanamina (206 ml, 1544 mmol), equipado con un condensador a reflujo, luego se calentó a 110°C durante 3 horas y luego se dejó a temperatura ambiente durante 16 horas. El precipitado se recogió por filtración. Se concentró el licor madre para proporcionar un sólido amarillo, que se trituró con EtOAc y se recogió. Los sólidos se combinaron para proporcionar (E)–N'–(6–cloropiridazin–3–il)–N,N–dimetilformamidina (11.81 g, 82.9% de rendimiento) en forma de un sólido blanco.

e) (6–cloroimidazo[1,2–b]piridazin–3–il)(quinolin–6–il)metanona

Un frasco RN de 100 mL se cargó con 2–bromo–1–(quinolin–6–il)etanona (0.7011 g, 2.80 mmol), (E)–N'–(6–cloropiridazin–3–il)–N,N–dimetilformamidina (0.518 g, 2.80 mmol), y DMF (10.0 ml, 129 mmol), equipado con un condensador a reflujo, luego se calentó a 105°C durante 3 horas. La mezcla de reacción se concentró, luego se trituró con MeOH para proporcionar (6–cloroimidazo[1,2–b]piridazin–3–il)(quinolin–6–il)metanona (0.530 g, 1.72 mmol, 61%) en forma de un sólido marrón.

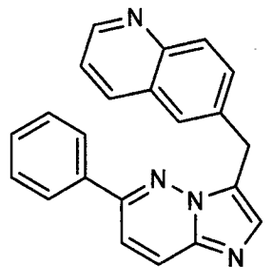
f) (6–fenilimidazo[1,2–b]piridazin–3–il)(quinolin–6–il)metanona

Un tubo sellado de 48 mL se cargó con (6–cloroimidazo[1,2–b]piridazin–3–il)(quinolin–6–il)metanona (0.530 g, 1.72 mmol), ácido fenilborónico (0.314 g, 2.58 mmol), carbonato de cesio (1.68 g, 5.15 mmol), aducto $PdCl_2$(dppf)–CH_2Cl_2 (0.0701 g, 0.0858 mmol), 1,4–dioxano (6.31 ml, 73.8 mmol), y agua (1.11 ml, 61.8 mmol), se inundó con argón, se selló, luego se colocó en un baño de aceite a 80°C durante 8 horas. La mezcla se concentró y luego se trituró con agua, seguido de MeOH/DCM para proporcionar (6–fenilimidazo[1,2–b]piridazin–3–il)(quinolin–6–il)metanona en forma de un sólido marrón rojizo.

g) 1–(6–fenilimidazo[1,2–b]piridazin–3–il)–1–(quinolin–6–il)etanol

Un frasco RB de 25 mL se cargó con (6–fenilimidazo[1,2–b]piridazin–3–il)(quinolin–6–il)metanona (0.200 g, 0.57 mmol) y THF (2.00 ml, 24 mmol), luego se enfrió a 0°C. Se agregó por goteo bromuro de metilmagnesio (0.76 ml, 2.2 mmol) y luego la mezcla se agitó a temperatura ambiente durante 5 horas. Esto se diluyó con HCl 2N (1 mL) y agua (25 mL), luego se extrajo con DCM (25 mL x 2) y EtOAc (25 mL). Los orgánicos combinados se lavaron con salmuera y se secaron con $MgSO_4$, se filtraron y se concentraron. El aceite resultante se purificó mediante MPLC usando una columna de 40 g RediSep, eluyendo con 2–6% de MeOH/DCM durante 40 minutos. Se aisló 1–(6–fenilimidazo[1,2–b]piridazin–3–il)–1–(quinolin–6–il)etanol (0.082 g, 39% de rendimiento) en forma de un sólido de color castaño. EM (ESI pos. ion) m/z: 367 (MH+). Calc. Exacto de Masa para $C_{23}H_{18}N_4O$: 366.

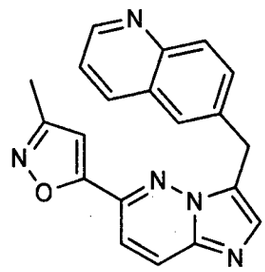
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Ejemplo 431

6–((6–fenilimidazo[1,2–b]piridazin–3–il)metil)quinolina

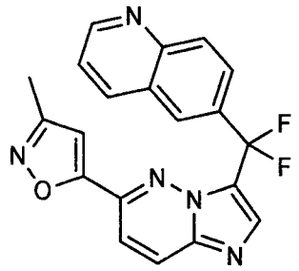
Un frasco para microondas de 10–20 mL se cargó con hidrato de hidrazina (0.0312 ml, 0.642 mmol), (6–fenilimidazo[1,2–b]piridazin–3–il)(quinolin–6–il)metanona (0.150 g, 0.428 mmol), KOH (0.0961 g, 1.71 mmol), y dietilen glicol (4.09 ml, 42.8 mmol), se selló, luego se colocó en un horno microondas Personal Chemistry a 130°C durante 20 minutos después de 5 minutos de pre–agitación. La mezcla se diluyó con agua (75 mL), luego se extrajo con DCM (2 x 75 mL). Los orgánicos combinados se lavaron con salmuera (75 mL), luego se secaron con $MgSO_4$, se filtraron y se concentraron para proporcionar un sólido marrón, luego se purificaron mediante HPLC preparativa para proporcionar el producto en forma de una sal de ácido fórmico. EM (ESI pos. ion) m/z: 337 (MH+). Calc. Exacto de masa para $C_{22}H_{16}N_4$: 336.



Ejemplo 432

6–((6–(3–Metilisoxazol–5–il)imidazo[1,2–b]piridazin–3–il)metil)quinolina

Un tubo de ensayo de 16 mm se cargó con hidrato de hidrazina (0.0273 ml, 0.563 mmol), (6–(3–metilisoxazol–5–il)imidazo[1,2–b]piridazin–3–il)(quinolin–6–il)metanona (preparado usando un procedimiento similar tal como (6–fenilimidazo[1,2–b]piridazin–3–il)(quinolin–6–il)metanona) (0.100 g, 0.281 mmol), ter–butóxido de sodio (0.0406 g, 0.422 mmol), y 1–butanol (0.670 ml, 7.32 mmol), se selló, luego se calentó a 150°C durante 2 horas (96979–1–1). La mezcla se diluyó con agua, se neutralizó con HCl 2N, luego se extrajo con DCM (3 x 30 mL). Se secaron los orgánicos combinados con $MgSO_4$, se filtraron, luego se concentraron. Se purificó 6–((6–(3–metilisoxazol–5–il)imidazo[1,2–b]piridazin–3–il)metil)quinolina mediante HPLC preparativa y se aisló como la sal de TFA. EM (ESI pos. ion) m/z: 341 (MH+). Calc. Exacto de masa para $C_{20}H_{15}N_5O$: 341.

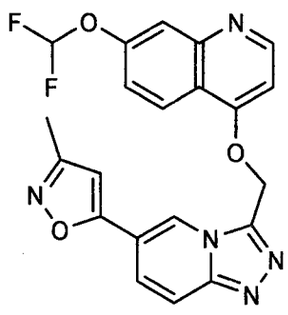


Ejemplo 433

6–(difluor(6–(3–metilisoxazol–5–il)imidazo[1,2–b]piridazin–3–il)metil)quinolina

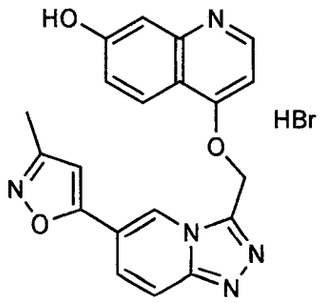
Un tubo de ensayo de 25 mm se cargó con 2,2–difluor–1,3–dimetilimidazolidina (DFI) (0.24 g, 1.8 mmol), (6–(3–metilisoxazol–5–il)imidazo[1,2–b]piridazin–3–il)(quinolin–6–il)metanona (0.125 g, 0.35 mmol), y MeCN (2.00 ml, 38 mmol), se selló, luego se calentó a 84°C durante 36 horas, agregando 2,2–difluor–1,3–dimetilimidazolidina adicional (DFI) (0.24 g, 1.8 mmol) después de 16 horas. La mezcla se diluyó con agua (50 mL), luego se extrajo con DCM (2 x 40 mL). Los orgánicos combinados se lavaron con salmuera (40 mL), se secaron con $MgSO_4$, se filtraron, luego se concentraron para proporcionar un residuo marrón. Esto se purificó mediante MPLC usando una columna de 40 g RediSep, eluyendo con 20 – 50% (mezcla 90:10:1 DCM:MeOH:NH_4OH) en EtOAc durante 40 minutos. Las fracciones más puras se recogieron –aquellas que aún contenían DFI, por lo tanto el residuo se trituró con EtOAc y se decantó. Se aisló 6–(difluor(6–(3–metilisoxazol–5–il)imidazo[1,2–b]piridazin–3–il)metil)quinolina en forma de un sólido amarillo claro.

EM (ESI pos. ion) m/z: 378 (MH+). Cálculo exacto de masa para $C_{20}H_{13}F_2N_5O$: 377.



Ejemplo 434

7–(difluormetoxi)–4–((6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metoxi)quinolina

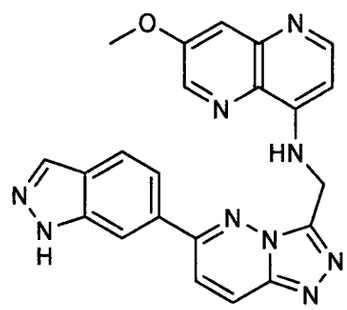


1) Bromhidrato de 4–((6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metoxi)quinolin–7–ol.

Un tubo de 150 mL se cargó con 7–metoxi–4–((6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metoxi)quinolina (1.44 g, 3.72 mmol) y HBr (30.3 ml, 558 mmol), se selló, luego se colocó a 120°C durante 5 horas. La mezcla de reacción se neutralizó lentamente con NaOH 6N hasta que surgió un precipitado de la solución (pH ~5)— el sólido se recogió para proporcionar bromhidrato de 4–((6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metoxi)quinolin–7–ol.

2) 7–(difluormetoxi)–4–((6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metoxi)quinolina.

Un tubo de 48 mL se cargó con 2–cloro–2,2–difluoracetato de sodio (0.15 g, 1.0 mmol), bromhidrato de 4–((6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metoxi)quinolin–7–ol (0.200 g, 0.44 mmol), carbonato de cesio (0.43 g, 1.3 mmol), y DMF (1.7 ml, 22 mmol), se inundó con argón, se selló, luego se colocó en un bañó de aceite de 100°C durante 5 horas. La mezcla de reacción se concentró, luego se diluyó con DCM y cloroformo. Esto se lavó con agua, $NaHCO_3$ saturado y salmuera, luego se secó con $MgSO_4$, se filtró y se concentró para proporcionar un aceite marrón. Esto se purificó mediante HPLC para proporcionar 7–(difluormetoxi)–4–((6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metoxi)quinolina (0.025 g, 13% de rendimiento) en forma de una sal de ácido fórmico. EM (ESI pos. ion) m/z: 424 (MH+). Calc. Exacto de masa para $C_{21}H_{15}F_2N_5O_3$: 423.



Ejemplo 435

N–((6–(1H–indazol–6–il)–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)–7–metoxi–1,5–naftiridin–4–amina

a) 6–(3–((7–Metoxi–1,5–naftiridin–4–ilamino)metil)–[1,2,4]triazol[4,3–b]piridazin–6–il)–1H–indazol–1–carboxilato. Un tubo se cargó con N–((6–cloro–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)–7–metoxi–1,5–naftiridin–4–amina (0.250 g, 0.732 mmol), 6–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–indazol–1–carboxilato de ter–butilo (0.378 g, 1.10 mmol), aducto PdCl2(dppf)–CH2Cl2 (0.0597 g, 0.0732 mmol), carbonato de potasio (0.303 g, 2.19 mmol), DMF (5.01 ml, 64.4 mmol), y agua (1.16 ml, 64.4 mmol), se inundó con argón, se

selló, luego se colocó en un baño de aceite a 60°C durante 6 horas. La mezcla de reacción se concentró, luego se trituró con agua para proporcionar un sólido negro. El material se usó directamente en la siguiente etapa.

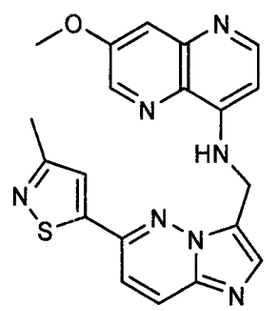
b) N–((6–(1H–indazol–6–il)–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)–7–metoxi–1,5–naftiridin–4–amina . Se preparó el compuesto del título de la misma manera que 7–metoxi–4–((6–(6–(piperazin–1–il)piridin–3–il)–[1,2,4]triazol[4,3–b]piridazin–3–il)metoxi)quinolina. EM (ESI pos. ion) m/z: 424 (MH+). Calc. exacto de masa para $C_{22}H_{17}N_9O$: 423.

4–bromo–1–(2,2,2–trifluoretil)–1H–pirazol

Un frasco RB de 250 mL se cargó com 4–bromo–1H–pirazol (2.00 g, 13.6 mmol), trifluormetansulfonato de 2,2,2–trifluoretilo (2.35 ml, 17.0 mmol), carbonato de cesio (8.87 g, 27.2 mmol), y 1,4–dioxano (40.0 ml, 468 mmol), se tapó y se agito a temperatura ambiente durante 20 horas. La mezcla de reacción se filtró y el sólido se lavó con dioxano; el filtrado luego se concentró para proporcionar 4–bromo–1–(2,2,2–trifluoretil)–1H–pirazol (2.402 g, 77.1% de rendimiento) en forma de un aceite crudo.

4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1–(2,2,2–trifluoretil)–1H–pirazol.

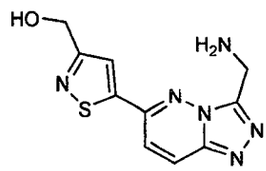
El compuesto del título se preparó de la misma manera que 1–etil–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol a partir de 4–bromo–1–(2,2,2–trifluoretil)–1H–pirazol.



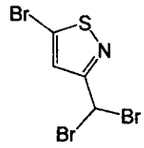
Ejemplo 436

7–metoxi–N–((6–(3–metilisotiazol–5–il)imidazo[1,2–b]piridazin–3–il)metil)–1,5–naftiridin–4–amina .

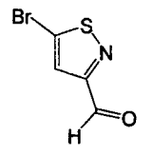
El compuesto del título se preparó de la misma manera que 7–metoxi–N–((6–(3,4,5–trifluorfenil)imidazo[1,2–b]piridazin–3–il)metil)–1,5–naftiridin–4–amina . EM (ESI pos. ion) m/z: 404 (MH+). Calc. Exacto de masa para $C_{20}H_{17}N_7OS$: 403.



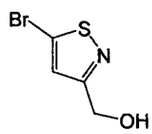
(5–(3–(aminometil)–[1,2,4]triazol[4,3–b]piridazin–6–il)isotiazol–3–il)metanol.



1) 5–bromo–3–(dibromometil) isotiazol. Se disolvió 5–bromo–3–metilisotiazol (2.15 g, 12 mmol) en dicloroetano (20 mL) luego se agregó N–bromosuccinimida (4.5 g, 25 mmol) y AIBN (0.50 g, 3.0 mmol). La mezcla de reacción se calentó a 100 °C durante 4 horas. Se agregaron AIBN adicional (0.50 g, 3.0 mmol) y bromo (0.062 ml, 1.2 mmol) a la mezcla y se continuó calentando a 100 °C durante 4 horas. Se agregaron N–bromosuccinimida (4.5 g, 25 mmol) y AIBN (0.50 g, 3.0 mmol) y luego se continuó calentando a 100 °C durante 4 horas. Nuevamente, se agregaron N–bromosuccinimida (4.5 g, 25 mmol) y AIBN (0.30 g, 1.8 mmol) y la mezcla se calentó a 100 °C durante 4 horas. La mezcla de reacción se diluyó con acetato de etilo y se lavó con agua, bicarbonato de sodio saturado y salmuera. La capa orgánica se secó sobre sulfato de sodio y se concentró bajo vacío. La muestra se purificó mediante cromatografía evaporativa eluyendo con 0–10% acetato de etilo/hexano para proporcionar 5–bromo–3–(dibromometil)isotiazol (2.07 g, 51% de rendimiento) en forma de un líquido incoloro.

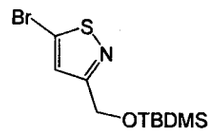


2) 5–bromoisotiazol–3–carbaldehído. Se disolvió 5–bromo–3–(dibromometil)isotiazol (1.00 g, 3.0 mmol) en DME (10 mL) luego se agregó a una solución de nitrato de plata (0.56 g, 3.3 mmol) en agua (1.6 mL). Se formó un precipitado blanco. La mezcla de reacción se calentó a 100 °C durante 1,5 horas. Se agregó nitrato de plata adicional (0.56 g, 3.3 mmol) en agua (1.6 mL) y se continuó el calentamiento a 100 °C durante 2.5 horas. La mezcla de reacción se filtró a través de una almohadilla de Celite lavando con THF luego con acetato de etilo. El filtrado se concentró bajo vacío y el aceite remanente se diluyó con acetato de etilo. La capa orgánica se lavó con agua y luego sobre sulfato de sodio y se concentró bajo vacío para proporcionar 5–bromoisotiazol–3–carbaldehído (0.536 g, 94% de rendimiento) en forma de un aceite amarillo claro.

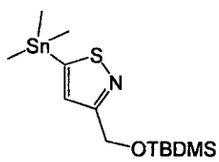


3)(5–bromoisotiazol–3–il)metanol. Se disolvió 5–bromoisotiazol–3–carbaldehído (0.533 g, 2.8 mmol) en etanol (40 mL) luego se agregó borohidruro de sodio (0.11 g, 2.8 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 3 horas. Se agregó más

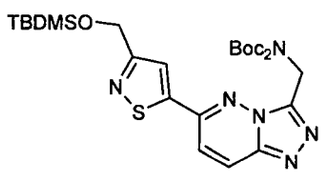
borohidruro de sodio (0.026 g, 0.69 mmol) y se continuó la agitación a temperatura ambiente durante 4,5 horas. Se agregó una vez más borohidruro de sodio (0.11 g, 2.8 mmol) y la agitación se continuó a temperatura ambiente durante la noche. La reacción se apagó con cloruro de amonio acuoso saturado, luego se concentró bajo vacío. La capa acuosa remanente se diluyó con agua y luego se extrajo con acetato de etilo (2x). La capa orgánica se secó sobre sulfato de sodio y se concentró bajo vacío para proporcionar (5–bromoisotiazol–3–il)metanol (0.430 g, 80% de rendimiento) en forma de un aceite naranja. MS (ESI pos. ion) m/z: 194.0 y 196.0 (MH^+).



4) 5–bromo–3–((ter–butildimetilsililoxi)metil)isotiazol. Se disolvió (5–bromoisotiazol–3–il) metanol (0.380 g, 1.96 mmol) en DMF (4 mL) luego se agregó cloruro de ter–butildimtilsililo (0.443 g, 2.94 mmol) e imidazol (0.400 g, 5.87 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se combinó con reacciones previas y se concentró bajo vacío. La muestra se purificó mediante cromatografía evaporativa eluyendo con 0–15% de acetato de etilo/hexano para proporcionar 5–bromo–3–((ter–butildimetilsililoxi)metil)isotiazol en forma de un líquido amarillo pálido. MS (ESI pos. ion) m/z: 308.0 y 310.0 (MH^+).

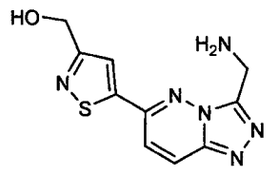


5) 3–((ter–butildimetilsililoxi)metil)–5–(trimetilstanilo)isotiazol. Se disolvió 5–bromo–3–((ter–butildimetilsililoxi)metil)isotiazol (0.100 g, 0.324 mmol) en THF (1 mL) luego se enfrió a –78 °C y se agregó por goteo n–BuLi en hexano 1.6M (0.223 ml, 0.357 mmol) a través de una jeringa. La mezcla de reacción se tornó amarilla y se continuó la agitación a –78 °C durante 45 minutos. Se agregó por goteo a la mezcla cloruro de trimetilestaño 1M en THF (0.324 ml, 0.324 mmol) a través de una jeringa. No se observó cambio de color. Se continuó la agitación a –78 °C durante 1,5 horas. La reacción se apagó con bicarbonato de sodio acuoso saturado a –78 °C luego se calentó a temperatura ambiente. La mezcla se diluyó con agua y luego se extrajo con éter. La capa orgánica se secó sobre sulfato de sodio y se concentró bajo vacío para proporcionar 3–((ter–butildimetilsililoxi)metil)–5–(trimetilstanilo)isotiazol (0.121 g, 95.1% de rendimiento) en forma de un líquido amarillo claro.

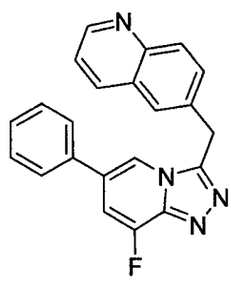


6) (6–(3–((((1,1–dimetiletil)(dimetil)silil)oxi)metil)–5–isotiazolil)[1,2,4]triazol[4,3–b]piridazin–3–il)metilimidodicarbonato de bis(1,1–dimetiletilo). (6–cloro[1,2,4]triazol[4,3–b]piridazin–3–

il)metilimidodicarbonato de bis(1,1–dimetiletilo) (0.200 g, 0.521 mmol) se suspendió en dioxano (3 mL) luego se agregó 3–((ter–butildimetilsililoxi)metil)–5–(trimetilestanilo)isotiazol (0.429 g, 1.09 mmol), xantfos (0.0301 g, 0.0521 mmol), acetato de paladio (II) (0.00585 g, 0.0261 mmol), y agua (0.0188 ml, 1.04 mmol). La mezcla de reacción se calentó a 100 °C durante 3 horas. La mezcla de reacción se concentró bajo vacío. La muestra se purificó mediante cromatografía evaporativa eluyendo con 0–100% de acetato de etilo para proporcionar (6–(3–((((1,1–dimetiletil)(dimetil)silil)oxi)metil)–5–isotiazolil)[1,2,4]triazol[4,3–b]piridazin–3–il)metilimidodicarbonato de bis(1,1–dimetiletilo) (0.170 g, 56.6% de rendimiento) en forma de un aceite amarillo. MS (ESI pos. ion) m/z: 577.2 (MH^+).



7) (5–(3–(aminometil)–[1,2,4]triazol[4,3–b]piridazin–6–il)isotiazol–3–il)metanol. (6–(3–((((1,1–dimetiletil)(dimetil)silil)oxi)metil)–5–isotiazolil)[1,2,4]triazol[4,3–b]piridazin–3–il)metilimidodicarbonato de bis(1,1–dimetiletilo) (0.170 g, 0.29 mmol) se disolvió en acetato de etilo (5 mL) luego se hizo burbujear ácido clorhídrico gaseoso a través de la mezcla durante aproximadamente 5 minutos. Se formó un precipitado y se continuó la agitación a temperatura ambiente durante 1.5 horas. La reacción se concentró bajo vacío y luego la mayoría se redisolvió en metanol (3.5 mL) y se agregó hidróxido de amonio (0.052 ml, 1.3 mmol). La mezcla se agitó a temperatura ambiente durante 2 horas y luego se concentró bajo vacío. La muestra se purificó mediante cromatografía evaporativa eluyendo con 50–100% 90:10:1 diclorometano/metanol/NH4OH seguido de 100% 90:10:1 diclorometano/metanol/NH4OH para proporcionar (5–(3–(aminometil)–[1,2,4]triazol[4,3–b]piridazin–6–il)isotiazol–3–il)metanol (0.066 g, 85% de rendimiento) en forma de un sólido blanco. EM (ESI pos. ion) m/z: 263.0 (MH^+).



Ejemplo 437

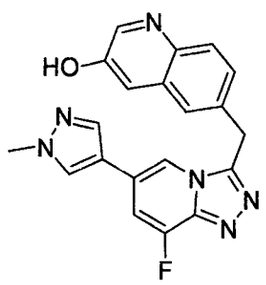
6–((8–fluor–6–fenil–[1,2,4]triazol[4,3–a]piridin–3–il)metil)quinolina

1) 6–((6–cloro–8–fluor–[1,2,4]triazol[4,3–a]piridin–3–il)metil)quinolina. Una mezcla de 1–(5–cloro–3–fluorpiridin–2–il)hidrazina (500 mg, 3095 µmol) y 2–(quinolin–6–il)acetato de metilo (600 mg, 2982 µmol) en HCl (conc., 600 µL, 7200 µmol) se calentó a 100 °C durante 20 min. La mezcla se calentó luego en un horno microondas a 180 °C durante 40 min. La

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mezcla se apagó con NaOH (5 N, 1.5 mL) y la suspensión se filtró y se lavó con H_2O. El sólido marrón resultante es principalmente el producto deseado. El sólido se trituró luego con NaOH (5 N, 1 mL), se filtró y se lavó con H_2O. LCMS (ESI pos. ion): Calc. para $C_{16}H_{10}ClFN_4$: 312.0; hallado: 313.1 (M+1).

2) 6–((8–fluor–6–fenil–[1,2,4]triazol[4,3–a]piridin–3–il)metil)quinolina. Una mezcla de $Pd(OAc)_2$ (6.46 mg, 28.8 µmol), fosfato de potasio (367 mg, 1727 µmol), ácido fenilborónico (211 mg, 1727 µmol), diciclohexil(2–(2,4,6–triisopropilciclohexa–1,3–dienil)fenil)fosfina (27.6 mg, 57.6 µmol), y 6–((6–cloro–8–fluor–[1,2,4]triazol[4,3–a]piridin–3–il)metil)quinolina (180 mg, 576 µmol) en dioxano (6 mL)–H_2O (2 mL) se calentó a 100 °C bajo nitrógeno durante 20 h. La mezcla se enfrió a temperatura ambiente y se dividió entre H_2O y CH_2Cl_2. La capa orgánica se secó sobre $MgSO_4$ y se concentró. El residuo se purificó sobre sílice usando MeOH en DCM (0–5%) para proporcionar un sólido rosa. Este sólido se trituró con hexano–EtOAc–DCM (caliente) para proporcionar un sólido marrón (105 mg). LCMS (ESI pos. ion): calc. Para $C_{22}H_{15}FN_4$: 354.1; hallado: 355.2 (M+1).

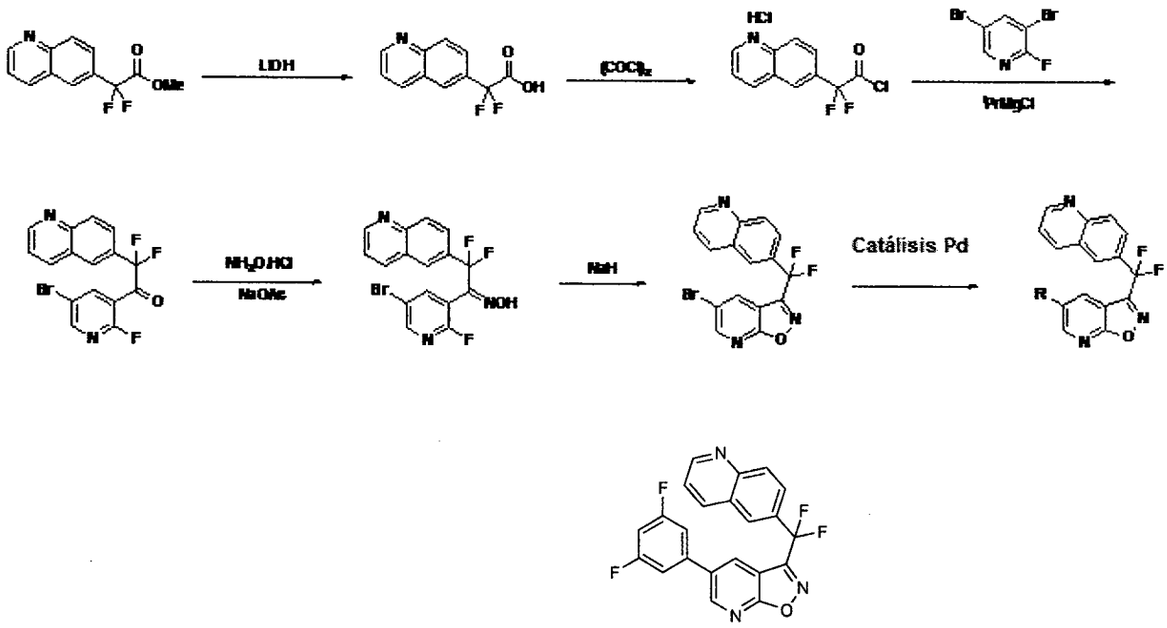


Ejemplo 438

6–((8–fluor–6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metil)quinolin–3–ol.

Una mezcla de 6–((6–cloro–8–fluor–[1,2,4]triazol[4,3–a]piridin–3–il)metil)–3–metoxiquinolina crudo (200 mg, 584 µmol), 1–metil–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol (600 mg, 2884 µmol), aducto $PdCl_2(dppf)$–CH_2Cl_2 (24 mg, 29 µmol), y Na_2CO_3 (500 mg, 4717 µmol) en DME (7 mL)–H_2O (5 mL) se calentó a 100 °C bajo nitrógeno. Después de la noche el sedimento se trato con DMSO (10 mL) y se filtró. La solución de DMSO se purificó sobre HPLC (10–60%/10min). La fracción del producto se concentró hasta sequedad con tolueno. El sólido se trituró luego con MeOH–hexano (1:2) para proporcionar un polvo marrón (60 mg). LCMS (ESI pos. ion): calc. para $C_{20}H_{15}FN_6O$: 374.1; hallado 375.1 (M+1).

Método General F



Ejemplo 439

6-((5-(3,5-difluorfenil)isoxazol[5,4-b]piridin-3-il)difluormetil)quinolina

1) Acido 2,2-difluor-2-(quinolin-6-il)acético. A una solución de 2,2-difluor-2-(quinolin-6-il)acetato de metilo (2.0g, 8.4 mmol) en dioxano (4 mL) y agua (12 mL) se agregó monohidrato de hidróxido de litio (0.53 g, 12 mmol). Después de agitar a 50 °C durante 30 minutos, la solución se llevó a pH 4 con HCl 2.0N. La solución se concentró y se secó sobre un liofilizador durante la noche para producir el producto en forma de un sólido naranja. EM m/z = 224.0 [M+1

2) Clorhidrato de cloruro de 2,2-difluor-2-(quinolin-6-il)acetilo. A una suspensión de ácido 2,2-difluor-2-(quinolin-6-il)acético (1.9 g, 8.4 mmol) en diclorometano (16 mL) se agregó cloruro de oxalilo (7.4 mL, 84 mmol). La mezcla se agitó a 45 °C durante una hora. La suspensión se filtró y el filtrado resultante se concentró para proporcionar el producto en forma de un aceite naranja (1.8 g, 73% etapas 1 y 2 combinadas).

3) 1-(5-bromo-2-fluorpiridin-3-il)-2,2-difluor-2-(quinolin-6-il)etanona. A una solución de 3,5-dibromo-2-fluorpiridina (3.1 g, 12 mmol) en THF anhidro (12 mL) bajo argón se agregó cloruro de isopropilmagnesio (2.0 M en THF, 6.0 mL, 12 mmol). La solución se agitó a temperatura ambiente durante 10 minutos, luego se agregó a través de una cánula a una solución de clorhidrato de cloruro de 2,2-difluor-2-(quinolin-6-il)acetilo (1.8 g, 6.1 mmol) en THF anhidro (20 mL) a -78 °C. La solución se dejó enjuagar a -40 °C durante una hora, luego se agitó a 0 °C durante una hora. La reacción se apagó con agua y se extrajo con acetato de etilo; Los extractos orgánicos se secaron sobre sulfato de magnesio y se concentraron. La purificación mediante MPLC (eluido con un gradiente de 20 a 80% de

000336

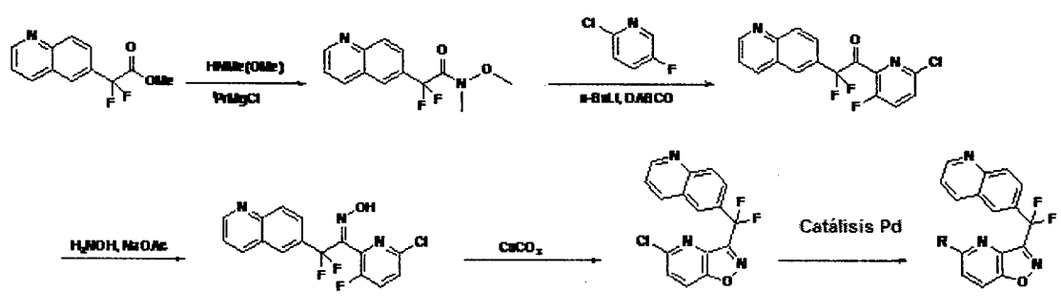
acetato de etilo en hexanos) proporcionó el producto en forma de un sólido de color castaño (0.90 g, 38%).

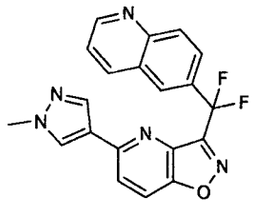
4) Oxima 1–(5–bromo–2–fluorpiridin–3–il)–2,2–difluor–2–(quinolin–6–il)etanona. A un recipiente de presión se agregó clorhidrato de hidroxilamina (1.6 g, 24 mmol), acetato de sodio (2.9 g, 35 mmol) y 1–(5–bromo–2–fluorpiridin–3–il)–2,2–difluor–2–(quinolin–6–il)etanona (0.90 g, 2.4 mmol) en ácido acético (20 mL). La suspensión se selló y se agitó a 100 °C durante 50 minutos, luego se concentró, se trituró con agua y se filtró. La purificación del sólido resultante mediante MPLC (eluido con un gradiente de 0–10% de metanol en diclorometano) proporcionó el producto en forma de un sólido beige (0.59 g, 63%). EM m/z = 396.0 $[M+1]^+$

5) 6–((5–bromoisoxazolo[5,4–b]piridin–3–il)difluormetil)quinolina. A una solución de oxima 1–(5–bromo–2–fluorpiridin–3–il)–2,2–difluor–2–(quinolin–6–il)etanona (0.59 g, 1.5 mmol) en THF anhidro (10 mL) se agregó hidruro de sodio (0.090 g, 2.3 mmol) a 0 °C. Después de 10 minutos, la solución se diluyó con acetato de etilo y se lavó con agua, los extractos orgánicos se secaron sobre sulfato de magnesio. La purificación mediante MPLC (eluida con un gradiente de 20–50% de acetato de etilo en hexanos) proporcionó el producto en forma de un sólido blanco (0.39g, 70%). EM m/z = 377.0 $[M+1]^+$ Calc. para $C_{16}H_8BrF_2N_3O$: 376.2

6) 6–((5–(3,5–difluorfenil)isoxazol[5,4–b]piridin–3–il)difluormetil)quinolina. A un recipiente de presión se agregó aducto $PdCl_2(dppf)–CH_2Cl_2$ (0.0076 g, 0.0093 mmol), carbonato de cesio (0.13 g, 0.40 mmol), 6–((5–bromoisoxazolo[5,4–b]piridin–3–il)difluormetil)quinolina (0.050 g, 0.13 mmol) y ácido 3,5–difluorfenilborónico (0.031g, 0.020 mmol) en DMF (1.0 mL) agua (0.25 mL). El recipiente se purgó con argón, se selló, y se agitó a 80 °C durante dos horas. La mezcla se concentró, se trituró con agua y se filtró; la purificación del precipitado resultante mediante MPLC (eluido con un gradiente de 20 a 50 % de acetato de etilo en hexanos proporcionó el producto en forma de un sólido blanco (27 mg, 53%).

Método General G





Ejemplo 440

6–(difluor(5–(1–metil–1H–pirazol–4–il)isoxazol[4,5–b]piridin–3–il)metil)quinolina

1) 2,2–difluor–N–metoxi–N–metil–2–(quinolin–6–il)acetamida. A una solución de clorhidrato de N–metoximetanamina (3.7 g, 38 mmol) y 2,2–difluor–2–(quinolin–6–il)acetato de metilo (6.0 g, 25 mmol) en THF anhidro (30 mL) se agregó cloruro de isopropilmagnesio (2.0 M, 38 mL, 76 mmol) a –20 °C. Después de 30 minutos la reacción se apagó con cloruro de amonio saturado y se extrajo con éter dietílico; los extractos orgánicos se secaron sobre sulfato de magnesio. La purificación mediante MPLC (eluida con un gradiente de 10 a 70 % de acetato de etilo en hexanos) proporcionó el producto en forma de un sólido naranja. EM m/z = 267.2 $[M+1]^+$.

2) 1–(6–cloro–3–fluorpiridin–2–il)–2,2–difluor–2–(quinolin–6–il)etanona. Se agregó n–butilitio (2.5M en hexanos, 3.70 ml, 9.25 mmol) a una solución agitada de DABCO (1.04 g, 9.25 mmol) en Et_2O (46 mL) a –78°C. La mezcla de reacción se agitó 1 h a –20°C. y luego se enfrió nuevamente a–78°C. Se agregó 2–cloro–5–fluorpiridina (0.939 ml, 9.25 mmol) en Et_2O (5 mL). La agitación se continuó a –78°C durante 1h. Se agregó a través de una cánula 2,2–difluor–N–metoxi–N–metil–2–(quinolin–6–il)acetamida (2.24 g, 8.41 mmol) en Et_2O (20 mL). La mezcla de reacción se agitó a–78°C durante 70 min. El baño de enfriamiento se reemplazó por un baño de hielo/agua. Después de 10 min de agitación a 0°C, la mezcla de reacción se apagó con agua. La capa acuosa se extrajo con EtOAc y DCM/MeOH(9/1). Las capas orgánicas se combinaron, se secaron sobre $MgSO_4$, se filtraron y se concentraron al vacío. La purificación mediante MPLC (hexanos/EtOAc: 100/0 to 40/60) proporcionó el compuesto del título (2.27g, 80% de rendimiento).

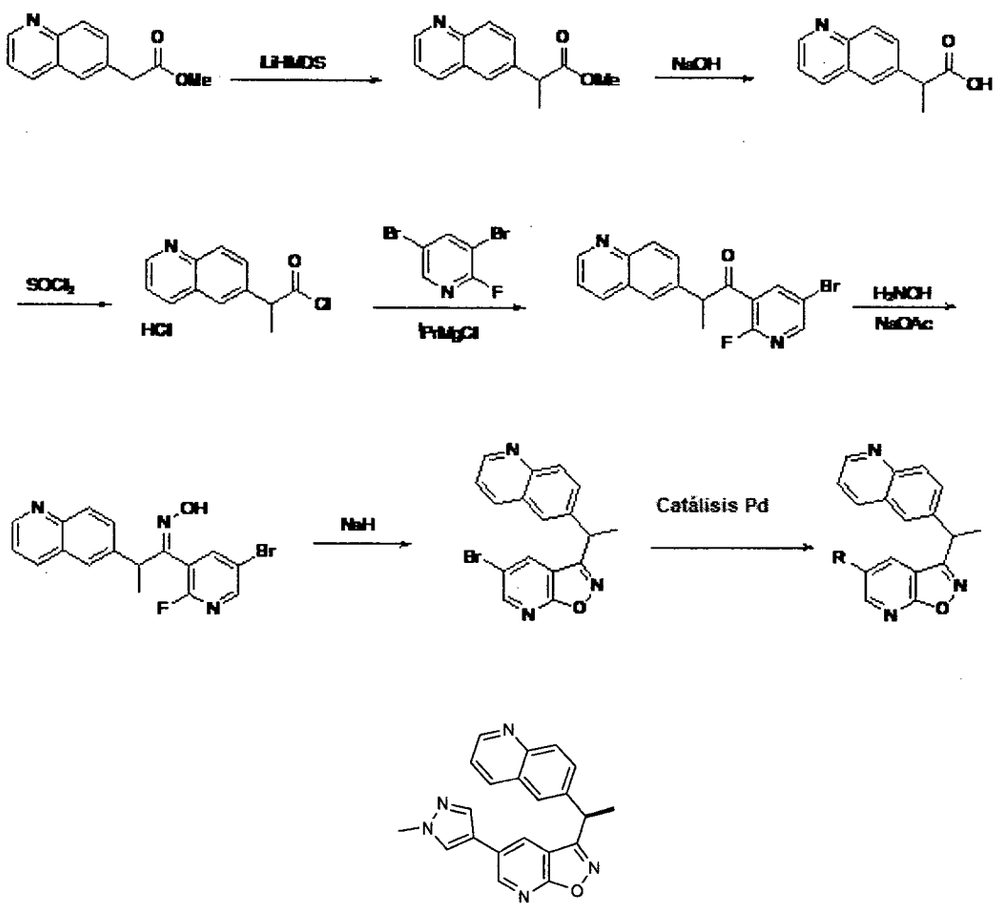
3) Oxima 1–(6–cloro–3–fluorpiridin–2–il)–2,2–difluor–2–(quinolin–6–il)etanona. A un recipiente de presión se agregó 1–(6–cloro–3–fluorpiridin–2–il)–2,2–difluor–2–(quinolin–6–il)etanona (1.0 g, 3.0 mmol), acetato de sodio (3.7 g, 45 mmol) y clorhidrato de hidroxilamina (2.1 g, 30 mmol) en ácido acético (15 mL). El recipiente se selló y la suspensión se agitó a 100 °C durante 20 minutos. A continuación de la concentración y trituración con agua, se recogió un precipitado blanco a través de filtración. La purificación del sólido mediante MPLC (eluido con 0–10% de metanol en diclorometano) proporcionó el producto en forma de un sólido blanco (0.85 g, 82%) EM m/z = 352.0 $[M+1]^+$.

4) 6–((5–cloroisoxazolo[4,5–b]piridin–3–il)difluormetil)quinolina. A un recipiente de presión se agregó oxima 1–(6–cloro–3–fluorpiridin–2–il)–2,2–difluor–2–(quinolin–6–il)etanona (0.050 g, 0.14 mmol) y carbonato de cesio (0.14 g, 0.43 mmol) en DMF anhidro (1 mL). Después de

agitar a 80 °C durante 30 minutos, la solución se diluyó con acetato de etilo y se lavó con agua. Se secaron los extractos orgánicos sobre sulfato de magnesio y se purificaron mediante MPLC (eluido con un gradiente de 10 a 50% de acetato de etilo en hexanos) para proporcionar el producto en forma de un sólido blanco (35 mg, 74%) EM m/z = 332.2 $[M+1]^+$. Calc. para C16H8ClF2N3O: 331.7.

5) 6–(difluor(5–(1–metil–1H–pirazol–4–il)isoxazolo[4,5–b]piridin–3–il)metil)quinolina. A un recipiente de presión se agregó 6–((5–cloroisoxazolo[4,5–b]piridin–3–il)difluormetil)quinolina) (0.10 g, 0.30 mmol), aducto $PdCl_2(dppf)–CH_2Cl_2$ (0.012 g, 0.015 mmol), carbonato de cesio (0.29 g, 0.90 mmol) y 1–metil–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol (0.094 g, 0.45 mmol) en DMF (2 mL) y agua (0.5 mL). El recipiente se purgó con argón, se selló y se agitó a 80 °C durante 40 minutos. La mezcla se diluyó con acetato de etilo y se lavó con agua, los extractos orgánicos se secaron sobre sulfato de magnesio. La purificación mediante MPLC (eluida con un gradiente de 0 a 10% de metanol en diclorometano) proporcionó el producto en forma de un sólido amarillo claro (45 mg, 40%). EM m/z = 378.2 $[M+1]^+$ Calc. para $C_{20}H_{13}F_2N_5O$: 377.3.

Método General H



000339

Ejemplo 441

6-((R)-1-(5-(1-metil-1H-pirazol-4-il)isoxazolo[5,4-b]piridin-3-il)etil)quinolina

1) 2-(quinolin-6-il)propanoato de metilo. A una solución de 2-(quinolin-6-il)acetato de metilo (7.0 g, 35 mmol) en THF anhidro (70 mL) se agregó bis(trimetilsilil)amida de litio (1.0 M en THF, 35 mL, 35 mmol) y una solución de yoduro de metilo (2.2 mL, 35 mmol) en THF anhidro (1mL) a -78 °C. Se removió el hielo seco en un baño de acetona y la mezcla se agitó durante 35 minutos, luego se apagó con cloruro de amonio saturado (30 mL), se diluyó con acetato de etilo y se lavó con bicarbonato de sodio saturado. Los extractos orgánicos se secaron sobre sulfato de magnesio y se purificaron a través de MPLC (eluido con un gradiente de 10 a 30% de acetato de etilo en hexanos) para proporcionar el producto en forma de un aceite amarillo claro (6.5 g, 87%).

2) Acido 2-(quinolin-6-il)propanoico. A una solución de 2-(quinolin-6-il)propanoato de metilo (1.4 g, 6.5 mmol) en metanol (7 mL) y agua (1.5 mL) se agregó hidróxido de sodio (6 N, 2.7 mL, 16 mmol) y la solución se agitó a 50 °C durante una hora. La solución se concentró, se llevó a pH 4 con HCl 2.0N y el producto se aisló a través de filtración en forma de un sólido blanco (0.94 g, 72%).

3) Clorhidrato de cloruro de 2-(quinolin-6-il)propanoilo. A una suspensión de ácido 2-(quinolin-6-il)propanoico (0.73 g, 3.6 mmol) en diclorometano anhidro (15 mL) se agregó cloruro de tionilo (1.3 mL, 18 mmol) y la solución se agitó a temperatura ambiente durante 10 minutos. La solución se concentró para proporcionar el producto en forma de un sólido naranja.

4) 1-(5-bromo-2-fluorpiridin-3-il)-2-(quinolin-6-il)propan-1-ona. A una solución de 3,5-dibromo-2-fluorpiridina (2.4 g, 9.3 mmol) en THF anhidro (10 mL) se agregó cloruro de isopropilmagnesio (2.0 M en THF, 4.7 mL, 9.3 mmol) y se agitó a temperatura ambiente durante 10 minutos. La solución se agregó a través de una cánula a una solución de clorhidrato de cloruro de 2-(quinolin-6-il)propanoilo (0.79 g, 3.1 mmol) en THF anhidro (10 mL) a -78 °C y la mezcla de reacción combinada se dejó enjuagar a -40 °C durante una hora. La mezcla se agitó a -40 °C durante 90 minutos adicionales, luego se apagó con bicarbonato de sodio saturado y se extrajo con acetato de etilo. Los extractos orgánicos se secaron sobre sulfato de magnesio y se purificaron a través de MPLC (eluido con un gradiente de 10-80% de acetato de etilo en hexanos) para proporcionar el producto en forma de un aceite amarillo (0.60 g, 54%).

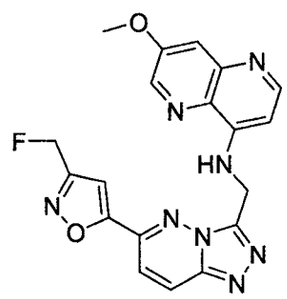
5) Oxima 1-(5-bromo-2-fluorpiridin-3-il)-2-(quinolin-6-il)propan-1-ona. A un recipiente de presión se agregó acetato de sodio (2.0 g, 24 mmol), clorhidrato de hidroxilamina (1.1 g, 16 mmol) y 1-(5-bromo-2-fluorpiridin-3-il)-2-(quinolin-6-il)propan-1-

000540

ona (0.58 g, 1.6 mmol) en ácido acético (10 mL). El recipiente se selló y se agitó a 100 °C durante una hora, luego se concentró, se diluyó con acetato de etilo y se lavó con agua. Los extractos orgánicos se concentraron y purificaron mediante MPLC (eluido con 0–10% de metanol en diclorometano) para proporcionar el producto en forma de un aceite de color castaño (0.50 g, 83%).

6) 6–(1–(5–bromoisoxazol[5,4–b]piridin–3–il)etil)quinolina. A una solución de oxima 1–(5–bromo–2–fluorpiridin–3–il)–2–(quinolin–6–il)propan–1–ona (0.58 g, 1.6 mmol) en THF (15 mL) se agregó hidruro de sodio (60% en aceite mineral, 0.093, 2.3 mmol) a 0 °C. La solución se agitó a 0 °C durante 10 minutos, luego se diluyó con acetato de etilo y se lavó con agua. Los extractos orgánicos se concentraron y purificaron mediante MPLC (eluido con un gradiente de 10 a 50% de acetato de etilo en hexanos) para proporcionar el producto en forma de un aceite incoloro (0.10 g, 19%). EM m/z = 354.0 $[M+1]^+$. Calc. para $C_{17}H_{12}BrN_3O$: 354.2

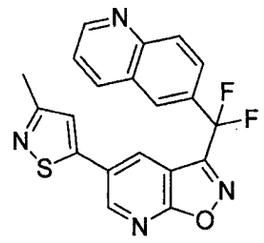
7) 6–((R)–1–(5–(1–metil–1H–pirazol–4–il)isoxazolo[5,4–b]piridin–3–il)etil)quinolina. A un recipiente de presión se agregó 6–(1–(5–bromoisoxazol[5,4–b]piridin–3–il)etil)quinolina (0.09 g, 0.25 mmol), aducto $PdCl_2$(dppf)–CH_2Cl_2 (0.010 g, 0.013 mmol), carbonato de cesio (0.25 g, 0.76 mmol) y 1–metil–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol (0.079 g, 0.38 mmol) en DMF (2.5 mL) y agua (0.5 mL). El recipiente se inundó con argón, se selló y agitó a 90°C durante una hora. La mezcla se concentró, se trituró en agua y se recogió un sólido marrón por filtración. La purificación mediante MPLC (eluida con un gradiente de 10 a 50% de acetato de etilo) proporcionó una mezcla racémica del producto. El enantiómero deseado (>99% ee) se obtuvo a través de SFC. EM m/z = 356.2 $[M+1]^+$ Calc. para $C_{21}H_{17}N_5O$: 355.4



Ejemplo 442

N–((6–(3–(fluormetil)isoxazol–5–il)–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)–7–metoxi–1,5–naftiridin–4–amina: A una suspensión de (5–(3–((7–metoxi–1,5–naftiridin–4–ilamino)metil)–[1,2,4]triazol[4,3–b]piridazin–6–il)isoxazol–3–il)metanol (0.080 g, 0.20 mmol) en diclorometano anhidro (3 mL) se agregó deoxofluor (0.10 mL, 0.060 mmol) bajo argón a 0 °C. La solución se llevó a temperatura ambiente durante una hora y se agitó tres horas adicionales. La reacción se apagó con bicarbonato de sodio saturado y se agitó durante 15

minutos; se recogió una goma marrón mediante filtración. La purificación mediante MPLC (eluida con un gradiente de 0 a 10% de metanol en diclorometano) proporcionó el producto en forma de un sólido blancuzco (9.0 mg, 11%). EM m/z = 407.2 $[M+1]^+$. Calc. para $C_{19}H_{15}FN_8O_2$: 406.4



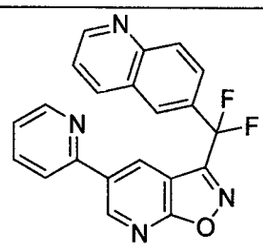
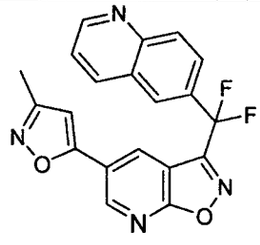
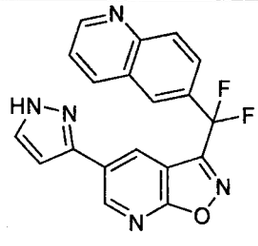
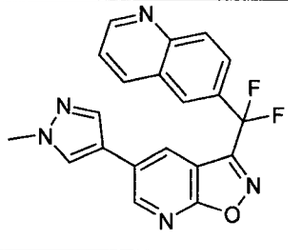
Ejemplo 443

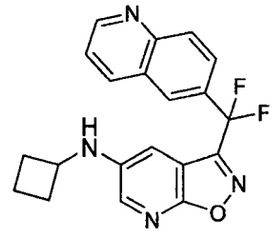
6–(difluor(5–(3–metilisotiazol–5–il)isoxazolo[5,4–b]piridin–3–il)metil)quinolina

A un recipiente de presión se agregó 2–(diciclohexilfosfino)bifenilo (9.3 mg, 0.013 mmol), 6–((5–bromoisoxazolo[5,4–b]piridin–3–il)difluormetil)quinolina (0.10 g, 0.27 mmol), 3–metil–5–(trimetilestanilo)isotiazol (0.14g, 0.53 mmol) y $Pd_2(dba)_3$ (12 mg, 0.013 mmol) en DMF anhidro (5 mL). El recipiente se purgó con argón, se selló y se agitó a 80 °C durante 90 minutos. La mezcla se concentró y purificó mediante MPLC (eluida con un gradiente de 10 a 50% de acetato de etilo en hexanos) para proporcionar el producto en forma de un sólido amarillo claro. EM m/z = 395.0 $[M+1]^+$ Calc. para $C_{20}H_{12}F_2N_4OS$: 394.4.

Los siguientes ejemplos de compuestos 444–448 se prepararon usando un método similar a 6–(difluor(5–(3–metilisotiazol–5–il)isoxazolo[5,4–b]piridin–3–il)metil)quinolina:

000342

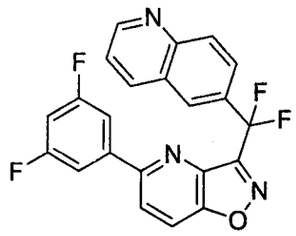
Ej	Estructura	MW	Masa Hallada
444		374	375
445		380	381
446		378	379
447		363	364
448		377	378



Ejemplo 449

N–ciclobutil–3–(difluor(quinolin–6–il)metil)isoxazolo[5,4–b]piridin–5–amina

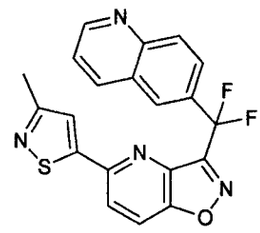
A un recipiente de presión se agregó ter–butóxido de sodio (38 mg, 0.40 mmol), xantfos (0.12 g, 0.20 mmol), $Pd_2(dba)_3$ (61 mg, 0.066 mmol), 6–((5–bromoisoxazol[5,4–b]piridin–3–il)difluormetil)quinolina (0.10 g, 0.27 mmol), y ciclobutanamina (0.025 mL, 0.29 mmol) en tolueno (3 mL). La mezcla se agitó a 80 °C durante dos horas, luego se diluyó con diclorometano y se filtró a través de celite. La purificación del filtrado mediante MPLC (eluido con un gradiente de 10 a 50% de acetato de etilo en hexanos) proporcionó el producto en forma de un aceite amarillo (5.1 mg, 5%). EM m/z = 367.0 $[M+1]^+$ Calc. para $C_{20}H_{16}F_2N_4O$: 366.4



Ejemplo 450

6–((5–(3,5–difluorfenil)isoxazolo[5,4–b]piridin–3–il)difluormetil)quinolina

A un recipiente de presión se agregó carbonato de cesio (0.61 g, 1.9 mmol), aducto $PdCl_2(dppf)–CH_2Cl_2$ (26 mg, 0.031 mmol), oxima 1–(6–cloro–3–fluorpiridin–2–il)–2,2–difluor–2–(quinolin–6–il)etanona (0.26 g, 0.63 mmol) y ácido 3,5–difluorfenilborónico (0.15 g, 0.94 mmol) en DMF anhidro (5 mL) y agua (1mL). La mezcla se inundó con argón, se selló y agitó a 80 °C durante una hora. La suspensión se concentró, se trituró con agua y se filtró para proporcionar un sólido de color castaño, la purificación mediante MPLC (eluida con un gradiente de 20 a 50% de acetato de etilo en hexanos) proporcionó el producto en forma de un sólido blanco (23 mg, 9%). EM m/z = 410.0 $[M+1]^+$ Calc. para $C_{22}H_{11}F_4N_3O$: 409.3.



Ejemplo 451

6–(difluor(5–(3–metilisotiazol–5–il)isoxazolo[4,5–b]piridin–3–il)metil)quinolina

A una solución de 5–bromo–3–metilisotiazol (0.19 g, 1.1 mmol) en THF anhidro (3 mL) se agregó cloruro de litio de isopropilmagnesio (1.0 M en THF, 1.5 mL, 1.5 mmol) a –40 °C. La mezcla se agitó a–40 °C durante veinte minutos seguido de adición de cloruro de zinc (0.5 M en THF, 3.1 mL, 1.6 mmol). La mezcla se llevó a temperatura ambiente y se agitó durante 30 minutos seguido de adición de Q–Phos (0.12 g, 0.17 mmol), $Pd_2(dba)_3$ (0.097 g, 0.110 mmol), 6–((5–cloroisoxazol[4,5–b]piridin–3–il)difluormetil)quinolina (0.10 g, 0.30 mmol), y dimetilacetamida anhidra (3.5 mL). La mezcla se agitó a 50 °C durante 90 minutos luego

000344

se diluyó con acetato de etilo y se lavó con agua. Los extractos orgánicos se secaron sobre sulfato de magnesio y se purificaron mediante MPLC (eluido con un gradiente de 10 a 50% de acetato de etilo en hexanos), luego se purificó mediante HPLC (eluido con un gradiente de 15 a 90% de acetonitrilo en agua) para proporcionar el producto en forma de un sólido blanco (4.2 mg, 3%). EM m/z = 395.2 $[M+1]^+$ Calc. para $C_{23}H_{15}F_2N_3O$: 394.4.

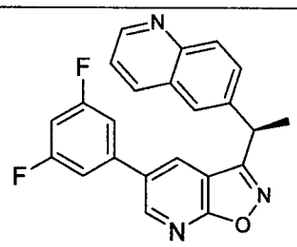
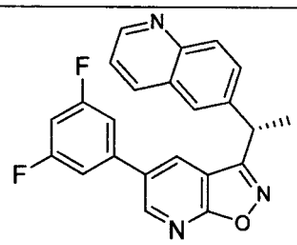


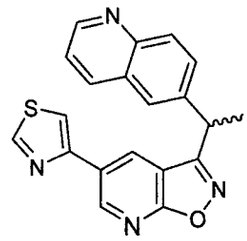
Ejemplo 452

3–(difluor(quinolin–6–il)metil)–N,N–dimetilisoxazolo[4,5–b]piridin–5–amina

A un frasco para microondas se agregó dimetilamina (2.0 M en THF, 0.75 mL, 1.5 mmol) y 6–((5–cloroisoxazol[4,5–b]piridin–3–il)difluormetil)quinolina (0.10 g, 0.30 mmol) en etanol (3 mL). La mezcla se agitó a 140° bajo irradiación microondas durante dos horas y luego se concentró y purificó mediante MPLC (eluido con un gradiente de 10 a 50% de acetato de etilo en hexanos) para proporcionar el producto en forma de un sólido amarillo claro (87 mg, 85%). EM m/z = 341.2 $[M+1]^+$ Calc. para $C_{18}H_{14}F_2N_4O$: 340.3.

000345

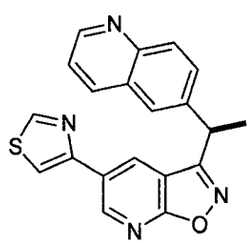
Ej	Estructura	MW	Masa Hallada	Método
453		387	388	H
454		387	388	H



Ejemplo 455

6–(1–(5–(tiazol–4–il)isoxazol[5,4–b]piridin–3–il)etil)quinolina

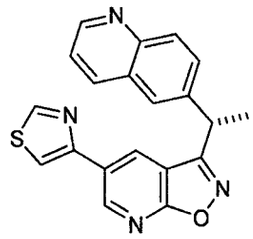
A un recipiente a presión, se agregó 2–(diciclohexilfosfin)bifenilo (12 mg, 0.42 mmol), 6–(1–(5–bromoisoxazol[5,4–b]piridin–3–il)etil)quinolina (0.10 g, 0.28 mmol), y 4–(tributiletanilo)tiazol (0.16 g, 0.42 mmol) en DMF anhidro (3 mL). El frasco se inundó con argón, se selló y se agitó a 90 °C durante dos horas. La mezcla se concentró y se purificó mediante MPLC (eluido con un gradiente de 0 a 10% de metanol en diclorometano) para proporcionar el producto en forma de un sólido blancuzco. EM m/z = 359.0 $[M+1]^+$ Calc. para $C_{20}H_{14}N_4OS$: 358.4.



Ejemplo 456

6–((R)–1–(5–(tiazol–4–il)isoxazol[5,4–b]piridin–3–il)etil)quinolina

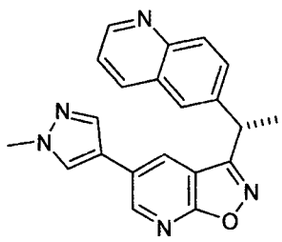
A un recipiente de presión se agregó 2–(diciclohexilfosfin)bifenilo (12 mg, 0.42 mmol), 6–(1–(5–bromoisoxazol[5,4–b]piridin–3–il)etil)quinolina (0.10 g, 0.28 mmol), 4–(tributilestanilo)tiazol (0.16 g, 0.42 mmol) en DMF anhidro (3 mL). El frasco se inundó con argón, se selló y agitó a 90 °C durante dos horas. La mezcla se concentró y purificó mediante MPLC (eluido con un gradiente de 0 a 10% de metanol en diclorometano) para proporcionar el producto racémico en forma de un sólido blancuzco. Se obtuvo el enantiómero deseado (>99% ee) a través de SFC. EM m/z = 359.0 $[M+1]^+$ Calc. para $C_{20}H_{14}N_4OS$: 358.4



Ejemplo 457

6–((S)–1–(5–(tiazol–4–il)isoxazolo[5,4–b]piridin–3–il)etil)quinolina

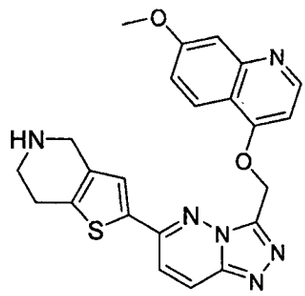
Preparado mediante un método similar a 6–((R)–1–(5–(tiazol–4–il)isoxazolo[5,4–b]piridin–3–il)etil)quinolina. EM m/z = 359.0 $[M+1]^+$ Calc. para $C_{20}H_{14}N_4OS$: 358.4.



Ejemplo 458

6–((S)–1–(5–(1–metil–1H–pirazol–4–il)isoxazol[5,4–b]piridin–3–il)etil)quinolina

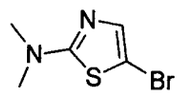
Preparado mediante un método similar a 6–((R)–1–(5–(1–metil–1H–pirazol–4–il)isoxazol[5,4–b]piridin–3–il)etil)quinolina. EM m/z = 356.2 $[M+1]^+$ Calc. para $C_{21}H_{17}N_5O$: 355.4



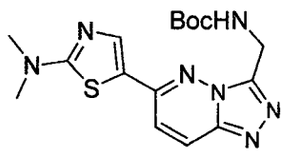
Ejemplo 459

7–metoxi–4–((6–(4,5,6,7–tetrahidrotieno[3,2–c]piridin–2–il)–[1,2,4]triazol[4,3–b]piridazin–3–il)metoxi)quinolina

A una solución de 2–(3–((7–metoxiquinolin–4–iloxi)metil)–[1,2,4]triazol[4,3–b]piridazin–6–il)–6,7–dihidrotieno[3,2–c]piridin–5(4H)–carboxilato de ter–butilo (0.27 g, 0.50 mmol) (preparado de acuerdo con el Método General A) se agregó ácido trifluoracético (0.77 mL, 10 mmol). La mezcla se agitó a temperaratura ambiente durante 90 minutos, luego se concentró, se extrajo en amoníaco en metanol 2,0M y se purificó mediante MPLC (eluido con un gradiente de 0 a 10% de metanol en diclorometano) para proporcionar el producto en forma de un sólido rosa. EM m/z = 445.0 $[M+1]^+$ Calc. para $C_{23}H_{20}N_6O_2S$: 444.51.



5–bromo–N,N–dimetiltiazol–2–amina : A un frasco para microondas se agregó N–etil–N–isopropilpropan–2–amina (0.72 mL, 4.1 mmol), 2,5–dibromotiazol (1.00 g, 4.1 mmol) y dimetilamina (40% en agua, 0.52 mL, 4.1 mmol) en etanol (10 mL). El frasco se selló y se agitó a 140 °C bajo irradiación microondas durante una hora, luego se concentró y purificó mediante MPLC (eluido con un gradiente de 0–50% de acetato de etilo en hexanos) para proporcionar el producto en forma de un sólido blanco, cristalino (0.25 g, 29%).



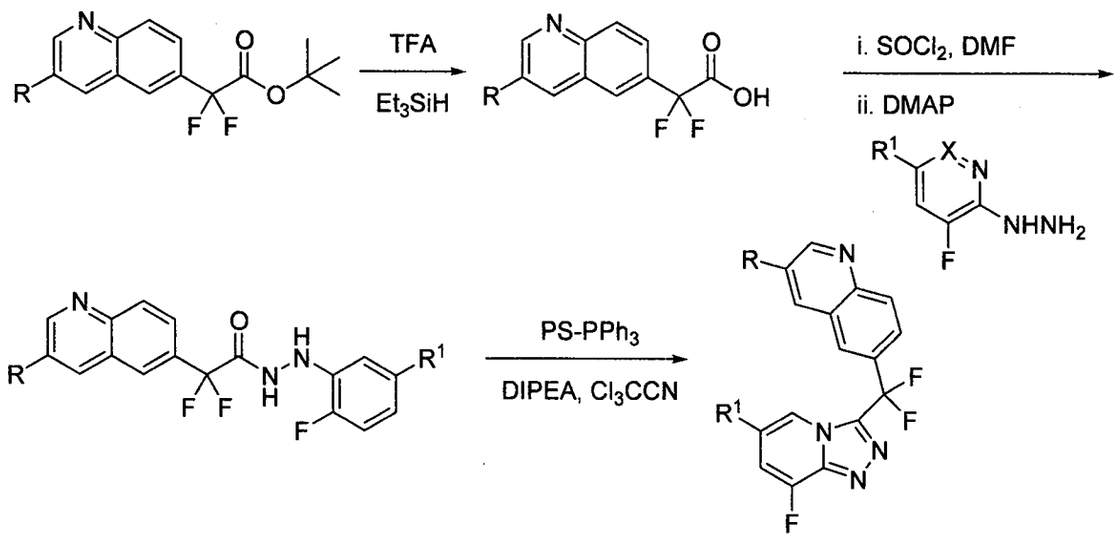
(6–(2–(dimetilamino)tiazol–5–il)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo: A una solución de 5–bromo–N,N–dimetiltiazol–2–amina (0.73 g, 3.53 mmol) en THF

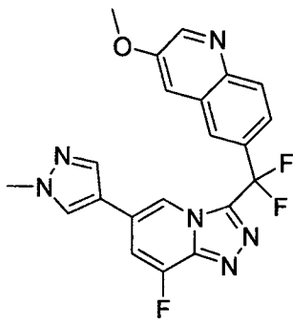
000348

anhidro (9 mL) se agregó cloruro de isopropilmagnesio (1.0 M en THF, 4.8 mL, 4.8 mmol) a –40 °C. La solución se agitó durante veinte minutos seguido de adición por goteo de cloruro de zinc (0,5 M en THF, 10 mL, 5.2 mmol). La mezcla se llevó a temperatura ambiente y se agitó durante treinta minutos seguido de adición de dimetilacetamida (12 mL), $Pd_2(dba)_3$, (0.32 g, 0.35 mmol), Q–Phos (0.34 g, 0.56 mmol), y (6–cloro–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo (0.29 g, 1.0 mmol). La mezcla se agitó a 50° durante dos horas luego se apagó con cloruro de amonio saturado y se purificó mediante cromatografía MPLC (eluido con un gradiente de 0 a 10% (1:10:90 NH_4OH:MeOH:DCM) en DCM) para proporcionar el producto en forma de un sólido naranja claro (0.27 g, 71%).

000349

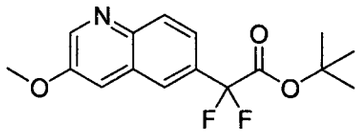
Método General I



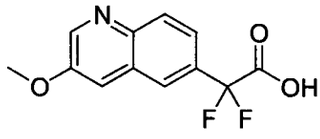


Ejemplo 460

6–(difluor(8–fluor–6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metil)–3–metoxiquinolina



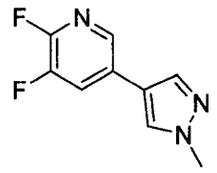
1) 2,2–difluor–2–(3–metoxiquinolin–6–il)acetato de ter–butilo. Se preparó el compuesto del título a partir de 2–(3–metoxiquinolin–6–il)acetato de ter–butilo de manera similar al procedimiento detallado para la síntesis de 2,2–difluor–2–(quinolin–6–il)acetato de metilo.



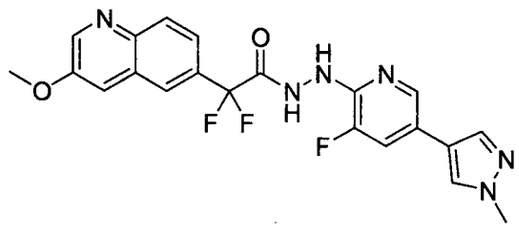
2) Acido 2,2–difluor–2–(3–metoxiquinolin–6–il)acético. Un frasco de fondo redondo de 200 mL se cargó con 2,2–difluor–2–(3–metoxiquinolin–6–il)acetato de ter–butilo (5.06 g, 16 mmol) luego con CH_2Cl_2, luego con ácido trifluoracético (16 ml, 213 mmol) seguido de

000350

trietilsilano (6.5 ml, 41 mmol). La solución se mantuvo a temperatura ambiente durante 24 h hasta que la LCMS mostró la desaparición del material de partida. La solución se concentró y se sometió a alto vacío durante 40 h para proporcionar 4.1 g (99% de rendimiento) de ácido 2,2–difluor–2–(3–metoxiquinolin–6–il)acético en forma de un sólido marrón. El material tenía la suficiente pureza para ser usado en las etapas siguientes.



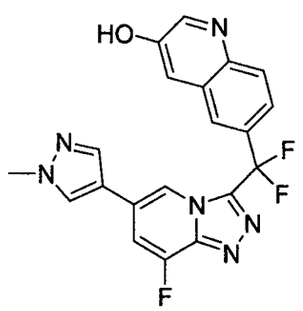
3) 2,3–difluor–5–(1–metil–1H–pirazol–4–il)piridina. Un frasco sellable se cargó con 5–cloro–2,3–difluorpiridina (1.541 g, 10.3 mmol), acetato de paladio (ii) (0.116 g, 0.515 mmol), fosfato de potasio tribásico (6.56 g, 30.9 mmol), 1–metil–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol (2.57 g, 12.4 mmol), y X–Phos (0.491 g, 1.03 mmol). El frasco se selló con una tapa de septo, luego se agregaron dioxano (20 mL) y H2O (2 mL). La mezcla resultante se roció con N_2 durante 10 min, y luego se calentó a 100 °C durante 2 h. La solución se enfrió a temperatura ambiente y luego se concentró y purificó mediante cromatografía evaporativa usando un gradiente de eluyente 99:1 Hexanos: EtOAc a 60:40 Hexanos : EtOAc para proporcionar 2,3–difluor–5–(1–metil–1H–pirazol–4–il)piridina (1.78 g, 88.5% de rendimiento) en forma de una película incolora. LRMS (ESI) *m/z* calc. para $C_9H_7F_2N_3$ (M+H) 197.1, Hallado 197.4.



4) 2,2–difluor–N'–(2–fluor–5–(1–metil–1H–pirazol–4–il)fenil)–2–(3–metoxiquinolin–6–il)acetohidrazida. Un frasco de fondo redondo se cargó con ácido 2,2–difluor–2–(3–metoxiquinolin–6–il)acético (389 mg, 1536 µmol) y DMF (8 mL). La solución se enfrió a 0 C, se agregó cloruro de tionilo (224 µl, 3073 µmol), y la solución resultante se mantuvo 1 h a 0 °C. Luego se agregó trietilamina (641 µl, 4609 µmol) a través de una jeringa, seguido de 1–(3–fluor–5–(1–metil–1H–pirazol–4–il)piridin–2–il)hidrazina (382 mg, 1844 µmol) y 4–(dimetilamino)piridina (18.8 mg, 154 µmol); ambos agregados como sólidos. La solución hetereogénea se agitó a 0 °C durante 1 h, luego se dejó calentar a temperatura ambiente y se agitó durante 18 h. La mezcla se apagó con $NaHCO_3$ acuoso saturado (50 mL) y la mezcla resultante se extrajo con CH_2Cl_2 (3x50 mL). Las capas orgánicas combinadas se concentraron (calentamiento a 50 °C) y el residuo se purificó mediante sistema de solvente de cromatografía SiO_2: CH_2Cl_2:MeOH 99%:1% gradiente 90:10 CH_2Cl_2 para proporcionar

2,2–difluor–N'–(3–fluor–5–(1–metil–1H–pirazol–4–il)piridin–2–il)–2–(3–metoxiquinolin–6–il)acetohidrazida (225 mg, 33.1% de rendimiento) en forma de un sólido amorfo marrón.

5) 6–(difluor(8–fluor–6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metil)–3–metoxiquinolina. Un frasco para microondas sellable se cargó con 2,2–difluor–N'–(3–fluor–5–(1–metil–1H–pirazol–4–il)piridin–2–il)–2–(3–metoxiquinolin–6–il)acetohidrazida (225 mg, 509 µmol) y polímero de trifenilfosfina sostenido (2.3 mmol/g, 221 mg, 509 µmol). El frasco se selló y se agregó dicloroetano (4 mL) seguido de diisopropiletilamina (89 µl, 509 µmol) y 2,2,2–tricloroacetonitrilo (127 µl, 1271 µmol). La mezcla resultante se irradió en un horno microondas (Iniciador de Biotage) a 150 °C durante 40 min. La mezcla de reacción se filtró y la torta de filtración se lavó con CH_2Cl_2 (15 mL) y MeOH (10 mL). El filtrado se concentró al vacío y el residuo crudo resultante se purificó mediante MPLC usando 100% de CH_2Cl_2 a 98:2 CH_2Cl_2 : MeOH para proporcionar 6–(difluor(8–fluor–6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metil)–3–metoxiquinolina (94 mg, 44% de rendimiento) en forma de un sólido amorfo. LRMS (ESI) *m/z* calc. para $C_{21}H_{16}F_3N_6O$ (M+H) 425.1, Hallado 425.4.

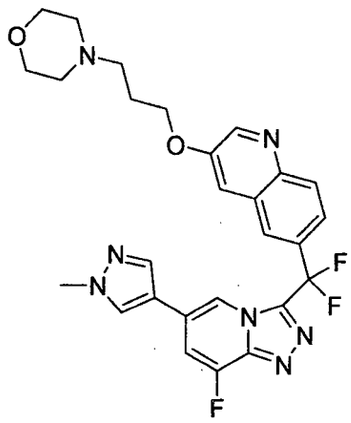


Ejemplo 461

6–(difluor(8–fluor–6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metil)quinolin–3–ol.

A un frasco cargado con 3–(benciloxi)–6–(difluor(8–fluor–6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metil)quinolina (10 mg, 20 µmol) se agregó ácido trifluoracético (1.5 mL, 20 mmol). La solución resultante se calentó a 65 °C durante 18 h. La solución se concentró para purificación con MPLC usando un gradiente 98:2 CH_2Cl_2 : MeOH a 90:10 CH_2Cl_2 : MeOH para proporcionar 6–(difluor(8–fluor–6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metil)quinolin–3–ol (3.6 mg, 44% de rendimiento) en forma de un sólido incoloro. LRMS (ESI) *m/z* calc. para $C_{20}H_{14}F_3N_6O$ (M+H) 411.1, Hallado 411.3.

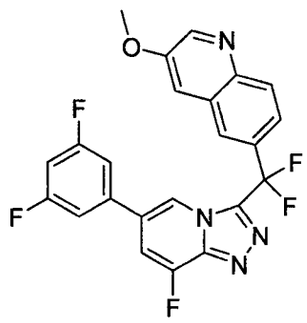
000352



Ejemplo 462

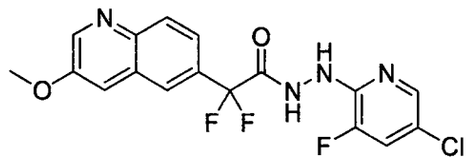
6–(difluor(8–fluor–6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metil)–3–(3–morfolinpropoxi)quinolina.

A un frasco cargado con 6–(difluor(8–fluor–6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metil)quinolin–3–ol (17.3 mg, 42 µmol), se agregó trifenilfosfina (55 mg, 211 µmol), THF (1 mL), y 4–(3–hidroxipropil)–morfolina, 95% (31 µl, 211 µmol). La mezcla se colocó bajo N_2 y se enfrió a 0 °C. Se agregó azodicarboxilato de ter–butilo (49 mg, 211 µmol) en forma de un sólido en una sola porción y la solución se dejó calentar a temperatura ambiente y se mantuvo durante 48 h. La solución se concentró para purificación con MPLC (Teledine Isco combiFlash Companion). El residuo crudo se extrajo en un mínimo de CH_2Cl_2 y se absorbió en un cartucho de carga de 5 g y se pasó a través de una columna de gel de sílice pre–empaquetada Redi–Sep® (40 g) usando un gradiente 99:1 CH_2Cl_2 : MeOH a 90:10 CH_2Cl_2 : MeOH para proporcionar 6–(difluor(8–fluor–6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metil)–3–(3–morfolinpropoxi)quinolina (7.5 mg, 33% de rendimiento) en forma de un sólido incoloro; . LRMS (ESI) *m/z* calc. para $C_{27}H_{27}F_3N_7O_2$ (M+H) 538.2, Hallado 538.2.

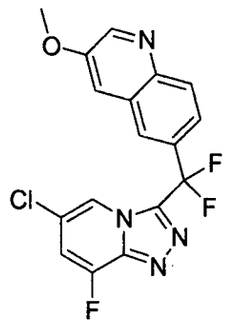


Ejemplo 463

6–((6–(3,5–difluorfenil)–8–fluor–[1,2,4]triazol[4,3–a]piridin–3–il)difluormetil)–3–metoxiquinolina

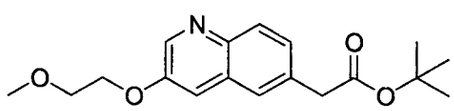


a) N'–(5–cloro–3–fluorpiridin–2–il)–2,2–difluor–2–(3–metoxiquinolin–6–il)acetohidrazida. Este compuesto se preparó a partir de ácido 2,2–difluor–2–(3–metoxiquinolin–6–il)acético y 1–(5–cloro–3–fluorpiridin–2–il)hidrazina de acuerdo con el Método General I. LRMS (ESI) *m/z* calc. para $C_{17}H_{13}ClF_3N_4O_2S$ (M+H) 397.1, Hallado 397.2.



b) 6–((6–cloro–8–fluor–[1,2,4]triazol[4,3–a]piridin–3–il)difluormetil)–3–metoxiquinolina. Este compuesto se preparó a partir de N'–(5–cloro–3–fluorpiridin–2–il)–2,2–difluor–2–(3–metoxiquinolin–6–il)acetohidrazida de acuerdo con el Método General I. LRMS (ESI) *m/z* calc. para $C_{17}H_{11}ClF_3N_4O$ (M+H) 379.1, Hallado 379.2.

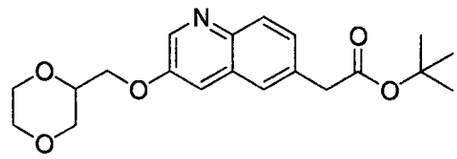
c) 6–((6–(3,5–difluorfenil)–8–fluor–[1,2,4]triazol[4,3–a]piridin–3–il)difluormetil)–3–metoxiquinolina. Un frasco sellable para microondas se cargó con 6–((6–cloro–8–fluor–[1,2,4]triazol[4,3–a]piridin–3–il)difluormetil)–3–metoxiquinolina (342.05mg, 903 µmol), acetato de paladio (II) (30 mg, 135 µmol), fosfato de potasio (575 mg, 2709 µmol), ácido 3,5–difluorfenilborónico (285 mg, 1806 µmol), y X–Phos (129 mg, 271 µmol). El tubo se selló, y se inundó con N_2. Se agregaron dioxano (9 mL), luego H_2O (1 mL) y la mezcla se roció con N_2 durante 10 min, luego se calentó a 100 °C durante 24 h. La mezcla se enfrió a temperatura ambiente y se concentró y se absorbió en un cartucho de carga de 5 g para purificación MPLC usando un gradiente 98:2 CH_2Cl_2 : MeOH a 90:10 CH_2Cl_2 : MeOH para proporcionar 6–((6–(3,5–difluorfenil)–8–fluor–[1,2,4]triazol[4,3–a]piridin–3–il)difluormetil)–3–metoxiquinolina (72 mg, 17% de rendimiento). LRMS (ESI) *m/z* calc. para $C_{23}H_{14}F_5N_4O$ (M+H) 457.1, Hallado 457.0.



2–(3–(2–metoxietoxi)quinolin–6–il)acetato de ter–butilo.

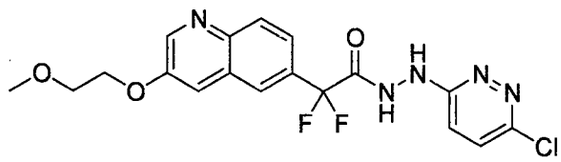
Un frasco se cargó con 2–(3–hidroxiquinolin–6–il)acetato de ter–butilo (581.04 mg, 2.241 mmol) y trifenilfosfina (1.175 g, 4.482 mmol) luego se selló con un septo y se colocó

bajo N_2. Se agregó benceno (10 mL), seguido de 2–metoxietanol (0.8838 ml, 11.20 mmol). La solución hetereogénea se enfrió a 0 °C, y se agregó azodicarboxilato de di–ter–butilo (1.032 g, 4.482 mmol) en forma de un sólido en una sola porción. La solución se dejó calentar a temperatura ambiente y se mantuvo 20 h. La solución se dividió luego entre NH_4Cl, acuoso saturado, y las capas se separaron. La capa acuosa se extrajo con EtOAc (2x50 mL), y las capas orgánicas combinadas se lavaron con salmuera, se secaron (MgSO4), y se concentraron *al vacío*. El residuo resultante se purificó mediante MPLC (Teledine Isco combiFlash Companion), 80 g SiO_2, sistema de solvente: gradiente 90:10 hexanos:EtOAc a 50:50 hexanos:EtOAc para proporcionar 2–(3–(2–metoxietoxi)quinolin–6–il)acetato de ter–butilo (585. 2 mg, 82% de rendimiento). LRMS (ESI) *m/z* calc. para $C_{18}H_{24}NO_4$ (M+H) 318.2, Hallado 318.3.



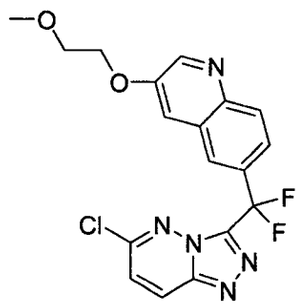
2–(3–((1,4–dioxan–2–il)metoxi)quinolin–6–il)acetato de ter–butilo (racemato).

El compuesto del título se preparó a partir de 2–(3–hidroxiquinolin–6–il)acetato de ter–butilo y (1,4–dioxan–2–il)metanol de acuerdo con el procedimiento descrito para 2–(3–(2–metoxietoxi)quinolin–6–il)acetato de ter–butilo.



N'–(6–cloropiridazin–3–il)–2,2–difluor–2–(3–(2–metoxietoxi)quinolin–6–il)acetohidrazida.

El compuesto del título se preparó a partir de 1–(6–cloropiridazin–3–il)hidrazina y 2–(3–(2–metoxietoxi)quinolin–6–il)acetato de ter–butilo tal como se describió en el Método General I. LRMS (ESI) *m/z* calc. para $C_{18}H_{17}ClF_2N_5O_3$ (M+H) 424.1, Hallado 424.2.

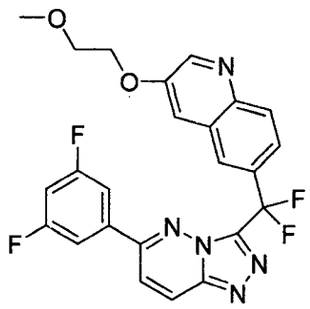


Ejemplo 464

6–((6–cloro–[1,2,4]triazol[4,3–b]piridazin–3–il)difluormetil)–3–(2–metoxietoxi)quinolina.

Un frasco sellable para microondas se cargó con N'–(6–cloropiridazin–3–il)–2,2–difluor–2–(3–(2–metoxietoxi)quinolin–6–il)acetohidrazida (46.98mg, 111 µmol), 1,2–dimetoxietano (1.5 mL), y 1 gota de HCl conc. El frasco se selló y se calentó a 130 °C

durante 40 min. La solución se concentró y se purificó mediante MPLC (Teledine Isco combiFlash Companion). El residuo se extrajo en un mínimo de CH_2Cl_2 y se absorbió en un cartucho de carga de 5 g y se pasó a través de una columna de gel de sílice pre-empaquetada Redi-Sep® (12 g) usando 98:2 CH_2Cl_2 : MeOH a 90:10 CH_2Cl_2 : MeOH para proporcionar 6-((6-cloro-[1,2,4]triazol[4,3-b]piridazin-3-il)difluormetil)-3-(2-metoxietoxi)quinolina (25.3mg, 56.2% de rendimiento) en forma de un sólido incoloro. LRMS (ESI) *m/z* calc. para $C_{18}H_{15}ClF_2N_5O_2$ (M+H) 406.1, Hallado 406.2.

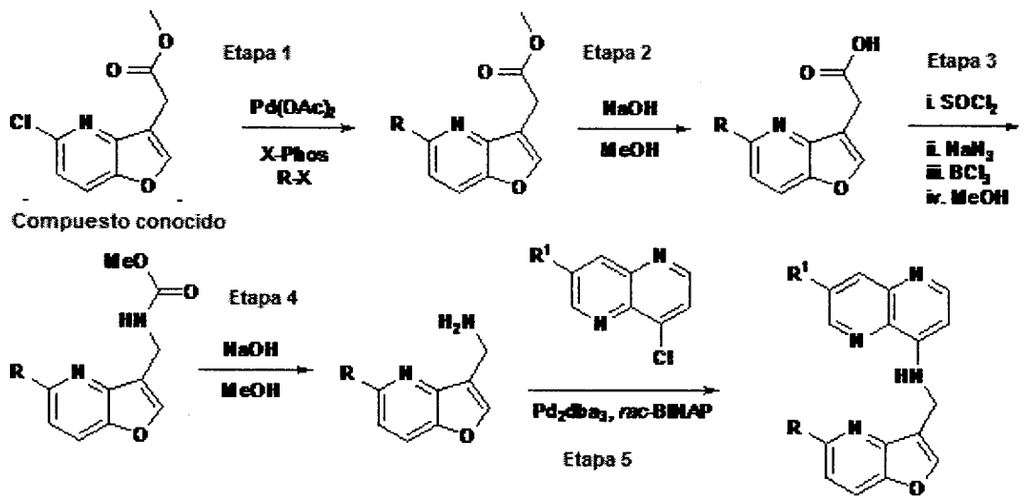


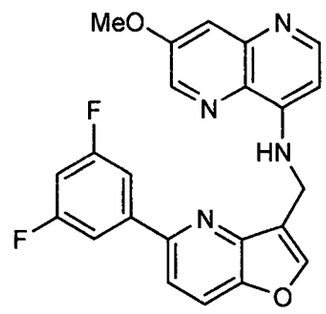
Ejemplo 465

6-((6-(3,5-difluorfenil)-[1,2,4]triazol[4,3-b]piridazin-3-il)difluormetil)-3-(2-metoxietoxi)quinolina.

Se sintetizó el compuesto del título a partir de 6-((6-cloro-[1,2,4]triazol[4,3-b]piridazin-3-il)difluormetil)-3-(2-metoxietoxi)quinolina y ácido 3,5-difluorfenilborónico de manera similar a la descrita para 6-((6-(3,5-difluorfenil)-8-fluor-[1,2,4]triazol[4,3-a]piridin-3-il)difluormetil)-3-metoxiquinolina. LRMS (ESI) *m/z* calc. para $C_{24}H_{18}F_4N_5O_2$ (M+H) 484.1, Hallado 484.2.

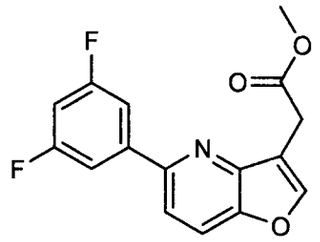
Método General J



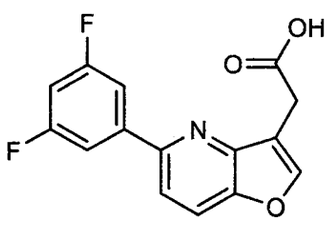


Ejemplo 466

N–((5–(3,5–difluorfenil)furo[3,2–b]piridin–3–il)metil)–7–metoxi–1,5–naftiridin–4–amina .



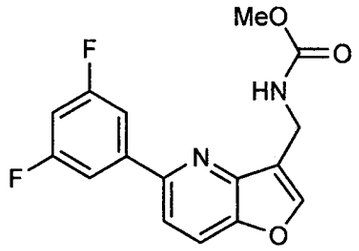
1) 2–(5–(3,5–difluorfenil)furo[3,2–b]piridin–3–il)acetato de metilo. Un frasco sellable para microondas se cargó con 2–(5–clorofuro[3,2–b]piridin–3–il)acetato de metilo (1.30 g, 5.74 mmol), acetato de paladio (II) (0.129 g, 0.574 mmol), fosfato de potasio (3.66 g, 17.2 mmol), ácido 3,5–difluorfenilborónico (1.81 g, 11.5 mmol), y X–Phos (0.548 g, 1.15 mmol). El frasco se selló, se inundó con N_2, luego se agregaron dioxano (20 mL) y H_2O (2 mL). La solución se roció con N_2 durante 10 min, luego se calentó a 100 °C durante 24 h. La mezcla se enfrió luego a temperatura ambiente y se concentró para purificación mediante MPLC (Teledine Isco combiFlash Companion). El residuo crudo se extrajo en un mínimo de CH_2Cl_2 y se absorbió en un cartucho de carga de 25 g y se pasó a través de una columna de gel de sílice pre–empaquetada Redi–Sep® (120 g) usando un gradiente 98:2 Hexanos : EtOAc a 70:30 Hexanos : EtOAc para proporcionar 2–(5–(3,5–difluorfenil)furo[3,2–b]piridin–3–il)acetato de metilo (1.46 g, 83.8% de rendimiento) en forma de un sólido amorfo incoloro. LRMS (ESI) *m/z* calc. para $C_{16}H_{12}F_2NO_3$ (M+H) 304.1, Hallado 304.2.



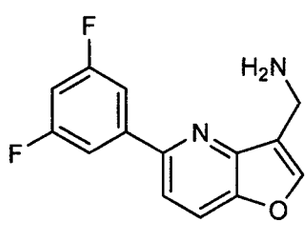
2) Acido 2–(5–(3,5–difluorfenil)furo[3,2–b]piridin–3–il)acético. A un frasco cargado con 2–(5–(3,5–difluorfenil)furo[3,2–b]piridin–3–il)acetato de metilo (1.46g, 5 mmol) se agregó MeOH (1.5 mL), H_2O (0.5 mL), seguido de NaOH (2 mL, 6 M, 12 mmol) para generar una solución amarilla, que se tapó y se mantuvo a temperatura ambiente durante 18 h. La solución se acidificó con HCl conc. a pH=3 y se vertió en CH_2Cl_2. Las capas se separaron y la capa orgánica se extrajo con CH_2Cl_2 (2x10 mL), seguido de EtOAc (2x10 mL). Los extractos

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orgánicos combinados se secaron sobre Na_2SO_4 y se concentraron al vacío para producir un sólido incoloro, que era lo suficientemente puro como para ser usado en la etapa siguiente.



3) (5–(3,5–difluorfenil)furo[3,2–b]piridin–3–il)metilcarbamato de metilo. A un frasco bajo N_2 cargado con ácido 2–(5–(3,5–difluorfenil)furo[3,2–b]piridin–3–il)acético (1.033 g, 3.57 mmol) se agregó CH_2Cl_2 anhidro (40 mL). La solución hetereogénea se enfrió a 0 °C y se agregó cloruro de oxalilo (1.6 mL, 17.8 mmol), seguido de una cantidad catalítica de DMF. La solución se calentó a temperatura ambiente y se mantuvo durante 1 h. La solución se concentró, luego se extrajo en acetona anhidra y se agregó a una solución acuosa agitada de azida de sodio (1.62 g, 25.0 mmol, en 10 mL H_2O) a 0 °C para producir una solución naranja homogénea. Después de 15 minutos a 0 °C, la mezcla se diluyó además con CH_2Cl_2 y se agitó 5 min adicionales para proporcionar una solución homogénea. La solución se dividió luego entre H_2O y CH_2Cl_2, y las capas se separaron. La capa acuosa se extrajo con CH_2Cl_2 (2x10 mL) y las capas orgánicas combinadas se secaron (Na_2SO_4) y se concentraron *al vacío*. El residuo se transfirió a un frasco seco y se evacuó y inundó con N_2 (5x), y se agregó CH_2Cl_2 anhidro (30 mL). La solución se enfrió a –78 °C, y se agregó por goteo tricloruro de boro (5.4 mL, 5.4 mmol, 1.0 M en CH_2Cl_2). Se removió el baño frío y la solución se dejó calentar a temperatura ambiente, y se mantuvo 48 h. Se agregó metanol anhidro (5 mL) y la solución se mantuvo a temperatura ambiente durante 3 h, momento en el cual se concentró para purificación con MPLC (Teledine Isco combiFlash Companion). El residuo se extrajo con un mínimo de CH_2Cl_2 y se absorbió en un cartucho de carga de 25 g y se pasó a través de una columna de gel de sílice pre–empaquetada Redi–Sep® (80 g) usando 99:1 CH_2Cl_2 : MeOH a 90:10:1 CH_2Cl_2 : MeOH : NH_4OH para proporcionar (5–(3,5–difluorfenil)furo[3,2–b]piridin–3–il)metilcarbamato de metilo (680 mg, 60% de rendimiento) en forma de un sólido amorfo marrón. LRMS (ESI) *m/z* calc. para $C_{16}H_{13}F_2N_2O_3$ (M+H) 319.1, Hallado 319.2.

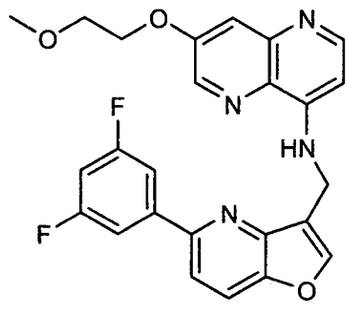


4) (5–(3,5–difluorfenil)furo[3,2–b]piridin–3–il)metanamina. A un frasco cargado con (5–(3,5–difluorfenil)furo[3,2–b]piridin–3–il)metilcarbamato de metilo (680 mg, 2137 µmol) se agregó MeOH (20 mL), y luego NaOH acuoso (18 mL, 6 N, 106 mmol). La solución se calentó a

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reflujo durante 60 h. La solución se concentró para remover MeOH, luego se dividió entre CH_2Cl_2 (30 mL) y $NaHCO_3$ (10 mL). Se separaron las capas y la capa acuosa se extrajo con CH_2Cl_2 (1x10 mL), luego con EtOAc (4x25 mL). Las capas orgánicas combinadas se concentraron para proporcionar un total de (5–(3,5–difluorfenil)furo[3,2–b]piridin–3–il)metanamina (306.6 mg, 55% de rendimiento) en forma de una espuma marrón. LRMS (ESI) *m/z* calc. para $C_{14}H_{11}F_2N_2O$ (M+H) 261.1, Hallado 261.2.

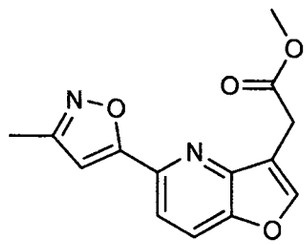
5) N–((5–(3,5–difluorfenil)furo[3,2–b]piridin–3–il)metil)–7–metoxi–1,5–naftiridin–4–amina . Un frasco sellable para microondas se cargó con (5–(3,5–difluorfenil)furo[3,2–b]piridin–3–il)metanamina (177.6 mg, 682 µmol), 8–cloro–3–metoxi–1,5–naftiridina (146 mg, 751 µmol), y fosfato de potasio (435 mg, 2047 µmol). Se unió un septo y el frasco se inundó con N_2, luego se agregaron tolueno (5 mL) y H2O (1 mL) y luego la solución se roció con N_2 durante 5 min. El septo se removió luego rápidamente y se agregaron tris(dibencilidenacetona)dipaladio (0) (15.6 mg, 17.1 µmol) y rac–2,2'–bis(difenilfosfino)–1,1'–binaftil (42.5 mg, 68.2 µmol) conjuntamente como sólidos. El frasco luego se selló y el sólido de color púrpura resultante se roció nuevamente durante 5 min. La mezcla se calentó luego a 100 °C durante 20 h. La mezcla se concentró *al vacío* para purificación con MPLC (Teledine Isco combiFlash Companion). El residuo crudo se extrajo en un mínimo de CH_2Cl_2 y se absorbió en un cartucho de carga de 25 g y se pasó a través de una columna de gel de sílice pre–empaquetada Redi–Sep® (80 g) usando un gradiente 98:2 CH_2Cl_2 : MeOH a 90:10 CH_2Cl_2 : MeOH para proporcionar un sólido amorfo. Este sólido se trituró adicionalmente con CH_2Cl_2 (2x0.5 mL) para proporcionar N–((5–(3,5–difluorfenil)furo[3,2–b]piridin–3–il)metil)–7–metoxi–1,5–naftiridin–4–amina (103 mg, 36.1% de rendimiento). LRMS (ESI) *m/z* calc. para $C_{23}H_{17}F_2N_4O_2$ (M+H) 419.1, Hallado 419.2.



Ejemplo 467

N–((5–(3,5–difluorfenil)furo[3,2–b]piridin–3–il)metil)–7–(2–metoxietoxi)–1,5–naftiridin–4–amina .

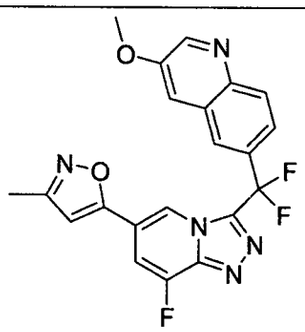
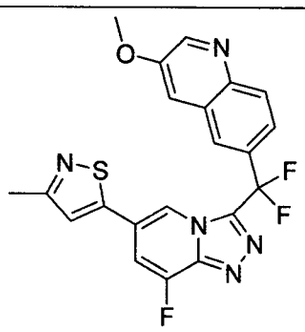
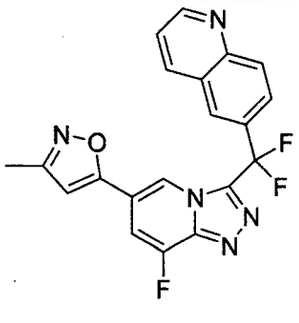
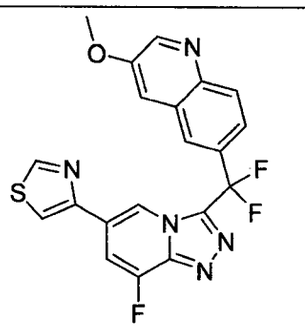
El compuesto del título se preparó a partir de (5–(3,5–difluorfenil)furo[3,2–b]piridin–3–il)metanamina y 8–cloro–3–(2–metoxietoxi)–1,5–naftiridina de la manera descrita para 7–metoxi–N–((5–(3–metilisoxazol–5–il)furo[3,2–b]piridin–3–il)metil)–1,5–naftiridin–4–amina . LRMS (ESI) *m/z* calc. para $C_{25}H_{21}F_2N_4O_3$ (M+H) 463.2, Hallado 463.2.

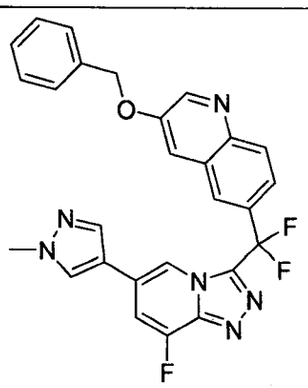
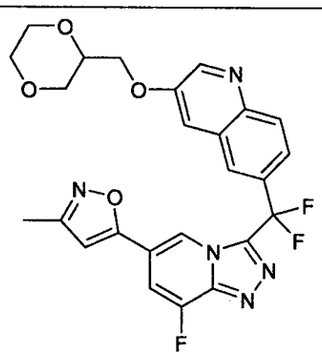
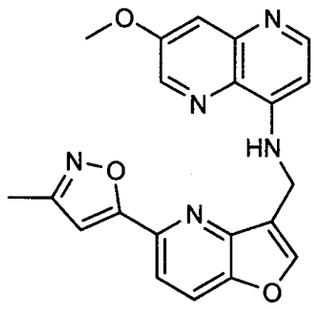


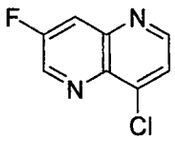
2–(5–(3–metilisoxazol–5–il)furo[3,2–b]piridin–3–il)acetato de metilo.

Un frasco sellable se cargó con 2–(5–clorofuro[3,2–b]piridin–3–il)acetato de metilo, acetato de paladio (II) (49.8 mg, 222 µmol), X–Phos (211 mg, 443 µmol), y 3–metil–5–(tributilestanilo)isoxazol (1319 mg, 3546 µmol). El frasco se selló y se agregó dioxano (20 mL). La mezcla se roció con N_2 durante 10 min, luego se calentó a 100 °C durante 48 h. La mezcla se enfrió a temperatura ambiente y se concentró para purificación con MPLC (Teledine Isco combiFlash Companion). El residuo crudo se extrajo en un mínimo de CH_2Cl_2 y se absorbió en un cartucho de carga de 25 g y se pasó a través de una columna de gel de sílice pre–empaquetada Redi–Sep® (40 g) usando 98:2 CH_2Cl_2 : MeOH a 90:10 CH_2Cl_2 : MeOH para proporcionar 2–(5–(3–metilisoxazol–5–il)furo[3,2–b]piridin–3–il)acetato de metilo (581 mg, 96.3% de rendimiento). LRMS (ESI) *m/z* calc. para $C_{14}H_{13}N_2O_4$ (M+H) 273.1, Hallado 273.3.

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Ej	Estructura	MW (M+H)	Masa Hallada	Método
468		426	426	I
469		442	442	I
470		396	396	I
471		428	428	I

472		501	501	I
473		512	512	I
474		388	388	J

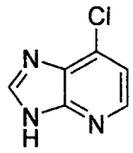


8–cloro–3–fluor–1,5–naftiridina

1) 5–((5–fluorpiridin–3–ilamino)metilen)–2,2–dimetil–1,3–dioxan–4,6–diona. Un tubo sellado de 150 mL se cargó con 2,2–dimetil–1,3–dioxan–4,6–diona (6.0 g, 41.6 mmol) y ortoformiato de trimetilo (41.6 mL, 41.6 mmol). Esto se calentó a 100 °C, y se agitó a esta temperatura durante 2 horas. La reacción luego se enfrió a 30°C y se agregó en porciones 5–fluorpiridin–3–amina (4.7 g, 41.6 mmol). El recipiente de reacción se re–selló y la mezcla se agitó a 100°C durante 23 h. La LC/MS mostró el completamiento. La mezcla de reacción se enfrió a temperatura ambiente, se diluyó con hexano, se filtró y se secó al aire para proporcionar 5–((5–fluorpiridin–3–ilamino)metilen)–2,2–dimetil–1,3–dioxan–4,6–diona (9.1 g, 82% de rendimiento) en forma de un sólido amarillo brillante. EM [M+H]= 267.2. Calc. para $C_{12}H_{11}FN_2O_4$=266.2.

2) 7–fluor–1,5–naftiridin–4(1H)–ona. Un frasco de fondo redondo de 500 mL equipado con un condensador a reflujo se cargó con 5–((5–fluorpiridin–3–ilamino)metilen)–2,2–dimetil–1,3–dioxan–4,6–diona (8.0 g, 30.0 mmol) y éter de difenilo (83.5 mL). Esto se calentó a 250 °C en un manto caliente y se dejó estar a esta temperatura durante 5 minutos. Se enfrió a temperatura ambiente, se diluyó con hexanos calientes, y se filtró para proporcionar 7–fluor–1,5–naftiridin–4(1H)–ona (2.2 g, 45% de rendimiento) en forma de un sólido marrón crudo. El compuesto del título se usó sin purificación adicional. EM [M+H]=165.2, Calc. para $C_8H_5FN_2O$=164.14.

3) 8–cloro–3–fluor–1,5–naftiridina. Un frasco resistente a presión se cargó con 7–fluor–1,5–naftiridin–4(1H)–ona (600 mg, 3.66 mmol) y POCl3 (6.8 mL, 73.1 mmol). El recipiente se selló y se agitó a 110°C durante 16hrs. La mezcla de reacción se enfrió a temperatura ambiente y se vertió sobre hielo mientras se agitaba vigorosamente. Mientras se mantenía la mezcla de reacción a 0°C, se basificó a pH~8 con NaOH 6N. El producto se extrajo con diclorometano. Se recogió la capa orgánica, se secó sobre sulfato de sodio y se concentró para proporcionar el material deseado. Esto se pasó a través de un tapón de sílice en 1–5% (90:10:1 DCM/MeOH/NH_4OH)/DCM para proporcionar 8–cloro–3–fluor–1,5–naftiridina (430mg, 64% de rendimiento) en forma de un sólido de color castaño. EM. Calc. para $C_8H_4ClFN_2$=182.58

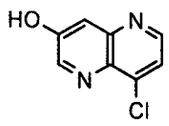


7–cloro–3H–imidazo[4,5–b]piridina

1) N–óxido de 4–azabenzimidazol. Se agregó peróxido de hidrógeno (30pt% de solución en agua, 38.0 ml, 372 mmol) a una suspensión de 3H–imidazo[4,5–b]piridina (4.93 g, 41.4 mmol) en AcOH (40 mL) a temperatura ambiente. La mezcla de reacción resultante se agitó a 80°C durante 3h, se enfrió a temperatura ambiente y se concentró al vacío a un volumen de ~50 mL. La concentración hasta sequedad se realizó usando un flujo de N_2. El residuo resultante se suspendió en agua (~10mL). La filtración proporcionó el compuesto del título (4.61g, 82.4% de rendimiento).

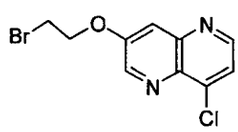
2) 7–cloro–3H–imidazo[4,5–b]piridina. Un frasco de fondo redondo de 50mL establecido con un condensador a reflujo bajo atmósfera de nitrógeno se cargó con N–óxido de 4–azabenzimidazol (1.2 g, 8.88 mmol) y 11 mL de DMF. Esto se calentó a 50°C y se agregó por goteo cloruro de metansulfonilo (1.86 ml, 23.98 mmol) a través de una jeringa. La mezcla resultante se calentó a 80°C y se agitó a esta temperatura durante 16 horas. Esto se enfrió a temperatura ambiente y se apagó con agua (aproximadamente 10 mL) y la mezcla de

reacción se llevó a un pH 7 mediante adición de una solución acuosa NaOH 6N. La reacción se extrajo con diclorometano (50mL). Un poco de producto estaba presente en la capa acuosa; esto se concentró y el residuo se apartó. Las capas orgánicas combinadas se secaron con sulfato de sodio, se filtraron y se concentraron. El material se purificó mediante cromatografía en columna (columna RediSep 40g, gradiente de elución 0–10% MeOH:DCM) para proporcionar 7–cloro–3H–imidazo[4,5–b]piridina (450mg, 33.0% de rendimiento). MS [M+H]=154.2. Calc. para $C_6H_4ClN_3$ = 153.56.



8–cloro–1,5–naftiridin–3–ol

Un frasco resistente a presión se cargó con 8–cloro–3–metoxi–1,5–naftiridina (2.5 g, 12.8 mmol), tribromuro de boro (13.4 mL, 141.3 mmol) y dicloroetano (0.6M, 21.4mL). El recipiente se selló y la mezcla se agitó a 60°C durante 16hrs. Al día siguiente la mezcla de reacción se enfrió en un baño de hielo y se diluyó con diclorometano (200mL). Esto se dejó reposar bajo un sistema de nitrógeno hasta que cesó todo la evaporación. Luego se filtró el material sólido amarillo resultante y se secó bajo alto vacío. Esto se suspendió en 40% (90:10:1 DCM/MeOH/NH4OH)/DCM y se purificó en este sistema mediante cromatografía sobre gel de sílice ISCO (80g) para proporcionar 8–cloro–1,5–naftiridin–3–ol (1.3g, 56% de rendimiento). EM [M+H]=181.2. Calc. para $C_8H_5ClN_2O$=180.59.



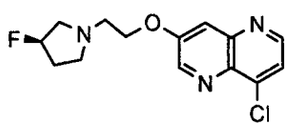
3–(2–bromoetoxi)–8–cloro–1,5–naftiridina.

Una botella de presión re–sellable se cargó con 8–cloro–1,5–naftiridin–3–ol (400mg, 2.2 mmol), 2–dibromoetano (3.2 mL, 37.7 mmol), y DMF (0.15M, 14.8 mL). El recipiente se selló y se colocó en un baño de aceite pre–calentado a 65°C. La reacción se dejó agitar a esta temperatura durante 4hrs. La reacción se enfrió a temperatura ambiente y se pasó a través de una almohadilla de celite. El filtrado se concentró y se purificó mediante cromatografía sobre gel de sílice ISCO (20–40%EtOAc/Hexanos) para proporcionar 3–(2–bromoetoxi)–8–cloro–1,5–naftiridina (460mg, 72% de rendimiento). EM [M+H]=289.0 Calc. para $C_{10}H_8BrClN_2O$=287.54

Los siguientes compuestos se prepararon usando el procedimiento para 3–(2–bromoetoxi)–8–cloro–1,5–naftiridina:

8–cloro–3–((tetrahidrofuran–2–il)metoxi)–1,5–naftiridina;

8–cloro–3–((tetrahidrotiofen–1,1–dióxido–3–il)metoxi)–1,5–naftiridina (a partir del cloruro de alquilo).

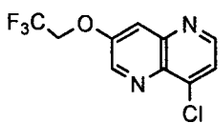


(R)–8–cloro–3–(2–(3–fluorpirrolidin–1–il)etoxi)–1,5–naftiridina.

Un frasco de fondo redondo de 25mL a temperatura ambiente se cargó con clorhidrato de (R)–3–fluorpirrolidina (124 mg, 0.99 mmol). A esto se agregó carbonato de potasio (365 mg, 2.64 mmol), 3–(2–bromoetoxi)–8–cloro–1,5–naftiridina (190mg, 0.66 mmol), yoduro de sodio (149 mg, 0.99 mmol) y DMF (2mL). La mezcla de reacción se colocó en un baño de aceite pre–calentado a 60°C y se dejó agitar durante 16hrs. La mezcla de reacción se pasó a través de una torta de celite, se enjuagó con 10% de MeOH/DCM y el filtrado se concentró para proporcionar el aceite amarillo. Esto se purificó mediante cromatografía sobre gel de sílice ISCO (20–40% EtOAC/Hexanos) para proporcionar (R)–8–cloro–3–(2–(3–fluorpirrolidin–1–il)etoxi)–1,5–naftiridina (105mg, 54% de rendimiento). EM [M+H]=296.2. Calc. para $C_{14}H_{15}ClFN_3O$=295.7.

Se prepararon los siguientes compuestos de manera similar a 8–cloro–3–(2–(3–fluorpirrolidin–1–il)etoxi)–1,5–naftiridina:

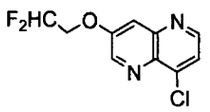
8–cloro–3–(2–(3–fluorpirrolidin–1–il)etoxi)–1,5–naftiridina;
8–cloro–3–(2–(3,3–difluorpirrolidin–1–il)etoxi)–1,5–naftiridina;
1–(2–(8–cloro–1,5–naftiridin–3–iloxi)etil)pirrolidin–3–ol;
3–(2–(1H–1,2,4–triazol–1–il)etoxi)–8–cloro–1,5–naftiridina (usando NaH como la base);
3–(2–(1H–pirazol–1–il)etoxi)–8–cloro–1,5–naftiridina;
3–(2–(1H–1,2,3–triazol–1–il)etoxi)–8–cloro–1,5–naftiridina.



8–cloro–3–(2,2,2–trifluoretoxi)–1,5–naftiridina

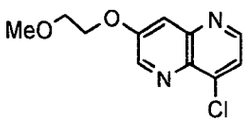
Una botella de presión re–sellable se cargó con 8–cloro–1,5–naftiridin–3–ol (80mg, 0.44 mmol), carbonato de cesio (433 mg, 1.3 mmol), 2,2,2–trifluoretil trifluormetansulfonato (360 mg, 1.55 mmol), y DMF (0.9 ml). El recipiente se selló y se colocó en un baño de aceite pre–calentado a 50°C. La reacción se dejó bajo agitación a esta temperatura durante 45 minutos. La LC/MS mostró la conversión completa. Se apagó con agua, se diluyó con una solución de bicarbonato de sodio y diclorometano. Se separaron las capas, se recogió la capa orgánica y se secó sobre suflato de sodio. Esto se concentró para proporcionar aceite amarillo; que se purificó mediante cromatografía sobre gel de sílice ISCO (20–

40%EtOAc/Hexanos) para proporcionar 8–cloro–3–(2,2,2–trifluoretoxi)–1,5–naftiridina (65mg, 56% de rendimiento). EM [M+H]=263.0@1.89minutos. Calc. para $C_{10}H_6ClF_3N_2O$=262.6.



8–cloro–3–(2,2–difluoretoxi)–1,5–naftiridina

Se preparó el compuesto del título usando el método descrito para 8–cloro–3–(2,2,2–trifluoretoxi)–1,5–naftiridina.

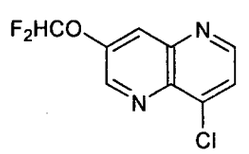


8–cloro–3–(2–metoxietoxi)–1,5–naftiridina

Un frasco de fondo redondo bajo atmósfera de nitrógeno se cargó con 8–cloro–1,5–naftiridin–3–ol (1.05 g, 5.8 mmol), 22.8 g de PS–Trifenilfosfina (carga: 2.2mmol/g), 2–metoxietanol (2.2 mL, 27.9 mmol), y THF (29.1 ml, 5814 µmol)/ DCM (58.1 mL). La mezcla se enfrió a 0°C y a esto se agregó por goteo DEAD (1.84 mL) a través de una jeringa. La mezcla de reacción se dejó agitar a temperatura ambiente durante 16 horas. Se diluyó con 50mL de 10%MeOH/diclorometano y la resina se unió al reactivo filtrado. El filtrado se concentró bajo presión reducida y se purificó mediante cromatografía sobre gel de sílice ISCO (10–30% de EtOAc/Hexanos) para proporcionar 8–cloro–3–(2–metoxietoxi)–1,5–naftiridina (770mg, 55% de rendimiento) en forma de un sólido blanco. EM [M+H]=238.9. Calc. para $C_{11}H_{11}ClN_2O_2$=238.67.

Se prepararon los siguientes compuestos de manera similar a 8–cloro–3–(2–metoxietoxi)–1,5–naftiridina:

8–cloro–3–(2–(pirrolidin–1–il)etoxi)–1,5–naftiridina;
8–cloro–3–(3–morfolinpropoxi)–1,5–naftiridina;
3–((1,4–dioxan–2–il)metoxi)–8–cloro–1,5–naftiridina;
8–cloro–3–(pirrolidin–2–ilmetoxi)–1,5–naftiridina.

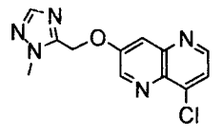


8–cloro–3–(difluormetoxi)–1,5–naftiridina

Un frasco de fondo redondo bajo atmósfera de nitrógeno se cargó con 2–cloro–2,2–difluoracetato de sodio (0.49 g, 3.2 mmol), 8–cloro–1,5–naftiridin–3–ol (0.25 g, 1.4 mmol),

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carbonato de cesio (1.4 g, 4.2 mmol), y DMF (2.8 mL, 0.5M). Esto se colocó luego en un baño de aceite pre–calentado a 100°C y se agitó a esta temperatura durante 3 h. La mezcla de reacción se diluyó con 10% de Metanol/ Diclorometano y se filtró sobre celite. El filtrado se concentró y se purificó mediante cromatografía sobre gel de sílice ISCO (40g) en 1% de MeOH/DCM para proporcionar 8–cloro–3–(difluormetoxi)–1,5–naftiridina pura (0.18 g, 56% de rendimiento) en forma de un sólido blanco. EM [M+H]=231.2. Calc. para $C_9H_5ClF_2N_2O$=230.60.



8–cloro–3–((2–metil–2H–1,2,4–triazol–3–il)metoxi)–1,5–naftiridina

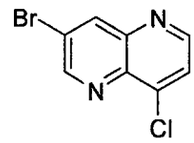
1) 2–metil–2H–1,2,4–triazol–3–carbaldehído. Un frasco de fondo redondo seco bajo atmósfera de nitrógeno se cargó con 1–metil–1H–1,2,4–triazol (1.0 g, 12.04 mmol) y THF (6.0 ml, 2M). Esto se enfrió a 0°C seguido de adición de una solución 2M de cloruro de isopropilmagnesio en THF (6.6 mL, 13.24 mmol) a través de una jeringa. Se removió el baño de hielo y la reacción se dejó agitar a temperatura ambiente durante 1.5 horas. La mezcla de reacción se volvió a enfriar a 0°C y se agregó por goteo N,N–dimetilformamida (1.39 ml, 18.05 mmol) a través de una jeringa. La mezcla de reacción se dejó calentar a temperatura ambiente durante 1 hora y se agitó a esta temperatura durante 16 horas. Al día siguiente la mezcla de reacción se apagó con HCl 2N y la mezcla se diluyó con diclorometano. Se separaron las capas, y la capa acuosa se neutralizó con una solución de bicarbonato de sodio acuoso y se extrajo con diclorometano. Todas las capas orgánicas se combinaron, se secaron sobre sulfato de sodio y se concentraron a temperatura ambiente (permaneció casi todo el THF) para proporcionar un material claro. Este se purificó mediante cromatografía sobre gel de sílice ISCO (10–40%EtOAc/Hex) para proporcionar 2–metil–2H–1,2,4–triazol–3–carbaldehído (1.0 g, 75% de rendimiento). El rendimiento se estimó basado en H'RMN. El producto se aisló en forma de una solución en EtOAc (no se removió todo el EtOAc debido a la volatilidad del aldehído, p.f..~60°C). EM [M+H] = 112.2; EM [M+H+H_2O] = 130.2@0.23 minutos . Calc. para $C_4H_5N_3O$ = 111.10.

2) (2–metil–2H–1,2,4–triazol–3–il)metanol. Se trató 2–metil–2H–1,2,4–triazol–3–carbaldehído (0.50 g, 4.50 mmol) en MeOH (10 mL) con borohidruro de sodio (0.17 g, 4.50 mmol) a temperatura ambiente y se dejó agitar durante 2 horas. La mezcla de reacción se apagó con una solución de bicarbonato de sodio, se diluyó con 10% de MeOH/DCM, y se recogió la capa orgánica. La capa acuosa se saturó con sulfato de sodio y se extrajo con 50 mL de diclorometano (3 veces). Se combinaron las porciones orgánicas, se secaron sobre sulfato de sodio y se concentraron hasta 1/4 de volumen a temperatura ambiente. Esto se diluyó luego con éter, causando la formación de un precipitado. Esto se concentró

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proporcionando 2–metil–2H–1,2,4–triazol–3–il)metanol en forma de un sólido blanco espumoso (0.44 g, 86.4% de rendimiento). Esto se usó 'tal cual' en la etapa siguiente. EM [M+H]= 114.2. Calc. para $C_4H_7N_3O$=113.1.

3) 8–cloro–3–((2–metil–2H–1,2,4–triazol–3–il)metoxi)–1,5–naftiridina. Se preparó el compuesto del título de manera similar a 8–cloro–3–(2–metoxietoxi)–1,5–naftiridina.



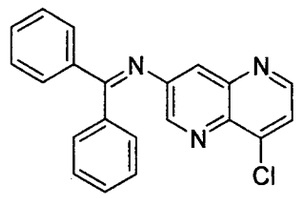
3–bromo–8–cloro–1,5–naftiridina

1) 5–((5–bromopiridin–3–ilamino)metilen)–2,2–dimetil–1,3–dioxan–4,6–diona. Un tubo sellado de 350 mL se cargó con 2,2–dimetil–1,3–dioxan–4,6–diona (21.6 g, 150.0 mmol) y ortoformiato de trietilo (150 mL, 150.0 mmol). Esto se calentó a 100 °C, y se agitó a esta temperatura durante 2 horas. La reacción se enfrió luego a 30°C y se agregó en porciones 55–bromopiridin–3–amina (25.95 g, 150.0 mmol). El recipiente de reacción se re–selló y la mezcla se agitó a 100 °C durante 3 horas. La LC/MS mostró el completamiento. La mezcla de reacción se enfrió a temperatura ambiente, se diluyó con hexano, se filtró y se secó al aire para proporcionar 5–((5–bromopiridin–3–ilamino)metilen)–2,2–dimetil–1,3–dioxano–4,6–diona (41.5 g, 85% de rendimiento) en forma de un sólido amarillo. EM [M+H]= 327.0. Calc. para $C_{12}H_{11}BrN_2O_4$=327.1.

2) 7–bromo–1,5–naftiridin–4(1H)–ona. Un frasco de fondo redondo de 500 mL equipado con un condensador a reflujo se cargó con 5–((5–bromopiridin–3–ilamino)metilen)–2,2–dimetil–1,3–dioxan–4,6–diona (10.5 g, 32.1 mmol) y éter difenilo (84.5 mL, 32.1 mmol). Esto se calentó a 250 °C en un manto caliente y se dejó permanecer a esta temperatura durante 1 h. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con 300mL de hexanos. Esto se calentó a 60°C y se trituró en este sistema durante 3 hrs para proporcionar 7–bromo–1,5–naftiridin–4(1H)–ona (6.05 g, 84% de rendimiento) en forma de un sólido crudo marrón. Esto se usó sin purificación adicional. EM[M+H]=227.0. Calc. para $C_8H_5BrN_2O$=225.0.

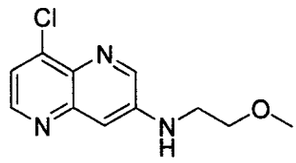
3) 3–bromo–8–cloro–1,5–naftiridina. 7–bromo–1,5–naftiridin–4(1H)–ona (23.8 g, 105.8 mmol), acetonitrilo (192 mL, 105.8 mmol), y DMF (2.05 mL, 26.5 mmol) se colocaron en un frasco de fondo redondo de 3 cuellos establecido con un condensador a reflujo. Se hizo burbujear a través de argón. La mezcla de reacción se llevó a reflujo (~95°C). Se agregó por goteo cloruro de oxalilo (28.7 ml, 328.1mmol) a través de un embudo de adición durante 40 minutos y la reacción se dejó agitar a esta temperatura durante 16 horas. La mezcla de reacción se enfrió a 0°C y se basificó a pH ~8 con una solución de bicarbonato de sodio

acuoso. El producto se extrajo con DCM (500mL) tres veces. Se combinaron las capas orgánicas, se secaron sobre sulfato de sodio y se concentraron para proporcionar un sólido marrón. Esto se purificó mediante cromatografía sobre gel de sílice para proporcionar 3–bromo–8–cloro–1,5–naftiridina (3.6 g, 14% de rendimiento) en forma de un sólido esponjoso de color castaño. MS[M+H]=245.0@. Calc. para $C_8H_4BrClN_2$=243.5.

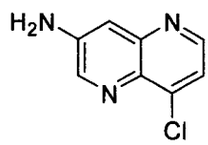


8–cloro–N–(difenilmetilen)–1,5–naftiridin–3–amina

Un frasco de fondo redondo de 25 ml establecido bajo nitrógeno se cargó con $Pd_2(dba)_3$ (301mg, 0.33mmol), BINAP (614 mg, 0.99 mmol) y ter–butóxido de sodio (237mg, 2.46 mmol). El sistema se purgó con argón y se agregaron 3–bromo–8–cloro–1,5–naftiridina (400mg, 1.64 mmol), difenilmetanimina (0.28 mL, 1.64 mmol), y tolueno (1M, 1.64 mL). Esto se colocó en un baño de aceite precalentado a 80°C y se agitó a esta temperatura durante 16 horas. La reacción se enfrió a temperatura ambiente, se diluyó con diclorometano, y se pasó sobre una torta de celite. El filtrado recolectado se concentró para proporcionar un aceite marrón. Esto se purificó mediante cromatografía sobre gel de sílice ISCO (40g, 1%MeOH/DCM durante 50 mins) para proporcionar 8–cloro–N–(difenilmetilen)–1,5–naftiridin–3–amina limpio (280mg, 50% de rendimiento). MS[M+H]=344.0. Calc. para $C_{21}H_{14}ClN_3$ =343.8.

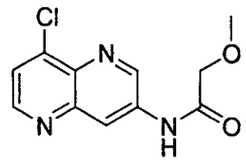


8–cloro–N–(2–metoxietil)–1,5–naftiridin–3–amina .



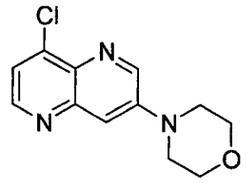
1) 8–cloro–1,5–naftiridin–3–amina . Un frasco de fondo redondo bajo nitrógeno se cargó con 8–cloro–N–(difenilmetilen)–1,5–naftiridin–3–amina (315mg, 0.92 mmol), HCl acuoso 2M (1.42 mL, 2.84 mmol), y tetrahidrofurano (0.25M, 3.67mL). Esto se agitó a temperatura ambiente durante 30 minutos.La reacción se basificó con una solución de bicarbonato de sodio acuoso y el producto se extrajo con diclorometano. Esto se secó sobre sulfato de sodio y se concentró para proporcionar un sólido naranja; que se purificó mediante cromatografía sobre gel de sílice ISCO, columna 40 g, 30% (90/10/1 DCM:MeOH:NH4OH)/DCM durante 40 minutos para proporcionar 7–amino–1,5–naftiridin–4–ol (140mg, 95% de rendimiento) en forma de un sólido amarillo. MS[M+H]=180.2. Calc. para $C_8H_6ClN_3$=179.6.

2) 8–cloro–N–(2–metoxietil)–1,5–naftiridin–3–amina . Un frasco de fondo redondo bajo atmósfera de nitrógeno se cargó con 8–cloro–1,5–naftiridin–3–amina (160mg, 0.89 mmol), DMF (2.2 mL, 0.89 mmol). Esto se enfrió a 0°C y se agregó en porciones hidruro de sodio (60% dispersión en aceite) (107 mg, 4.45 mmol). Esto fue seguido rápidamente de adición en porciones de 1–bromo–2–metoxietano (0.12 mL, 1.25 mmol) a través de una jeringa. Se removió el baño de hielo y la mezcla de reacción se calentó a 85°C y se agitó a esta temperatura durante 16 horas. La reacción se diluyó con 5mL de 5% MeOH/diclorometano, se cargó sobre una columna de gel de sílice y se eluyó con 2% MeOH/DCM para proporcionar 8–cloro–N–(2–metoxietil)–1,5–naftiridin–3–amina (70mg, 33% de rendimiento) en forma de un sólido amarillo claro. EM [M+H]=238.2. Calc. para $C_{11}H_{12}ClN_3O$=237.7.



N–(8–cloro–1,5–naftiridin–3–il)–2–metoxiacetamida

Un frasco de fondo redondo bajo nitrógeno se cargó con 8–cloro–1,5–naftiridin–3–amina (41mg, 0.23 mmol), trietilamina (64 µl, 0.46 mmol), y diclorometano (1mL). A esto se agregó por goteo a través de una jeringa cloruro de 2–metoxiacetilo (42 µl, 0.46 mmol) y la reacción se dejó agitar durante la noche a temperatura ambiente. Al día siguiente la mezcla de reacción se diluyó con diclorometano y se lavó con una solución de bicarbonato de sodio acuoso. Se separaron las capas y la capa orgánica se secó sobre sulfato de sodio para proporcionar un aceite amarillo. Esto se purificó mediante cromatografía sobre gel de sílice ISCO (2–5%MeOH/DCM) para proporcionar N–(8–cloro–1,5–naftiridin–3–il)–2–metoxiacetamida (43mg, 75% de rendimiento) en forma de un sólido amarillo claro. EM [M+H]=251.9. Calc. para $C_{11}H_{10}ClN_3O_2$=251.7.



8–cloro–3–morfolin–1,5–naftiridina

Un frasco de fondo redondo bajo atmósfera de nitrógeno se cargó con $Pd_2(dba)_3$ (578 mg, 0.63 mmol), Xantfos (1.1 g, 1.89 mmol) , y ter–butóxido de sodio (364 mg, 3.79 mmol). Esto se purgó con argón seguido de adición de 3–bromo–8–cloro–1,5–naftiridina (615 mg, 2.53 mmol), morfolina (0.22 mL, 2.53 mmol), y tolueno (1M, 2.53 mL). Esto se colocó luego en un baño de aceite pre–calentado a 80°C. Después de 2.5 horas, se detuvo la reacción, se enfrió a temperatura ambiente y se diluyó con diclorometano. Esto se pasó sobre una torta de celite y el filtrado se concentró para proporcionar un aceite marrón; que se purificó

mediante cromatografía sobre gel de sílice ISCO (40g, 1%MeOH/DCM durante 50 mins) para proporcionar 8–cloro–3–morfolin–1,5–naftiridina (200mg, 32% de rendimiento). EM [M+H]=250.2. Calc. para $C_{12}H_{12}ClN_3O$=249.7.

4–bromo–1–fenil–1H–pirazol.

Un tubo sellable se cargó con 4–bromopirazol (4.000 g, 27.2 mmol), 1–yodobenceno (3.64 ml, 32.7 mmol), (+/–)–trans–1,2–diaminociclohexano (0.654 ml, 5.44 mmol), yoduro de cobre (I) (0.518 g, 2.72 mmol), carbonato de potasio (8.28 g, 59.9 mmol) y se agregó 13 mL de dioxano. La mezcla se cubrió con N_2, el recipiente se selló y se calentó a 100 C durante 16 h. La mezcla se dejó enfriar a temperatura ambiente, se diluyó con EtOAc, se lavó con agua y se formó una emulsión. Se separó la capa orgánica y se filtró la mezcla de emulsión acuosa a través de una almohadilla de celite y se enjuagó con EtOAc, y $NaHCO_3$. saturado. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se evaporaron. La mezcla se purificó mediante cromatografía evaporativa usando un gradiente de 0 % a 100 % de CH_2Cl_2 en hexano. Se recogió el compuesto del título en forma de un sólido amarillo (3.18 g)

1–fenil–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol.

El compuesto del título se preparó de la misma manera que 1–etil–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol a partir de 4–bromo–1–fenil–1H–pirazol.

4–bromo–1–(tetrahidrofuran–3–il)–1H–pirazol

El compuesto del título se preparó de la misma manera que 4–bromo–1–(ciclobutil)–1H–pirazol, pero usando metansulfonato de tetrahidrofuran–3–ilo (preparado de acuerdo con los procedimientos conocidos en la materia).

1–(tetrahidrofuran–3–il)–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol.

El compuesto del título se preparó de la misma manera que 1–etil–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol a partir de 4–bromo–1–(tetrahidrofuran–3–il)–1H–pirazol.

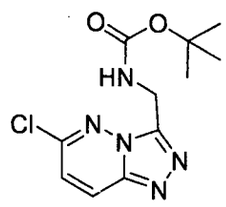
4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il) –1–ciclopropil–1H–pirazol

a) 1–ciclopropil–1H–pirazol. En un frasco de 3 cuellos de 1000 mL, a una mezcla de hidróxido de potasio (104 g, 1857 mmol) en agua (200 mL) se agregó ciclopropilamina (131 ml, 1857 mmol) y la mezcla se agitó a 50 C. Se agregó por goteo una solución de hidroxilamina de ácido –O–sulfónico (HOS)(30.00 g, 265 mmol) en 100 mL de agua dando como resultado la formación de un precipitado blanco después de las pocas primeras gotas. Se detuvo el agitamiento durante la primera mitad de la adición y se condensó un poco de ciclopromilamina en la parte superior de la solución de HOS. Se agregó amina adicional (10 mL) a la reacción y se continuó la adición de una solución HOS. La mezcla burbujeo durante

la adición. El frasco se removió del calor y se enfrió en un baño de hielo a 25 C. Se agregó lentamente HCl (conc), 150–200 mL, hasta alcanzar pH 3. La mezcla se filtró para remover el sólido blanco y el filtrado se calentó con 1,1,3,3–tetrametoxipropano (43.7 ml, 265 mmol). La mezcla tomó 1,5 h en alcanzar los 90 C, se mantuvo la temperatura a 90 durante 1 h, luego se dejó enfriar la mezcla a 40 C con agitación durante 17 h más. La mezcla se dejó enfriar a ~35 C y se extrajo con Et_2O (400 mL luego 2 x100 mL), las capas orgánicas combinadas se lavaron con agua, NaOH 6N, NaOH 2N, luego con NaHCO3 sat., y la capa orgánica se secó sobre Na_2SO_4, se filtró y se evaporó ligeramente. En la evaporación, cuando se redujo el volumen de ~600 mL a ~100 mL, se filtró el sólido blanco que había precipitado. Se obtuvo el compuesto del título en forma de un líquido dorado (~ 2g).

b) 4–bromo–1–ciclopropil–1H–pirazol. A una solución dorada de 1–ciclopropil–1H–pirazol (2.360 g, 22 mmol) en 100 mL de cloroformo, se agregó por goteo bromo (1.2 ml, 24 mmol) en forma de solución en 100 mL de $CHCl_3$ durante 1,5 h. La mezcla se calentó en un baño de aceite a 60 C durante 2 h. La mezcla se dejó enfriar a temperatura ambiente, se lavó con $NaHCO_3$ saturado, se secó sobre Na_2SO_4, se filtró y se evaporó para proporcionar el compuesto del título en forma de un líquido de color castaño (3.64 g).

c) 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il) –1–ciclopropil–1H–pirazol. El compuesto del título se preparó de la misma manera que 1–etil–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol a partir de 4–bromo–1–ciclopropil–1H–pirazol.

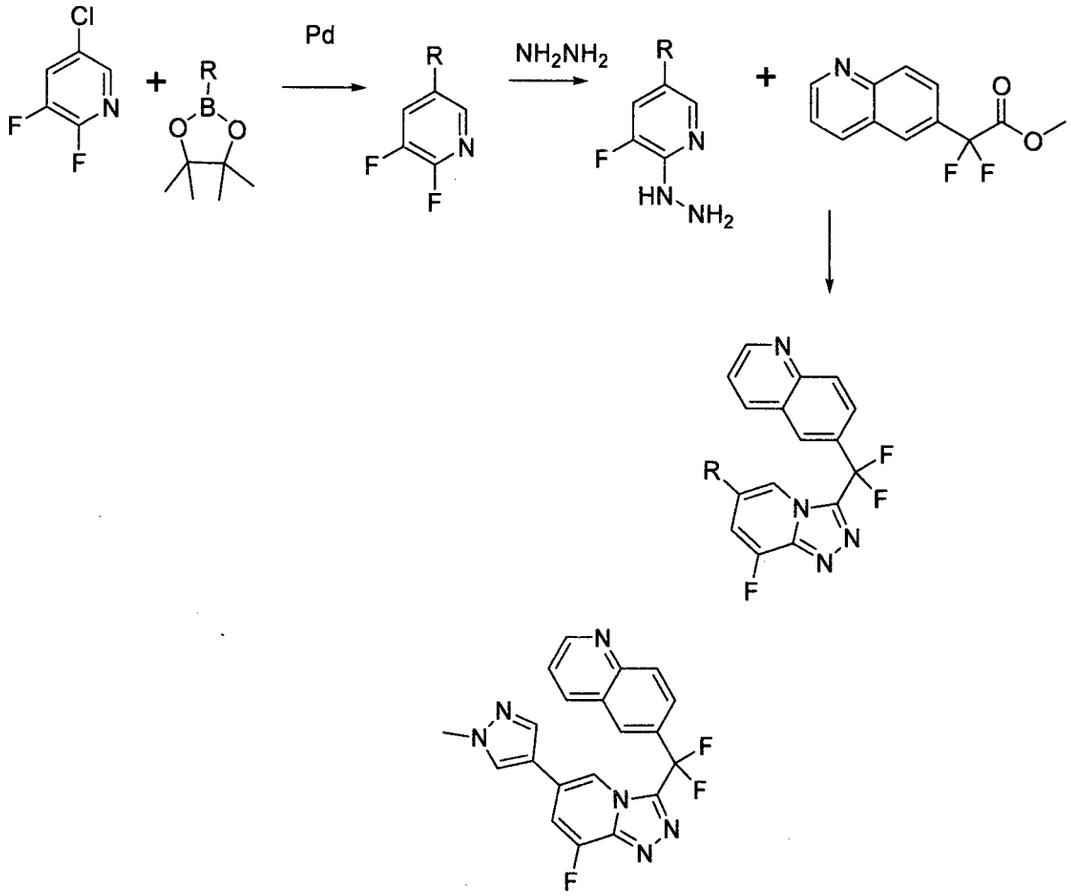


(6–cloro–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo .

Un frasco de fondo redondo de 2–L equipado con un agitador magnético se cargó con di(1H–imidazol–1–il)metanona (121 g, 749 mmol) y acetonitrilo (500 mL). La suspensión bajo agitación se enfrió mediante inmersión en un frasco en un baño de aceite. Se agregó una solución de N–Boc glicina (125 g, 714 mmol) en acetonitrilo (500 mL) a través de un embudo de adición de 500–mL durante el curso de 30–45 min. La mezcla se dejó madurar durante 1 h mientras un frasco de fondo redondo de tres cuellos de 5–L, equipado con agitador mediano y una termocupla s/adaptador se cargó con 1–(6–cloropiridazin–3–il)hidrazina (108 g, 749 mmol) y acetonitrilo (900 mL) y se enfrió a < 5° C en un baño de hielo. La solución fria del aciclimidazol se transfirió luego a través de una cánula de polietileno a la suspensión espesa de la hidrazina durante un período de 30–45 min). Se removió el baño de hielo, y la mezcla se dejó calentar. Después de 2.5 h de agitación se agregó hidrato de ácido 4–metilbencensulfónico (143 g, 749 mmol). El frasco se equipó luego

con un manto caliente y un condensador a reflujo y se calentó a reflujo (82° C) durante 13 h, luego se enfrió hasta aproximadamente 60° C. En este momento, la solución caliente se filtró al vacío a través de un papel. El filtrado marrón se concentró luego mediante rotación giratoria. La suspensión espesa amarillo–amarronado resultante se agitó en un baño de hielo y se diluyó con ACN (aproximadamente 100 mL). Después de agitar durante 1h, se aislaron los sólidos por filtración al vacío, se lavaron con hielo 1:1 ACN/H_2O (2x150 mL) y se secaron al aire en el filtro hasta que se obtuvo un sólido que fluía libremente (159 g, 78.5% de rendimiento).

Método General K



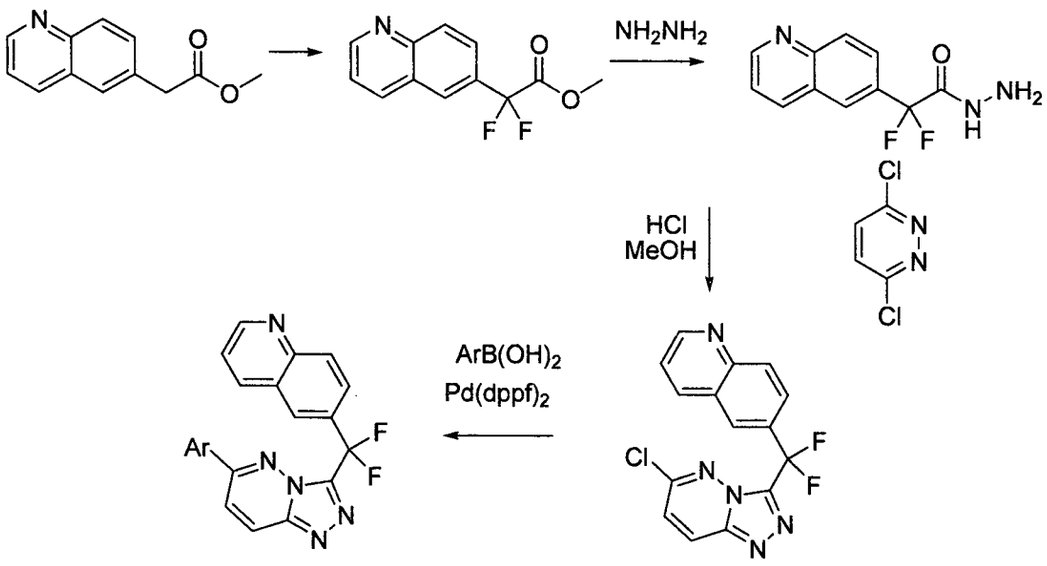
Ejemplo 475

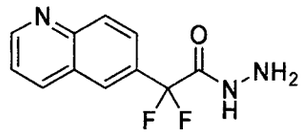
6–(difluor(8–fluor–6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)metil)quinolina.

A una suspensión bajo agitación de 1–(3–fluor–5–(1–metil–1H–pirazol–4–il)piridin–2–il)hidrazina (190 mg, 917 µmol), 2,2–difluor–2–(quinolin–6–il)acetato de metilo (218 mg, 917 µmol), polímero de trifenilfosfina sostenido en (241 mg, 917 µmol), DIEA (200 µl, 1146 µmol) en DCM (4mL) se agregó 2,2,2–tricloroacetonitrilo (92 µl, 917 µmol). El recipiente de reacción se selló luego apropiadamente y se calentó a 150 °C con microondas durante 15 min. La reacción luego se concentró en sílice seca bajo presión reducida y el producto se

purificó sobre sílice (40 g) eluyendo con 1–4% de 2 M NH_3 en MeOH/DCM. El producto luego se purificó adicionalmente con RP–HPLC eluyendo con agua /ACN (0.1% TFA). Las fracciones recogidas se concentraron bajo presión reducida, se disolvieron en MeOH/DCM (5mL) y se agitaron con Si–Carbonado (300 mg; 0.2 mmol) durante 30 min a 23 °C. Los sólidos luego se removieron por filtración y se lavaron con MeOH (3x1mL). El filtrado luego se concentró bajo presión reducida, y el producto se aisló en forma de un sólido blancuzco. EM (ESI pos. ion) m/z: 395 (MH+). Calc. masa exacta para $C_{20}H_{13}F_3N_6$: 394.

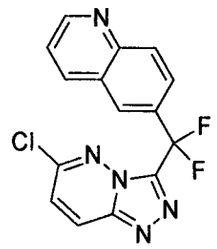
Método General L





2,2–difluor–2–(quinolin–6–il)acetohidrazida

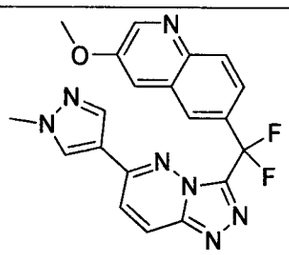
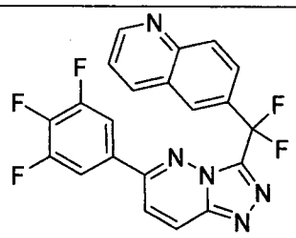
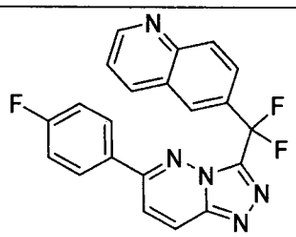
Una solución de 2,2–difluor–2–(quinolin–6–il)acetato de metilo (400 mg, 1686 µmol) e hidrazina anhidra (2153 µl, 67453 µmol) en MeOH (4 mL) se agitó durante 1 h a 23 °C. Los solventes luego se removieron bajo presión reducida para proporcionar el producto en forma de un sólido blanco. EM (ESI pos. ion) m/z: 238 (MH+). Calc. masa exacta para $C_{11}H_9F_2N_3O$: 237.

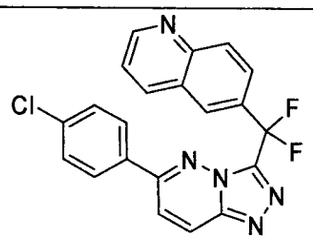
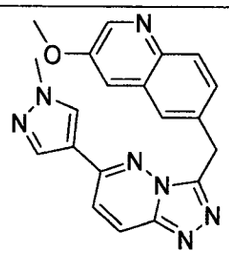
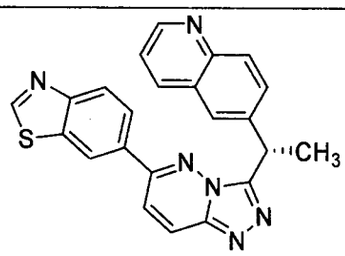
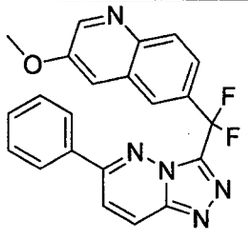


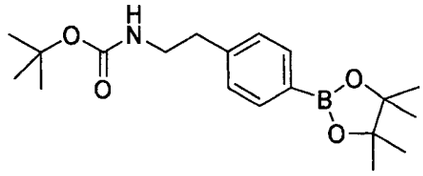
Ejemplo 476

6–((6–cloro–[1,2,4]triazol[4,3–b]piridazin–3–il)difluormetil)quinolina

Una suspensión de 2,2–difluor–2–(quinolin–6–il)acetohidrazida (2000 mg, 8432 µmol) y 3,6–dicloropiridazina (3768 mg, 25295 µmol) en 1.25 M de HCl en MeOH (20 mL) se calentó a 90 °C con microondas durante 50 min. Los solventes luego se removieron bajo presión reducida y el residuo se dividió entre 9:1 $CHCl_3$/IPA (60 mL) y 1 M NaOH (20 mL). La fase orgánica luego se secó sobre $MgSO_4$, se concentró, luego se purificó sobre sílice (120 g) eluyendo con 1>2.5% de 2 M NH_3 en MeOH/DCM para proporcionar el producto aislado en forma de un sólido castaño oscuro. EM (ESI pos. ion) m/z: 332 (MH+). Calc. exacto de masa para $C_{15}H_8ClF_2N_5$: 331.

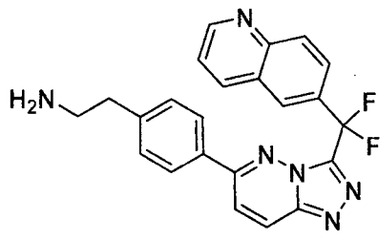
Ej	Estructura	MW	Masa Hallada	Método
477		407	408	L
478		427	428	L
479		391	392	L

480		407	408	L
481		371	372	M
482		408	409	M
483		403	404	M



4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenetilcarbamato de ter–butilo

Una suspensión de 4–bromofenetilcarbamato de ter–butilo (2700 mg, 8994 µmol), bis(pinacolato)diborónico (2284 mg, 8994 µmol), bis(pinacolato)diborónico (2284 mg, 8994 µmol), acetato de potasio (1765 mg, 17989 µmol) en dioxano (12mL) se roció con argón durante 5 minutos, luego se calentó a 120 °C en un recipiente apropiadamente sellado durante 1 h. La reacción se dividió luego entre éter (50 mL) y 5% de $NaHCO_3$ (25 mL). La fase orgánica se secó sobre $MgSO_4$, se concentró, luego se purificó sobre sílice (120 g) eluyendo con 10>30% EtOAc/Hexanos. El producto 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)fenetilcarbamato de ter–butilo (2200 mg, 70% de rendimiento) se aisló en forma de un sólido blanco. EM (ESI pos. ion) m/z: 292 (MH+1–56). Calc. exacto de masa para $C_{19}H_{30}BNO_4$: 347.



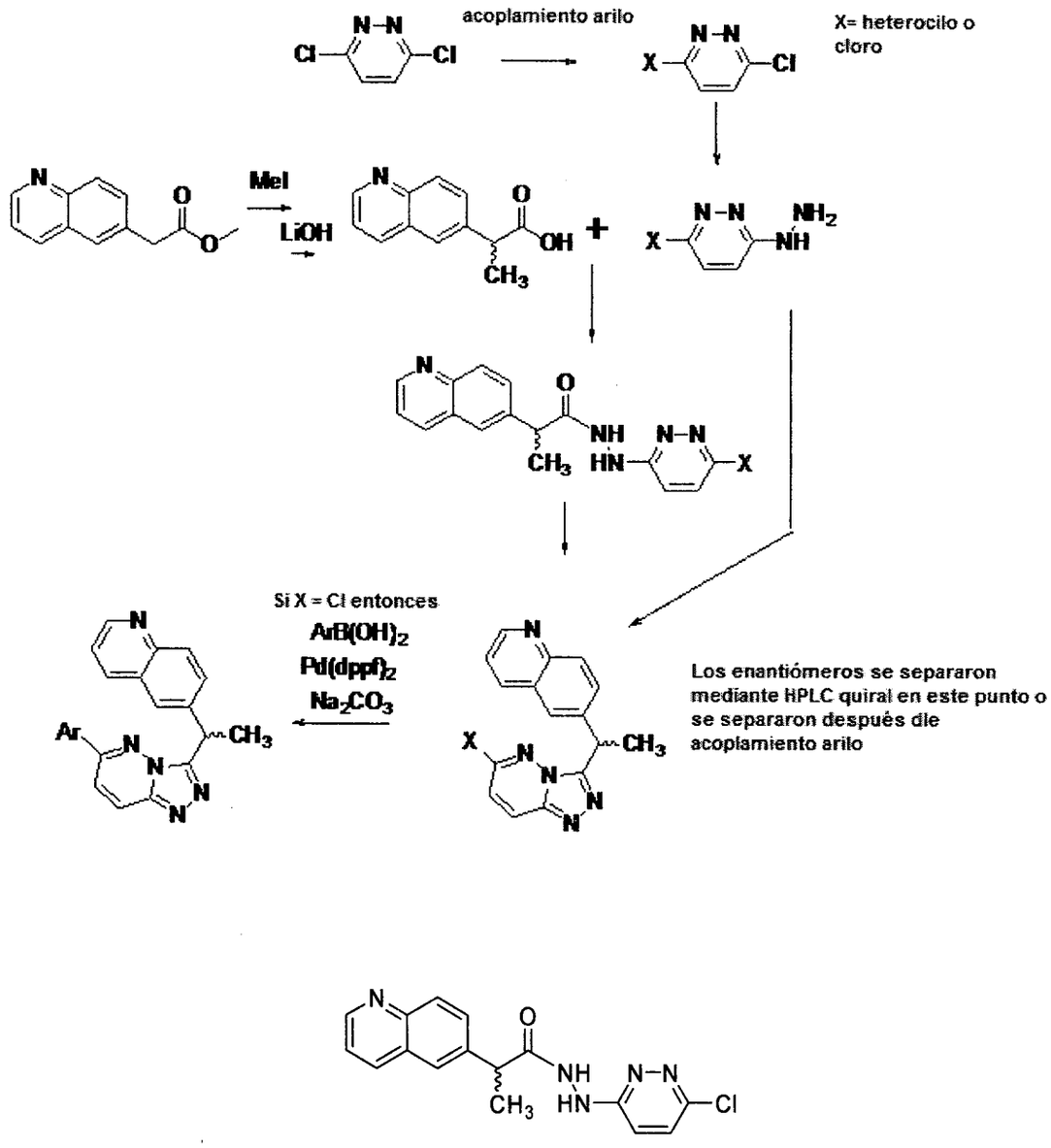
Ejemplo 484

2-(4-(3-(difluor(quinolin-6-il)metil)-[1,2,4]triazol[4,3-b]piridazin-6-il)fenil)etanamina

a) 2-(4-(3-(difluor(quinolin-6-il)metil)-[1,2,4]triazol[4,3-b]piridazin-6-il)fenil)etilcarbamato de ter-butilo. Una suspensión de 6-((6-cloro-[1,2,4]triazol[4,3-b]piridazin-3-il)difluormetil)quinolina (350 mg, 1055 µmol), 4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenetilcarbamato de ter-butilo (733 mg, 2110 µmol), complejo 1,1'-bis (difenilfosfino)ferroceno-paladio(ii)dicloruro diclorometano (77 mg, 106 µmol), Na2CO3 (447 mg, 4221 µmol) en DME (4mL) y agua (2mL) se roció con argón durante 5 min luego se calentó a 85 °C en un recpiente apropiadamente sellado durante 4 h. La reacción se dividó luego entre DCM (30 mL) y NaOH 1M (10 mL). La fase orgánica se secó luego sobre $MgSO_4$, se concentró, luego se purificó sobre sílice (40 g) eluyendo con 1>4% de NH_3 2M en MeOH/DCM. El producto se aisló en forma de un sólido blancuzco.

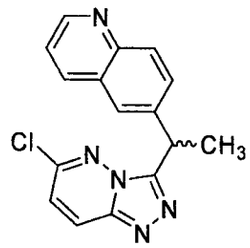
b) 2-(4-(3-(difluor(quinolin-6-il)metil)-[1,2,4]triazol[4,3-b]piridazin-6-il)fenil)etanamina. Una solución de 2-(4-(3-(difluor(quinolin-6-il)metil)-[1,2,4]triazol[4,3-b]piridazin-6-il)fenil)etilcarbamato de ter-butilo (70 mg, 136 µmol) en DCM (1 mL) y TFA (1 mL) se agitó durante 30 min a 23 °C. Los solventes se removieron luego bajo presión reducida y el producto crudo se purificó mediante RP-HPLC eluyendo con agua/ACN (0.1% TFA). Las fracciones deseadas recogidas se concentraron luego bajo presión reducida y el residuo resultante se disolvió en MeOH/DCM (5 mL). La solución se agitó luego como una suspensión con Si-carbonado (300 mg; 0.2 mmol) durante 30 min a 23 °C. Los sólidos se removieron luego mediante filtración, se lavaron con MeOH (3x1mL), y el filtrado se concentró bajo presión reducida. El producto se aisló en forma de un sólido esponjoso blanco. EM (ESI pos. ion) m/z: 417 (MH+). Calc. exacto de masa para $C_{23}H_{18}F_2N_6$: 416.

Método General M



N'–(6–cloropiridazin–3–il)–2–(quinolin–6–il)propanhidrazida

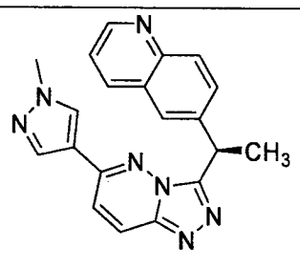
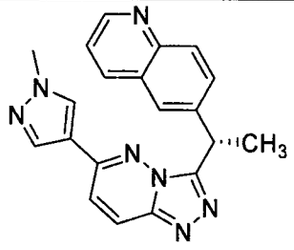
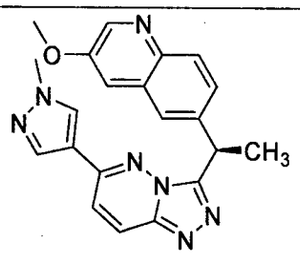
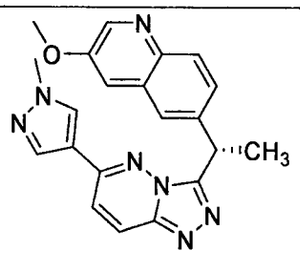
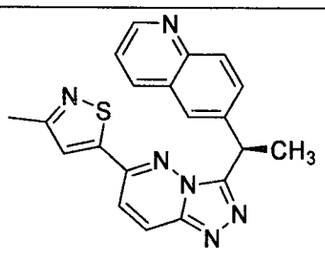
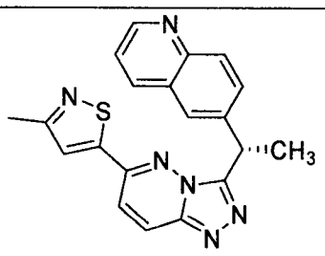
A una solución agitada de ácido 2–(quinolin–6–il)propanoico (3260 mg, 16201 µmol) y DIEA (2830 µl, 16201 µmol) en DMF (25 mL) se agregó íntegramente hexafluorfosfato de o–(7–azabenzotriazol–1–il)–n,n,n',n–tetrametil uronio (6160 mg, 16201 µmol) a 23 °C bajo nitrógeno. La solución se agitó durante 60 min, se enfrió a 0°C, luego se agregó 1–(6–cloropiridazin–3–il)hidrazina (2342 mg, 16201 µmol). Después de 20 h agitando a 23 °C, la reacción se dividió luego entre 9:1 $CHCl_3$/IPA (100 mL) y 5% de $NaHCO_3$ (50 mL). La fase orgánica se secó luego sobre $MgSO_4$, se concentró hasta un aceite, luego se purificó sobre sílice (120 g) eluyendo con 0>10% de NH_3 2M en MeOH/DCM. El producto se aisló en forma de un sólido blancuzco. EM (ESI pos. ion) m/z: 328 (MH+). Calc. exacto de masa para $C_{16}H_{14}ClN_5O$: 327.

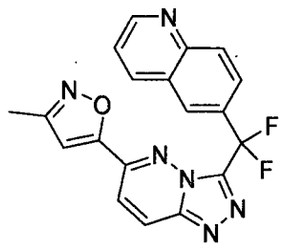


6–(1–(6–cloro–[1,2,4]triazol[4,3–b]piridazin–3–il)etil)quinolina.

Una solución de N'–(6–cloropiridazin–3–il)–2–(quinolin–6–il)propanhidrazida (2700 mg, 8238 µmol) en TFA (20 mL) se calentó a 120 °C con microondas (2 bar; 10 watts) durante 40 min. La solución se concentró bajo presión reducida y luego se dividió entre 9:1 CHCl3/IPA (75 mL) y NaOH 1M (100 mL). La capa acuosa se extrajo además con 9:1 $CHCl_3$/IPA (2x20 mL). Los orgánicos combinados se secaron sobre $MgSO_4$ luego se concentraron hasta un aceite de color ámbar bajo presión reducida. El producto se aisló en forma de un sólido cristalino blanco de ACN. EM (ESI pos. ion) m/z: 310 (MH+). Calc. exacto de masa para $C_{16}H_{12}ClN_5$: 309. El enantiómero se resolvió con: columna Chiralpak AD–H (3x25cm) usando 45% de etanol (0.1% DEA)/CO2

Los siguientes compuestos se prepararon usando el mismo método tal como 2–(4–(3–(difluor(quinolin–6–il)metil)–[1,2,4]triazol[4,3–b]piridazin–6–il)fenil)etilcarbamato de ter–butilo y se resolvió a partir de mezclas racémicas:

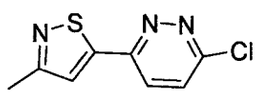
Ej	Estructura	MW	Masa Hallada	Pico #
485		355	356	1
486		355	356	2
487		385	386	1
488		385	386	2
489		372	373	1
490		372	373	2



Ejemplo 491

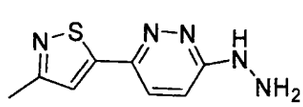
6–(difluor(6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)quinolina

Una suspensión de clorhidrato de 1–(6–(3–metilisoxazol–5–il)piridazin–3–il)hidrazina (200 mg, 879 µmol) y 2,2–difluor–2–(quinolin–6–il)acetato de metilo (208 mg, 879 µmol) en HCl 5M (1 mL) se selló apropiadamente y se calentó a 150 °C con microondas durante 4 h. La reacción se apagó luego mediante un goteo en NaOH 5M frío (2 mL) y se extrajo en agua con $CHCl_3$/IPA (25 mL). La fase orgánica se secó luego sobre $MgSO_4$, se concentró, y se purificó con sílice (40 g) eluyendo con 1>5% NH_3 2M en MeOH/DCM. El producto se purificó luego adicionalmente sobre RP–HPLC eluyendo con agua /ACN (0.1% TFA). Se concentraron las fracciones combinadas, se disolvieron en DCM (5 mL) y MeOH (5 mL), luego se agitaron con Si–Carbonado (0.5 g; 35 mmol) durante 1 h. Se removió Si–Carbonado mediante filtración y el filtrado se concentró con <0.5 mL de remanente con el producto aislado por trituración. EM (ESI pos. ion) m/z: 379 (MH+). Calc. exacto de masa para $C_{19}H_{12}F_2N_6O$: 378.



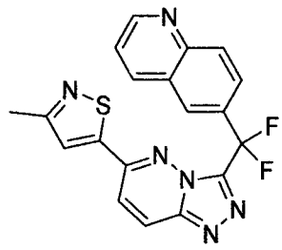
3–cloro–6–(3–metilisotiazol–5–il)piridazina

A una solución de 5–bromo–3–metilisotiazol (2.42 g, 14 mmol) en 20 mL de THF a –45 °C se agregó cloruro de isopropilmagnesio (19 ml, 19 mmol) en THF (1 M). Después de 20 minutos, se agregó cloruro de zinc (II) (41 ml, 20 mmol) en THF (0.5 M) y la solución se calentó a temperatura ambiente. Se agregaron 3,6–dicloropiridazina (2.4 g, 16 mmol), 3,6–dicloropiridazina (2.4 g, 16 mmol) y Q–fos (2.5 g) y la reacción se calentó a 50 °C durante 16 horas. La reacción se enfrió luego a 23 °C y se apagó con 60 mL de una solución NH_4Cl ac. saturada. La mezcla se mezcló con celite y 100 mL de EtOAc. El material insoluble se removió por filtración. El filtrado se diluyó con 40 mL de EtOAc y 30 mL de agua. Se separó la fase orgánica y se lavó con 60 mL de salmuera, se secó sobre Na_2SO_4 y se concentró *al vacío.* El residuo se purificó mediante cromatografía en columna de gel de sílice (10% a 80% de hex/EtOAc) para proporcionar un sólido rojo en forma del produto deseado. EM (ESI pos. ion) m/z: 212 (MH+). Calc. exacto de masa para $C_8H_6ClN_3S$: 211.



1–(6–(3–metilisotiazol–5–il)piridazin–3–il)hidrazina

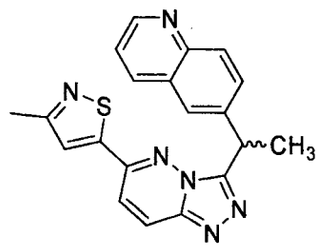
Una mezcla de 3–cloro–6–(3–metilisotiazol–5–il)piridazina (0.85 g, 4.0 mmol) e hidrazina anhidra (3.8 ml, 120 mmol) en 30 mL de sec–BuOH se calentó a 130 °C durante 3 horas. La mezcla se enfrió a 23 °C y se diluyó con 5 mL de agua. El sólido se recogió por filtración y se lavó con 2 mL de agua para producir un sólido amarillo. EM (ESI pos. ion) m/z: 208 (MH+). Calc. exacto de masa para $C_8H_6ClN_3S$: 207.



Ejemplo 492

6–(difluor(6–(3–metilisotiazol–5–il)–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)quinolina

Una mezcla de 2,2–difluor–2–(quinolin–6–il)acetato de metilo (0.50 g, 2.1 mmol), 1–(6–(3–metilisotiazol–5–il)piridazin–3–il)hidrazina (0.25 g, 1.2 mmol) y monohidrato de ácido p–toluensulfónico (0.40 g, 2.1 mmol) en 5 mL de dioxano se calentó a 150 °C durante 1 hora en un microondas. La mezcla se diluyó luego con 70 mL de EtOAc y 40 mL de una solución $NaHCO_3$ saturada. Se separó la fase orgánica y se lavó con 40 mL de salmuera, se secó sobre Na_2SO_4 y se concentró al vacío. El residuo se purificó mediante cromatografía en columna de gel de sílice (EtOAc a 10% de MeOH/EtOAc) para proporcionar un vidrio amarillo. El producto se purificó además mediante HPLC preparativa para proporcionar un vidrio amarillo. EM (ESI pos. ion) m/z: 395 (MH+). Calc. exacto de masa para $C_{19}H_{12}F_2N_6S$: 394.

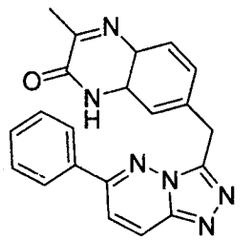


Ejemplo 493

6–(1–(6–(3–metilisotiazol–5–il)–[1,2,4]triazol[4,3–b]piridazin–3–il)etil)quinolina

A una solución de 5–bromo–3–metilisotiazol (1.00 g, 5.6 mmol) en 10 mL de THF a –45 °C (CH_3CN/hielo seco) se agregó un complejo LiCl de cloruro de isopropilmagnesio (7.9 ml, 7.9 mmol) (complejo LiCl, 1 M en THF). La mezcla se agitó a –45 °C durante 20 minutos y a esto se agregó lentamente a través de una jeringa cloruro de zinc, 0.5 M en THF (17 ml, 8.4 mmol). La mezcla se calentó luego a tempratura ambiente y se continuó la agitación durante 30 minutos adicionales. Se agregaron 6–(1–(6–cloro–[1,2,4]triazol[4,3–b]piridazin–3–il)etil)quinolina (0.5787 g, 1.9 mmol), tris(dibencilidenacetona)dipaladio (0) (0.51 g, 0.56 mmol) y Q–fos (0.65 g) en 15 mL de N,N–dimetil acetamida a la mezcla de reacción. La

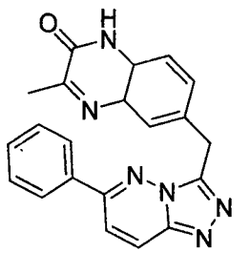
reacción se calentó a 50 °C durante 6 horas y se apagó con 50 mL de una solución NH_4Cl ac. saturada. La mezcla se extrajo con 150 mL de EtOAc y la fase orgánica se lavó con 60 mL de salmuera. Las fases acuosas se extrajeron además con 100 mL de EtOAc. Los orgánicos combinados se secaron sobre Na_2SO_4 y se concentraron *al vacío*. El residuo se purificó mediante cromatografía en columna sobre gel de sílice (EtOAc a 15% de MeOH en EtOAc) para proporcionar un sólido rojo. EM (ESI pos. ion) m/z: 373 (MH+). Calc. exacto de masa para $C_{20}H_{16}N_6S$: 372.



Ejemplo 494

3–metil–6–((6–fenil–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)quinoxalin–2(1H)–ona

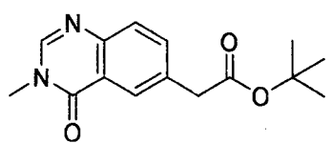
(Ver Ejemplo 495)



Ejemplo 495

3–metil–7–((6–fenil–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)quinoxalin–2(1H)–ona.

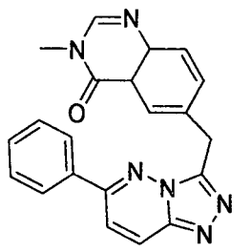
Una mezcla de 2–(2–metil–3–oxo–3,4–dihidroquinoxalin–6–il)acetato de ter–butilo (0.10 g, 0.36 mmol), 2–(3–metil–2–oxo–1,2–dihidroquinoxalin–6–il)acetato de ter–butilo (0.10 g, 0.36 mmol), 1–(6–fenilpiridazin–3–il)hidrazina (0.081 g, 0.44 mmol) y monohidrato de ácido p–toluensulfónico (0.069 g, 0.36 mmol) en 3 mL de dioxano se calentó con microondas a 150 °C durante 1 hora. La mezcla se diluyó con 70 mL de EtOAc y 40 mL de una solución $NaHCO_3$ saturada. La fase orgánica se separó y se lavó con 40 mL de salmuera, se secó sobre Na_2SO_4 y se concentró *al vacío*. El residuo se purificó mediante HPLC preparativa para resolver los regioestereómeros como los compuestos de los Ejemplos 494 y 495. Para cada regioestereómero EM (ESI pos. ion) m/z: 369 (MH+). Calc. exacto de masa para $C_{21}H_{16}N_6O$: 368.



2–(3–metil–4–oxo–3,4–dihidroquinazolin–6–il)acetato de ter–butilo

000383

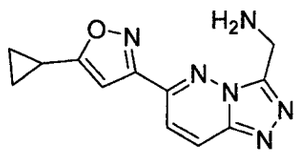
A una solución de 6–bromo–3–metilquinazolin–4(3H)–ona (0.485 g, 2.0 mmol), tris(dibencilidenacetona)dipaladio (0) (0.19 g, 0.20 mmol) y Q–fos (0.20 g) en 40 mL de THF se agregó cloruro de 2–ter–butoxi–2–oxoetilzinc 0,5 M en éter dietílico (8.1 ml, 4.1 mmol). La reacción se calentó a 50 °C durante 16 horas y se apagó con 40 mL de NH_4Cl saturado. La mezcla se diluyó con 60 mL de EtOAc. Se separó la fase orgánica, se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró al vacío para proporcionar un sólido rojo. El residuo se purificó mediante cromatografía sobre gel de sílice (5% de EtOAc/Hex a EtOAC) para proporcionar un sólido rojo. EM (ESI pos. ion) m/z: 275 (MH+). Calc. exacto de masa para $C_{15}H_{18}N_2O_3$: 274.



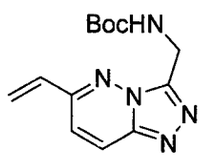
Ejemplo 496

3–metil–6–((6–fenil–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)quinazolin–4(3H)–ona:

Se preparó el compuesto del título usando el método para 3–metil–6–((6–fenil–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)quinoxalin–2(1H)–ona. EM (ESI pos. ion) m/z: 369 (MH+). Calc. exacto de masa para $C_{21}H_{16}N_6O$: 368.

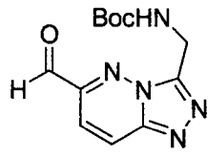


(6–(5–ciclopropilisoxazol–3–il)–[1,2,4]triazol[4,3–b]piridazin–3–il)metanamina

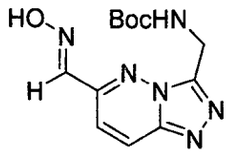


1) (6–vinil–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo. A un frasco purgado con argón se agregaron 4,4,5,5–tetrametil–2–vinil–1,3,2–dioxaborolano (7.65 ml, 45.1 mmol), (6–cloro–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo (3.20 g, 11.3 mmol), carbonato de cesio (11.0 g, 33.8 mmol), y $PdCl_2$(dppf)–CH_2Cl_2 (0.461 g, 0.564 mmol). La mezcla se disolvió en 38 mL de dioxano y 4 mL de agua (0.25M 10:1) y se calentó a 80 °C durante 12 h. La mezcla se enfrió a temperatura ambiente, se concentró y se purificó

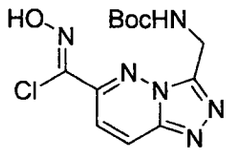
directamente a través de MPLC (DCM/MeOH+1%NH_4OH) para proporcionar el compuesto del título (3.0 g, 95% de rendimiento).



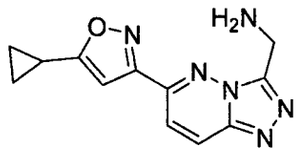
2) (6–formil–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo. (6–vinil–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo (485 mg, 1.76 mmol) se disolvió en 5 mL de THF y 5 mL de agua, luego se agregó tetróxido de osmio (0.687 mL (4% solución en agua), 0.0176 mmol) y se agitó durante 5 min. Se agregó periodato de sodio (141, 3.53 mmol) y la reacción se agitó durante 2 h. La reacción se extrajo luego con diclorometano (3 x 10 mL), se secó sobre Na_2SO_4 y se concentró. La purificación a través de MPLC (DCM/MeOH+1%NH_4OH) proporcionó el compuesto del título en forma de un sólido de color castaño (350 mg, 72% de rendimiento).



3) (6–((hidroxiimino)metil)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de (E)–ter–butilo. Se combinaron (6–formil–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo (400 mg, 1.44 mmol) y clorhidrato de hidroxilamina (200 mg, 2.86 mmol) en un frasco con 25 mL de THF y 25 mL de una solución NaOH 1N. Se agitó a temperatura ambiente durante 1 h. Luego se agregó diclorometano (50 mL) y se extrajo la capa acuosa 3 veces con DCM (50 mL), se secó sobre Na_2SO_4 y se concentró. Se purificó la oxima a través de MPLC (DCM/MeOH+1%NH_4OH) para proporcionar el compuesto del título (200 mg, 47% de rendimiento) en forma de un sólido de color castaño.

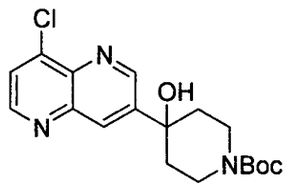


4) (6–(cloro(hidroxiimino)metil)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de (Z)–ter–butilo. Se disolvió (6–((hidroxiimino)metil)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de (E)–ter–butilo (200 mg, 0.684 mmol) en 25 mL de DMF y se agregó 1–cloropirrolidin–2,5–diona (95.9 mg, 0.718 mmol). Se agitó a temperatura ambiente durante 2 h. Se vertió la mezcla de reacción en agua (20 mL) y se extrajo con éter (3 x 20 mL). Se lavaron los orgánicos con agua (2 x 20 mL), salmuera (1 x 20 ml), se secaron sobre sulfato de sodio, se filtraron y se concentraron. El compuesto del título se usó sin purificación adicional (220 mg, 97% de rendimiento).



5) (6–(5–ciclopropilisoxazol–3–il)–[1,2,4]triazol[4,3–b]piridazin–3–Sil)metanamina.

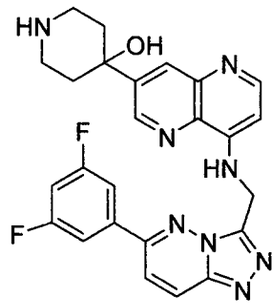
Se disolvió (6–(cloro(hidroxiimino)metil)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de (Z)–ter–butilo (110 mg, 337 µmol), etinilciclopropano (28 µl, 337 µmol), e hidrogencarbonato de potasio (67.4 mg, 673 µmol) en 0.3 mL de EtOAc y se calentó a 60 °C durante 12 h para proporcionar el intermediario protegido. El solvente se removió mediante evaporación giratoria y el residuo se re–disolvió en diclorometano (5 mL) y TFA (2 mL) y se agitó durante 30 min a temperatura ambiente. El solvente luego se removió y el residuo se re–disolvió en MeOH. Se agregó el sólido K_2CO_3 y la mezcla se agitó durante 1 h hasta base libre del compuesto del título. Se purificó la amina a través de MPLC (DCM/MeOH+1%NH_4OH) para proporcionar el compuesto del título (20 mg, 23% de rendimiento).



4–(8–cloro–1,5–naftiridin–3–il)–4–hidroxipiperidin–1–carboxilato de ter–butilo.

Se disolvió 3–bromo–8–cloro–1,5–naftiridina (210 mg, 862 µmol) en 8 mL de THF y se enfrió a –78 °C. Luego se agregó butillitio (517 µl, 1294 µmol) y se agitó durante 15 min. Se agregó 4–oxopiperidin–1–carboxilato de ter–butilo (258 mg, 1294 µmol) y se calentó a temperatura ambiente durante 1 h. La reacción se apagó con NH_4Cl saturado y se extrajo con diclorometano (3 X 20 mL), se secó sobre $NaSO_4$ y se concentró. Se purificó el intermediario a través de MPLC (DCM/MeOH/NHOH) para proporcionar 4–(8–cloro–1,5–naftiridin–3–il)–4–hidroxipiperidin–1–carboxilato de ter–butilo (120 mg, 38% de rendimiento).

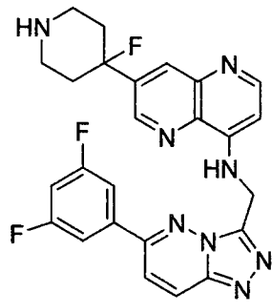
000386



Ejemplo 497

4–(8–((6–(3,5–difluorfenil)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilamino)–1,5–naftiridin–3–il)piperidin–4–ol.

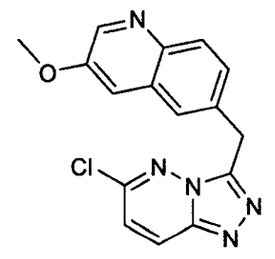
La desprotección de 4–(8–((6–(3,5–difluorfenil)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilamino)–1,5–naftiridin–3–il)–4–hidroxipiperidin–1–carboxilato de ter–butilo usando el método descrito para (6–(3–metilisotiazol–5–il)–[1,2,4]triazol[4,3–*b*]piridazin–3–il)metanamina . M/Z = 489.2 [M+H], calc 488.19 para $C_{25}H_{22}F_2N_8O$.



Ejemplo 498

N–((6–(3,5–difluorfenil)–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)–7–(4–fluorpiperidin–4–il)–1,5–naftiridin–4–amina .

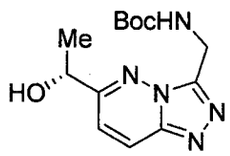
Una solución de 4–(8–((6–(3,5–difluorfenil)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilamino)–1,5–naftiridin–3–il)–4–hidroxipiperidin–1–carboxilato de ter–butilo (30 mg, 51 µmol) en 0.5 mL de DCM se enfrió a–78 C. Luego se agregó DAST (13 µl, 102 µmol) y se agitó a temperatura ambiente durante 30 min. Se agregó luego TFA a la mezcla de reacción y se agitó durante 30 min. El solvente se removió luego mediante evaporación giratoria y el residuo se re–disolvió en MeOH y base libre a través de una columna de intercambio de catión. La purificación a través de MPLC (DCM/MeOH+1%NH_4OH) proporcionó el compuesto del título (15 mg, 60% de rendimiento). M/Z = 491.2 [M+H], calc 490.18 para $C_{25}H_{21}F_3N_8$.

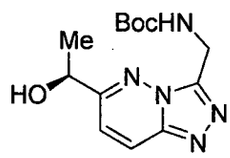


Ejemplo 499

6–((6–cloro–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)–3–metoxiquinolina

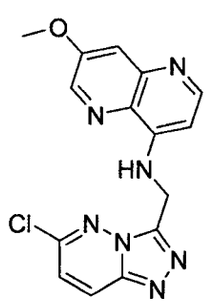
A un tubo para microondas CEM de 5 ml se agregó 2–(3–metoxiquinolin–6–il)acetato de ter–butilo (0.05 g, 0.2 mmol) , 1–(6–cloropiridazin–3–il)hidrazina (0.04 g, 0.3 mmol), agua (0.5 mL) y ácido clorhídrico (0.05 ml, 0.5 mmol). El frasco se selló y primero se calentó a 90 °C durante 30 min luego se colocó en un microondas CEM durante 10 min. a 100 °C, con 100 Watts de potencia a través de Powermax. La mezcla de reacción se ajustó a pH 7 mediante adición de NaOH 5N – se generó un ppt. marrón. El ppt. marrón se disolvió en DCM. El orgánico se lavó con agua, se secó sobre $MgSO_4$, y se removió el solvente *al vacío*. El producto crudo se purificó usando cromatografía SiO_2 (Teledyne Isco RediSep®, P/N 68–2203–026, 12 g SiO_2, DCM:EtOAc:MeOH=75%:20%:5%, Flujo = 30 mL/min). Se recogió un pico a los 25 min. El solvente se removió al vacío para proporcionar el producto deseado en forma de un sólido amarillento claro. Pt: 20.0 mg. EM (ESI pos. ion) m/z: 326.53. Calc. exacto de masa para $C_{16}H_{12}ClN_5O$: 325.75.





(6–(1–hidroxietil)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de (R/S)–ter–butilo

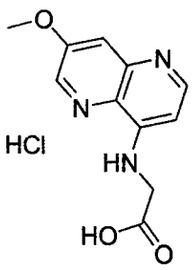
En un frasco de fondo redondo de 10 mL bajo N_2 se disolvió (6–formil–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo (200 mg, 721 µmol) en 3 mL de THF luego se enfrió a –78 °C y se trató con bromuro de metilmagnesio (721 µl, 2164 µmol). Después de 30 minutos, la mezcla de reacción se calentó a 0 °C durante 1h. Después de 1h la mezcla de reacción basada en LC–MS se neutralizó con NH_4Cl (sat.). La fase acuosa se extrajo 3X con DCM luego se secó la capa orgánica sobre Na_2SO_4, se filtró y se concentró bajo presión reducida. Se usó (6–(1–hidroxietil)–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo crudo (202 mg, 95.5% de rendimiento) sin purificación adicional en la etapa siguiente. EM *m/z* = 294.4 $[M+1]^+$. Calc. para $C_{13}H_{19}N_5O_3$: 293.3.



Ejemplo 500

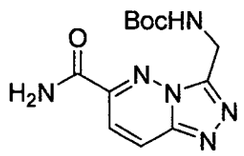
N–((6–cloro–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)–7–metoxiquinolin–4–amina .

000388



a) clorhidrato de ácido 2–(7–metoxi–1,5–naftiridin–4–ilamino)acético. En un frasco de fondo redondo de 100 mL se disolvieron 8–cloro–3–metoxi–1,5–naftiridina (5.00 g, 25.7 mmol) y clorhidrato de éster ter–butílico de glicina (17.2 g, 103 mmol) en 50 mL de 2–BuOH luego se agitó y calentó a 100 °C. Después de 5h el solvente basado en LC–MS se removió mediante presión reducida y luego el sólido se disolvió en 200 mL de HCl 1N y se agitó a 60 °C durante la noche. Después de 10 h la mezcla de reacción basada en LC–MS se enfrió a temperatura ambiente luego a 0°C y precipitó el ácido deseado. Se filtró el sólido (3.97 g) luego se evaporó la solución acuosa y trituró en 75 mL de H_2O a 0 °C luego se filtró nuevamente y se lavó con 25 mL de H_2O a 0 °C (1.58 g) para proporcionar un total de clorhidrato de ácido 2–(7–metoxi–1,5–naftiridin–4–ilamino)acético (5.55 g, 80.1% de rendimiento) en forma de un sólido de color castaño. EM *m/z* = 234.1 $[M+1]^+$. Calc. para $C_{11}H_{11}N_3O_3$: 233.1.

b) N–((6–cloro–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)–7–metoxi–1,5–naftiridin–4–amina. En un frasco de fondo redondo de 250 mL bajo N_2 se disolvieron HATU (1762 mg, 4635 µmol), 1–(6–cloropiridazin–3–il)hidrazina (536 mg, 3708 µmol), clorhidrato de ácido 2–(7–metoxi–1,5–naftiridin–4–ilamino)acético (1.00 g, 3708 µmol) en 25 mL de MeCN luego se agitaron y enfriaron a –40 °C luego se trataron con trietilamina (2584 µl, 18540 µmol) y calentaron a temperatura ambiente. Después de 30 min la mezcla de reacción basada en LC–MS se evaporó bajo presión reducida y se secó bajo alto vacío. El sólido crudo se disolvió en 100 mL de i–PrOH luego se trató con Ts–OH (2821 mg, 14832 µmol) y calentó a 80 °C. Después de 3h la mezcla de reacción basada en LC–MS se diluyó con DCM luego se neutralizó con NaOH (1N). La fase acuosa se extrajo 3X con DCM con 10% de MeOH luego la capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró bajo presión reducida. La mezcla cruda se trituró con i–PrOH caliente, luego se enfrió y filtró (662 mg) y se evaporó el licor madre bajo presión reducida y se purificó mediante MPLC (ISCO) (210 mg) con DCM:MeOH 100:0 a 90:10 para proporcionar en rendimientos combinados N–((6–cloro–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)–7–metoxi–1,5–naftiridin–4–amina (872 mg, 69% de rendimiento) en forma de un sólido blancuzco. EM *m/z* = 342.1 $[M+1]^+$. Calc. para $C_{15}H_{12}ClN_7O$: 341.7.



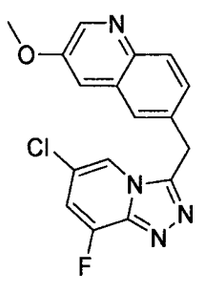
(6–carbamoil–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo

a) ácido 3–((ter–butoxicarbonil)metil)–[1,2,4]triazol[4,3–b]piridazin–6–carboxílico. En un frasco de fondo redondo de 25 mL se disolvieron 2–metil–2–buteno (21639 µl, 43278 µmol), fosfato de dihidrogeno de potasio (2356 mg, 17311 µmol) y (6–formil–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo (600 mg, 2164 µmol) en 5 mL de *t*–BuOH y 5 mL de agua, luego se agregó a 0 °C clorito de sodio (783 mg, 8656 µmol) y la mezcla de reacción se calentó a temperatura ambiente. Después de 10 h la mezcla de reacción basada en LC–MS se concentró bajo presión reducida y el ácido crudo se extrajo de la mezcla de sales sólidas con MeOH, se filtró y el solvente se concentró bajo presión reducida. El ácido 3–((ter–butoxicarbonil)metil)–[1,2,4]triazol[4,3–b]piridazin–6–carboxílico crudo (635 mg, 100% de rendimiento) se usó sin purificación adicional en la etapa siguiente. EM *m/z* = 294.2 $[M+1]^+$. Calc. para $C_{12}H_{15}N_5O_4$: 293.1

b) (6–carbamoil–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo. En un frasco de fondo redondo de 10 mL bajo N_2 se disolvieron ácido 3–((ter–butoxicarbonil)metil)–[1,2,4]triazol[4,3–b]piridazin–6–carboxílico (250 mg, 852 µmol), HATU (389 mg, 1023 µmol), trietilamina (356 µl, 2557 µmol) en 1.5 mL de DMF luego se trataron con a (92 µl, 4262 µmol) y se agitaron a temperatura ambiente. Después de 2h la mezcla de reacción basada en LC–MS se concentró bajo presión reducida y luego se purificó mediante MPLC (ISCO) con DCM:MeOH+NH_4OH (1%) 100:0 a 90:10 para proporcionar (6–carbamoil–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo (129 mg, 52% de rendimiento). EM *m/z* = 293.2 $[M+1]^+$. Calc. para $C_{12}H_{16}N_6O_3$: 292.3.

3–(aminometil)–N–metil–[1,2,4]triazol[4,3–b]piridazin–6–carboxamida.

Se preparó el compuesto del título usando las mismas condiciones que para (6–carbamoil–[1,2,4]triazol[4,3–b]piridazin–3–il)metilcarbamato de ter–butilo.



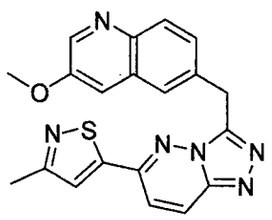
Ejemplo 501

6–((6–cloro–8–fluor–[1,2,4]triazol[4,3–a]piridin–3–il)metil)–3–metoxiquinolina

000390

a) 1–(5–cloro–3–fluorpiridin–2–il)hidrazina. Una mezcla de 5–cloro–2,3–difluorpiridina (10.0 g, 66.9 mmol) e hidrazina (10.0 ml, 319 mmol) en ^{i}PrOH (50 mL) se calentó a 65 – 70 °C durante 6 horas. La mezcla se enfrió a 23 °C, se filtró y se lavó con Na_2CO_3 (satd), y H_2O. El producto se aisló en forma de un sólido blanco. EM (ESI pos. ion) m/z: 162 (MH+). Calc. exacto de masa para $C_5H_5ClFN_3$: 161.

b) 6–((6–cloro–8–fluor–[1,2,4]triazol[4,3–a]piridin–3–il)metil)–3–metoxiquinolina. A una mezcla de ácido 2–(3–metoxiquinolin–6–il)acético (0.22 g, 1.0 mmol), 1–(5–cloro–3–fluorpiridin–2–il)hidrazina (0.11 g, 0.68 mmol) y trifenilfosfina (0.97 g, 2.0 mmol) (en soporte sólido) en DCM (5 mL) se agregó DIEA (0.24 ml, 1.4 mmol) seguido de 2,2,2–tricloroacetonitrilo (0.14 ml, 1.4 mmol) a través de una jeringa. La mezcla luego se calentó a 150 °C durante 15 minutos en un frasco apropidamente sellado. La mezcla se filtró y el filtrado se diluyó con 50 mL de EtOAc. La solución se lavó con 30 mL de. $NaHCO_3$ sat. seguido de 30 mL de salmuera, se secó sobre Na_2SO_4 y se concentró al vacío. El producto crudo se purificó mediante cromatografía en columna de gel de sílice (EtOAc a 10% de MeOH/EtOAc) para proporcionar un sólido amarillo claro como el producto deseado. EM (ESI pos. ion) m/z: 343 (MH+). Calc. exacto de masa para $C_{17}H_{12}ClFN_4O$: 342.



Ejemplo 502

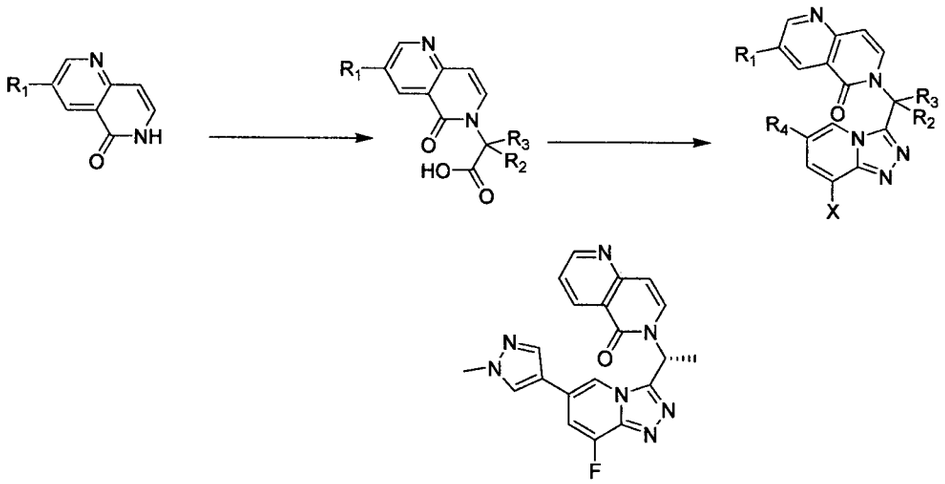
3–metoxi–6–((6–(3–metilisotiazol–5–il)–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)quinolina

Un frasco cargado con 5–bromo–3–metilisotiazol (0.049 g, 0.28 mmol) y 0.3 mL de THF seco se enfrió a 0 °C, y se agregó por goteo cloruro de isopropilmagnesio (0.30 ml, 0.30 mmol) durante 5 minutos y la mezcla se agitó 5 minutos más antes de dejar enfriar a temperatura ambiente. La mezcla se agitó a temperatura ambiente 10 minutos y la mezcla se canuló a una solución de cloruro de zinc (II) (0.30 ml, 0.30 mmol) [1M] y la suspensión se agitó 10 minutos. El zincato se trató con 6–((6–yodo–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)–3–metoxiquinolina (0.0890 g, 0.21 mmol), 1 mL de THF seco, y una solución pre–formada de 4,5–bis(difenilfosfino)–9,9–dimetil–9H–xanteno (0.012 g, 0.021 mmol) y Pd(OAc)2 (0.0024 g, 0.011 mmol) disuelto en 1 mL de THF seco. El frasco se cargó con un condensador a reflujo y se calentó con un baño de aceite de 90 °C durante 24 h. Se repitió la porción de zincato de este procedimiento, se agregó a la mezcla de reacción, y la mezcla se calentó a 90 °C durante 1 h. La mezcla se dejó enfriar a temperatura ambiente y se cargó en 10 g de SiO_2 empaquetado en húmedo con THF, y se eluyó con 200 mL de THF. Se concentraron los eluyentes *al vacío* y se extrajeron en 5 mL de EtOH. A la solución se agregó ácido Si–sulfónico (1.5 g, 1.1 mmol) y la mezcla se agitó a temperatura ambiente durante 24 h, y el

000391

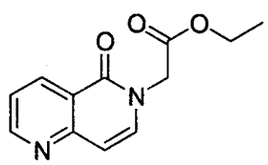
sólido se recogió. El sólido se lavó con EtOH (se descartó), y luego NH_3 2M en EtOH (5 x 5 mL). Los eluyentes amoniacales se concentraron y el residuo se purificó mediante HPLC para proporcionar 3–metoxi–6–((6–(3–metilisotiazol–5–il)–[1,2,4]triazol[4,3–b]piridazin–3–il)metil)quinolina (0.0013 g, 1.6% de rendimiento).

Método General N.



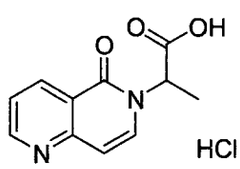
Ejemplo 503

(R)–6–(1–(8–fluor–6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona



1. 2–(5–oxo–1,6–naftiridin–6(5H)–il)acetato de etilo.

Se disolvieron 1,6–naftiridin–5–ol (1.00 g, 6.8 mmol), yodoacetato de etilo (1.6 ml, 14 mmol) y carbonato de cesio (4.5 g, 14 mmol) en 25 mL de THF luego se agitaron y calentaron a 100 °C durante 2h hasta que se completó la reacción. La reacción se concentró y purificó mediante MPLC usando un gradiente de 90% de DCM : 10% MeOH para proporcionar 2–(5–oxo–1,6–naftiridin–6(5H)–il)acetato de etilo (1.5 g, 94% de rendimiento).

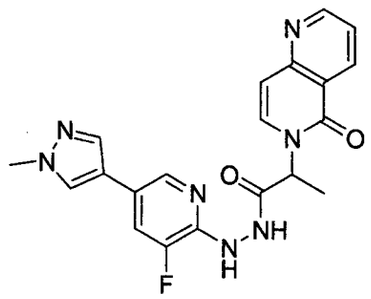


2. clorhidrato de ácido 2–(5–oxo–1,6–naftiridin–6(5H)–il)propanoico.

Se disolvió 2–(5–oxo–1,6–naftiridin–6(5H)–il)acetato (32.0 g) en 450 mL de una solución de HCl 6N, luego se agitó y calentó a 100 °C durante 1 hr hasta que se completó la reacción. La mezcla de reacción se concentró bajo presión reducida, y se azeotropeó 3

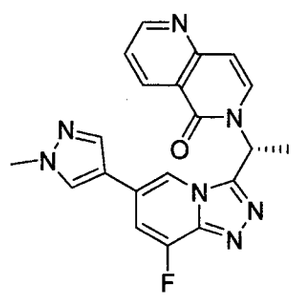
000392

veces con benceno (200 mL) para remover el agua. Se usó clorhidrato de ácido 2–(5–oxo–1,6–naftiridin–6(5H)–il)propanoico (30.56 g, 92.3% de rendimiento) sin purificación adicional.



3. <u>N'–(3–fluor–5–(1–metil–1H–pirazol–4–il)piridin–2–il)–2–(5–oxo–1,6–naftiridin–6(5H)–il)propanhidrazida.</u>

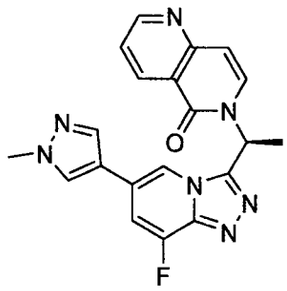
HATU (1053 mg, 2.7 mmol), clorhidrato de ácido 2–(5–oxo–1,6–naftiridin–6(5H)–il)propanoico (470 mg, 1.8 mmol) *y* 1–(3–fluor–5–(1–metil–1H–pirazol–4–il)piridin–2–il)hidrazina (421 mg, 2 mmol) (etapa 1 del Método General K) se extrajeron en 6 mL de acetonitrilo. Se agregó DIPEA (967 µl, 5.5 mmol) y la reacción se agitó durante 30 minutos, hasta que se completó la reacción. Se concentró el material crudo y luego se purificó mediante MPLC con un gradiente 100% de DCM a 90% de DCM / 10% de MeOH / 1% NH_4OH) para proporcionar N'–(3–fluor–5–(1–metil–1H–pirazol–4–il)piridin–2–il)–2–(5–oxo–1,6–naftiridin–6(5H)–il)propanhidrazida (500 mg, 67% de rendimiento).



4. <u>(R)–6–(1–(8–fluor–6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona.</u>

N'–(3–fluor–5–(1–metil–1H–pirazol–4–il)piridin–2–il)–2–(5–oxo–1,6–naftiridin–6(5H)–il)propanhidrazida (400 mg, 982 µmol) y trifenilfosfina (386 mg, 1.4 mmol) se extrajeron en THF (9.8 mL). Se agregó TMS–azida (195 µl, 1.4 mmol), seguido de adición lenta de DEAD (233 µl, 1.4 mmol) y la reacción se agitó a temperatura ambiente durante 1 hr hasta completar. La reacción se concentró y purificó mediante MPLC con un gradiente 100 % de DCM a 90% de DCM / 10% de MeOH / 1% de NH_4OH para proporcionar 6–(1–(8–fluor–6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona racémico (220 mg, 57% de rendimiento) en forma de un sólido de color castaño. Se separó mediante SFC preparativa (ChiralPak® OJ–H, (20 x 150 mm, 5 µm), 20% de MeOH, 80% de CO_2, 0.2% de DEA; sistema de presión de 100 bares; 70 mL/min; t_r : 3.5 min) para proporcionar (R)–6–(1–(8–fluor–6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona (60 mg, 15% de rendimiento). En base a datos

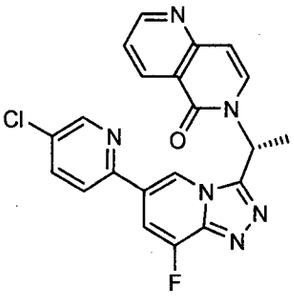
cristalográficos previos y la potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *R*. EM *m/z* = 390.2 [M+H], calc 389.14 para $C_{20}H_{16}FN_7O$. ^{1}H RMN (400 MHz, cloroformo–*d*) μ ppm 2.16 (d, *J*=5.18 Hz, 3 H) 3.97 (s, 3 H) 6.82 (d, *J*=6.55 Hz, 1 H) 7.01 – 7.13 (m, 2 H) 7.41 – 7.49 (m, 1 H) 7.54 (d, *J*=6.26 Hz, 1 H) 7.61 (s, 1 H) 7.71 (s, 1 H) 8.33 (s, 1 H) 8.78 (d, *J*=7.73 Hz, 1 H) 8.93 (s, 1 H).



Ejemplo 504

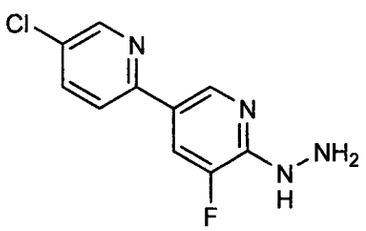
(S)–6–(1–(8–fluor–6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona

Se sintetizó el compuesto del título de la misma manera general tal como ha sido descrito previamente para el Ejemplo 503. Se separó mediante SFC preparativa (ChiralPak® OJ–H, (20 x 150 mm, 5 μm), 20% MeOH, 80% CO_2, 0.2% DEA; sistema de presión 100 bares; 70 mL/min; t_r : 4.3 min). En base a datos cristalográficos previos y la potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *S*. EM *m/z* = 390.2 [M+H], calc 389.14 para $C_{20}H_{16}FN_7O$.

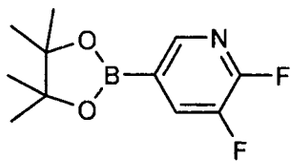


Ejemplo 505

(*R*)–6–(1–(6–(5–cloropiridin–2–il)–8–fluor–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona

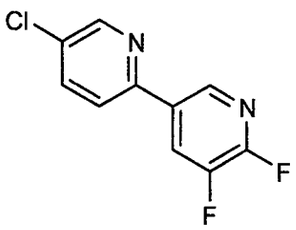


1. **1–(5–(5–cloropiridin–2–il)–3–fluorpiridin–2–il)hidrazina**



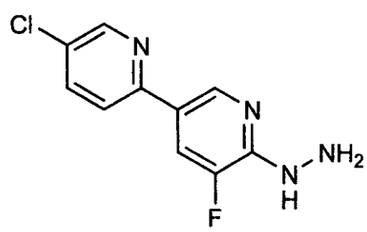
a. 2,3–difluor–5–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)piridina.

Un frasco de presión re–sellable de 350 mL se cargó con 5–cloro–2,3–difluorpiridina (5.0 g, 33 mmol), pinacol diborano (13 g, 50 mmol), x–fos (1.9 g, 4.0 mmol), Pd_2dba_3 (1.8 g, 2.0 mmol), y 1,4–dioxano (215 ml, 0.16 M), se inundó con argón, se selló, luego se calentó a 100°C durante 16 horas. La mezcla se concentró y diluyó con DCM (200 mL), luego se lavó con agua (50 mL). La capa orgánica se secó con $MgSO_4$, se filtró, luego se concentró para proporcionar un aceite marrón. El aceite se purificó mediante MPLC, eluyendo con 10–60% de EtOAc/Hexanos. 2,3–difluor–5–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)piridina (5.6 g, 69% de rendimiento) se aisló con forma de un aceite naranja claro que se solidificó por reposo. La LC/MS mostró el producto como ácido borónico. Sin embargo, la estructura del producto es tal como se graficó anteriormente. EM m/z = 160.2 $[M+1]^+$. Calc. para $C_{11}H_{14}BF_2NO_2$: 241.0



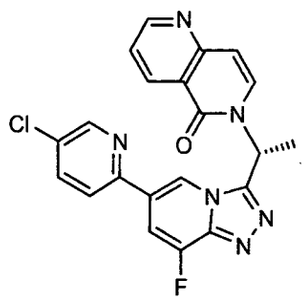
b. 5–(5–cloropiridin–2–il)–2,3–difluorpiridina.

A un recipiente de presión se agregó 2–bromo–5–cloropiridina (3.0 g, 16 mmol), carbonato de cesio (15 g, 47 mmol), complejo diclorometano de dicloruro de 1,1'–bis (difenilfosfino)ferroceno–paladio(ii) (2.5 g, 3.1 mmol), y 2,3–difluor–5–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)piridina (4.5 g, 19 mmol) en 1,4–dioxano (120 mL) y agua (22 mL). La mezcla se inundó con argón, se selló y se agitó a 90°C por tres horas. La mezcla se concentró, se diluyó con diclorometano y se lavó con agua. Se concentraron los extractos orgánicos y se purificaron mediante MPLC (eluido con 0–10% de metanol en diclorometano) para proporcionar 5–(5–cloropiridin–2–il)–2,3–difluorpiridina en forma de un sólido amarillo (2.4 g, 68%). EM m/z = 227.2 $[M+1]^+$. Calc. para $C_{10}H_5ClF_2N_2$: 226.6.



c. 1–(5–(5–cloropiridin–2–il)–3–fluorpiridin–2–il)hidrazina.

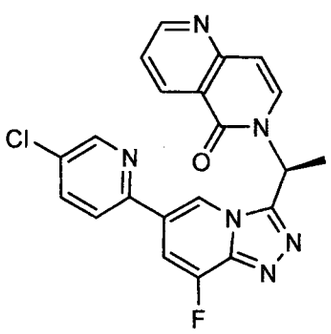
A una solución de 5–(5–cloropiridin–2–il)–2,3–difluorpiridina (2.4 g, 11 mmol) en IPA (35 mL, 0.3 M) a temperatura ambiente se agregó hidrazina (4 mL, 127 mmol). La mezcla de reacción se agitó a 60°C durante 2 h, momento en el cual la reacción se enfrió a temperatura ambiente y se concentró al vacío. El material concentrado se suspendió en $NaHCO_3$ saturado y se filtró para obtener el producto en forma de un sólido blanco esponjoso. El material se re–suspendió en agua (30 mL), y se filtró para obtener 1–(5–(5–cloropiridin–2–il)–3–fluorpiridin–2–il)hidrazina (2.1 g, 83% de rendimiento). EM m/z = 239.2 $[M+1]^+$. Calc. para $C_{10}H_8ClFN_4$: 238.6.



2. <u>(R)–6–(1–(6–(5–cloropiridin–2–il)–8–fluor–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona</u>

Preparado de acuerdo con el Método General N. Separación quiral mediante SFC preparativa (ChiralCel® OD–H (20 x 150 mm 5m), 30% de MeOH 0.2% de DEA, 70 mL/min y sistema de retropresión de 100 bares (t_r: 4.0min.). En base a datos cristalográficos previos y potencia registrada para compuestos relacionados en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *R*.

EM m/z = 420.8 $[M+1]^+$. Calc. para $C_{21}H_{14}ClFN_6O$: 420.8. 1H RMN (400 MHz, DMSO–d_6) δ ppm 2,01 (d, *J*=7,04 Hz, 3 H) 6,78 (d, *J*=7,82 Hz, 1 H) 7,03 (d, *J*=6,94 Hz, 1 H) 7,54 (dd, *J*=8,07, 4,55 Hz, 1 H) 7,78 (d, *J*=7,82 Hz, 1 H) 7,97 – 8,09 (m, 2 H) 8,16 (dd, *J*=8,56, 2,49 Hz, 1 H) 8,61 (dd, *J*=7,97, 1,71 Hz, 1 H) 8,70 – 8,78 (m, 1 H) 8,92 (dd, *J*=4,55, 1,81 Hz, 1 H) 9,03 (d, 1 H).

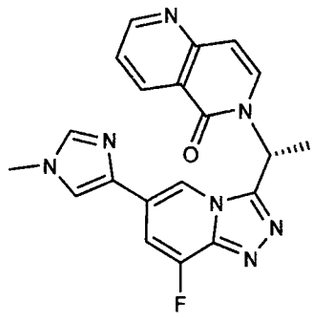


<u>Ejemplo 506</u>

<u>(S)–6–(1–(6–(5–cloropiridin–2–il)–8–fluor–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona</u>

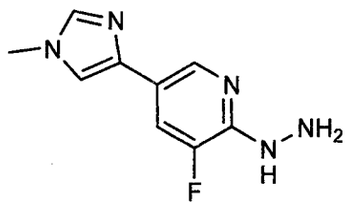
Preparado del mismo modo general tal como ha sido previamente descrito para el Ejemplo 505 usando el Método General N. La separación quiral mediante SFC preparativa

(ChiralCel® OD–H (20 x 150 mm 5m), 30% MeOH 0.2% DEA, 70 mL/min y sistema de retropresión de 100bares (t_r: 5.8 min.). En base a datos cristalográficos previos y potencia registrada para compuestos relacionados en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *S*. EM m/z = 420.8 $[M+1]^+$. Calc. para $C_{21}H_{14}ClFN_6O$: 420.8.



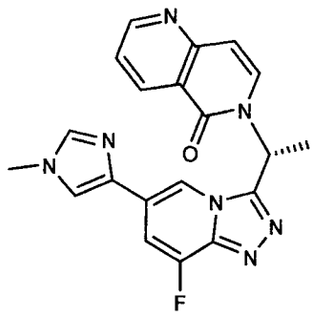
Ejemplo 507

***(R)*–6–(1–(8–fluor–6–(1–metil–1H–imidazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona**



1. 1–(3–fluor–5–(1–metil–1H–imidazol–4–il)piridin–2–il)hidrazina

Preparado del mismo modo general que ha sido previamente descrito para 1–(5–(5–cloropiridin–2–il)–3–fluorpiridin–2–il)hidrazina.



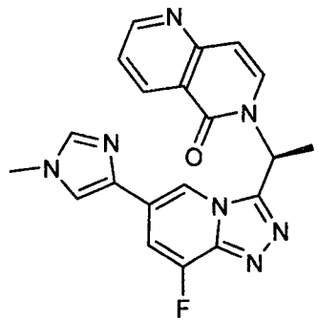
2. *(R)*–6–(1–(8–fluor–6–(1–metil–1H–imidazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona.

Preparado de acuerdo con el Método General N. Separación quiral mediante SFC preparativa (ChiralPak® AD–H (20 x 250 mm 5m), 40% MeOH 0.2% DEA, 70 mL/min y sistema de retropresión de 100bares (t_r 4.1mins).

En base a datos cristalográficos previos y potencia registrada para compuestos relacionados en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *R*. EM m/z = 389.8 $[M+1]^+$. Calc. para $C_{20}H_{16}FN_7O$: 389.4. 1H RMN (400 MHz, DMSO–d_6) δ ppm 1.97 (d, *J*=6.94 Hz, 3 H) 3.68 (s, 3 H) 6.75 (d, *J*=7.73 Hz, 1 H) 6.94 (d, *J*=6.85 Hz, 1 H) 7.52 –

000397

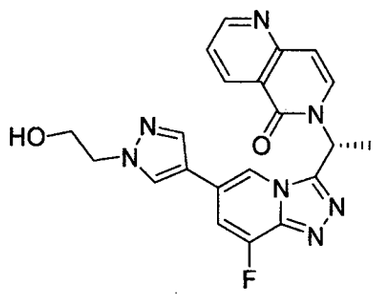
7.59 (m, 1 H) 7.64 (dd, *J*=7.78, 0.54 Hz, 1 H) 7.69 – 7.75 (m, 3 H) 8.46 (s, 1 H) 8.63 (dt, *J*=8.12, 0.88 Hz, 1 H) 8.90 – 8.94 (m, 1 H)



Ejemplo 508

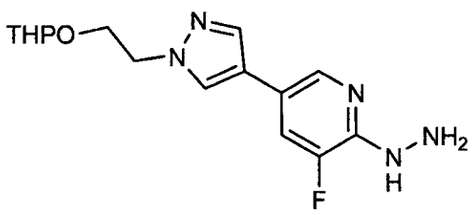
(S)–6–(1–(8–fluor–6–(1–metil–1H–imidazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona

Preparado del mismo modo general que ha sido descrito previamente para el Ejemplo 507 usando el Método General N. La separación quiral mediante SFC preparativa (ChiralPak® AD–H (20 x 250 mm 5m), 40% MeOH 0.2% DEA, 70 mL/min y sistema de retropresión de 100bares (t_r: 5.9 mins). En base a datos cristalográficos previos y potencia registrada para compuestos relacionados en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *S*. EM m/z = 389.8 $[M+1]^+$. Calc. para $C_{20}H_{16}FN_7O$: 389.4 .

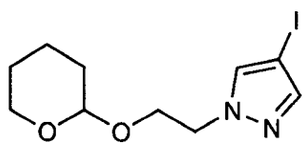


Ejemplo 509

(R)–6–(1–(8–fluor–6–(1–(2–hidroxietil)–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona

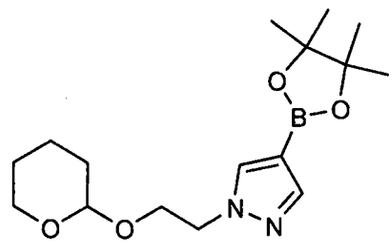


1. 1–(3–fluor–5–(1–(2–(tetrahidro–2H–piran–2–iloxi)etil)–1H–pirazol–4–il)piridin–2–il)hidrazina



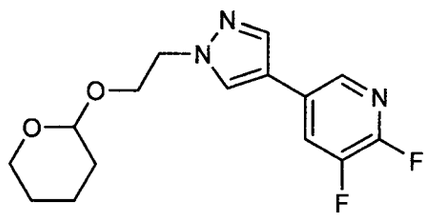
a. 4–yodo–1–(2–(tetrahidro–2H–piran–2–iloxi)etil)–1H–pirazol.

Una mezcla de carbonato de cesio (20.7 g, 63.4 mmol) y 4–yodopirazol (10.00 g, 51.6 mmol) en DMF (100 mL) se dejó agitar durante 10 min. A la mezcla se agregó 2–(2–bromoetoxi)tetrahidro–2h–piran (9.98 ml, 63.4 mmol) y se calentó a 80°C durante la noche. La mezcla se diluyó con agua y se extrajo con EtOAc (3 x 50 mL), y subsiguientemente se lavó con agua (2 x 50 mL) y salmuera, se secó sobre sulfato de sodio, y se filtró. La mezcla cruda se evaporó sobre gel de sílice y se purificó mediante MPLC (0% a 50%; EtOAc en hexanos). Se aisló 4–yodo–1–(2–(tetrahidro–2H–piran–2–iloxi)etil)–1H–pirazol (15.3 g, 92%) en forma de un aceite claro. EM m/z = 323.0 $[M+1]^+$. Calc. para $C_{10}H_{15}IN_2$: 322.1.



b. <u>1–(2–(tetrahidro–2H–piran–2–iloxi)etil)–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol.</u>

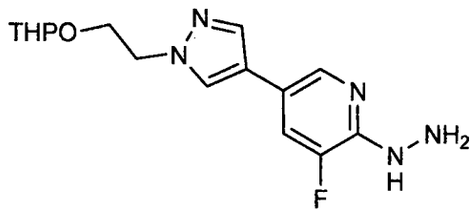
A una solución de 4–yodo–1–(2–(tetrahidro–2H–piran–2–iloxi)etil)–1H–pirazol (8.7 g, 27.1 mmol) en THF (75 mL) a 0°C bajo argón se agregó cloruro de isopropilmagnesio como una solución 2 M en THF (27.1 mL, 54.3 mmol). La reacción se agitó durante 1 h a 0°C. A esto se agregó 2–metoxi–4,4,5,5–tetrametil–1,3,2–dioxaborolano (6.7 mL, 40.7 mmol) y la mezcla se agitó durante 1 h adicional mientras se dejaba calentar a temperatura ambiente. Esto se trató luego con una solución de cloruro de amonio saturado (100 mL) y el producto se extrajo con EtOAc (3 x 100 mL). Los orgánicos cobminados se lavaron con salmuera, se secaron sobre sulfato de sodio y se filtraron. El material crudo se concentró bajo presión reducida para proporcionar 7.1 g (81%) de 1–(2–(tetrahidro–2H–piran–2–iloxi)etil)–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol en forma de un aceite amarillo claro. El material se extrajo en crudo hasta la etapa siguiente. EM m/z = 323.2 $[M+1]^+$. Calc. para $C_{16}H_{27}BN_2O_4$: 322.2



c. <u>2,3–difluor–5–(1–(2–(tetrahidro–2H–piran–2–iloxi)etil)–1H–pirazol–4–il)piridina.</u>

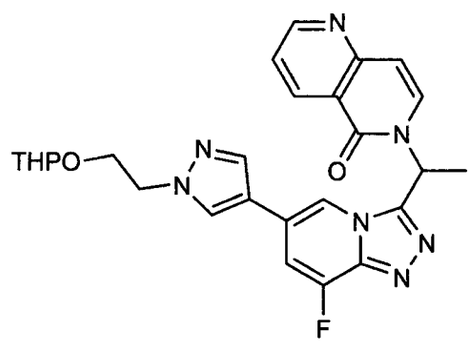
Un tubo de 48 mL cargado con 1–(2–(tetrahidro–2H–piran–2–iloxi)etil)–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol (6.4 g, 19.9 mmol), 5–cloro–2,3–difluorpiridina (1.7 mL, 16.6 mmol), X–fos (1.6 g, 3.3 mmol), fosfato de potasio (3.5 g, 16.6

mmol), $PdOAc_2$ (0.4 g, 1.7 mmol), 1,4–dioxano (50 mL), y agua (5.0 mL), se inundó con argón, se selló, luego se calentó a 100°C durante 3 horas. La mezcla se concentró y purificó mediante MPLC, eluyendo con 2.5% de MeOH/DCM durante 40 minutos para proporcionar 2,3–difluor–5–(1–(2–(tetrahidro–2H–piran–2–iloxi)etil)–1H–pirazol–4–il)piridina en forma de un aceite claro que solidificó por reposo a temperatura ambiente (3.1 g, 60.5% de rendimiento). La LC/MS mostró el producto en forma de un alcohol libre. Sin embargo, la estructura del producto es tal como se ha graficado anteriormente. EM m/z = 226.2 $[M+1]^+$. Calc. para $C_{15}H_{17}F_2N_3O_2$: 309.3



d. <u>1–(3–fluor–5–(1–(2–(tetrahidro–2H–piran–2–iloxi)etil)–1H–pirazol–4–il)piridin–2–il)hidrazina.</u>

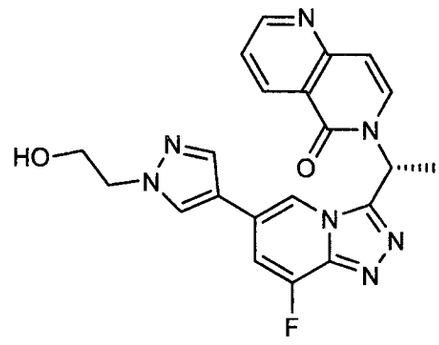
A una solución de 2,3–difluor–5–(1–(2–(tetrahidro–2H–piran–2–iloxi)etil)–1H–pirazol–4–il)piridina (3.0 g, 9.5 mmol) en IPA (47.7 mL, 0.2 M) a temperatura ambiente se agregó hidrazina (3.6 mL, 114.4 mmol). La mezcla de reacción se agitó a 60 °C durante 2 h, momento en el cual la reacción se enfrió a temperatura ambiente y se concentró al vacío. El material concentrado se suspendió en una solución $NaHCO_3$ saturada y se filtró hasta obtener el producto en forma de un sólido blanco esponjoso. El mateiral se re–suspendió en agua (30 mL), se filtró y se secó bajo alto vacío para obtener 1–(3–fluor–5–(1–(2–(tetrahidro–2H–piran–2–iloxi)etil)–1H–pirazol–4–il)piridin–2–il)hidrazina (2.2 g, 72% de rendimiento) en forma de un sólido naranja. MS m/z = 322.2 $[M+1]^+$. Calc. para $C_{15}H_{20}FN_5O_2$: 321.4.



2. <u>6–(1–(8–fluor–6–(1–(2–(tetrahidro–2H–piran–2–iloxi)etil)–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona.</u>

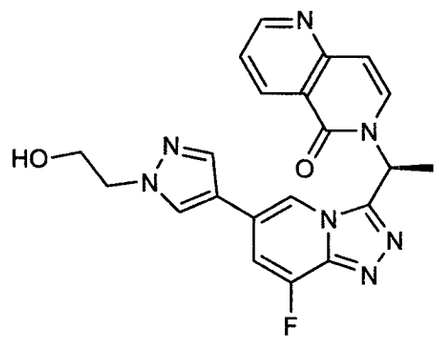
El compuesto THP–protegido se sintetizó de acuerdo con el Método General N.

000400



3. **(R)–6–(1–(8–fluor–6–(1–(2–hidroxyetil)–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona.**

Se disolvió 6–(1–(8–fluor–6–(1–(2–(tetrahidro–2H–piran–2–iloxi)etil)–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona (0.5 g, 1.0 mmol) en EtOH (12 mL) y a la solución se agregó ácido clorhídrido (2.0 mL, 4.0 mmol). La reacción se agitó a temperatura ambiente durante 3 horas, momento en el cual se diluyó con 5 mL de agua y 10 mL de una solución de bicarbonato de sodio acuoso saturado. El producto se extrajo con DCM (30mL) tres veces. Se combinaron las capas orgánicas, se secaron sobre sulfato de sodio y se concentraron hasta sequedad para proporcionar 6–(1–(8–fluor–6–(1–(2–hidroxietil)–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona (0.4 g, 96%).Separación quiral mediante SFC preparativa (Chiralpak® AD–H (20 x 150 m, 5µm), 35% EtOH, 65% CO2, 0.2 DEA; sistema de presión de 100 bares, 50 mL/min; t_r :4.4 min). En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *R*. M/Z = 420.2 [M+H], calc 419.15 for $C_{21}H_{18}FN_7O_2$. ^{1}H RMN (400 MHz, CLOROFORMO–*d*) δ ppm 2.17 (d, *J*=7.14 Hz, 3 H) 4.00 – 4.09 (m, 2 H) 4.29 – 4.33 (m, 2 H) 6.91 (d, *J*=7.92 Hz, 1 H) 7.04 (dd, 1 H) 7.10 (dd, *J*=10.56, 1.17 Hz, 1 H) 7.51 (dd, *J*=8.17, 4.74 Hz, 1 H) 7.59 (d, *J*=7.82 Hz, 1 H) 7.72 (d, *J*=0.68 Hz, 1 H) 7.76 (d, *J*=0.78 Hz, 1 H) 8.34 (d, *J*=1.17 Hz, 1 H) 8.84 (dd, *J*=8.07, 1.22 Hz, 1 H) 8.92 (dd, *J*=4.74, 1.81 Hz, 1 H)

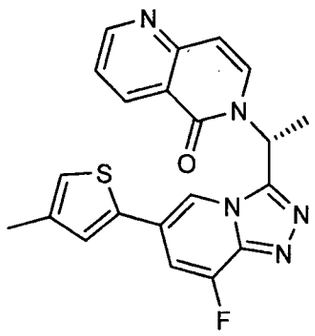


Ejemplo 510

(S)–6–(1–(8–fluor–6–(1–(2–hidroxietil)–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona

Preparada del mismo modo general que ha sido descrito para el Ejemplo 509 usando el Método General N. La separación quiral mediante SFC preparativa (Chiralpak® AD–H (20 x 150 m, 5µm), 35% EtOH, 65% CO2, 0.2 DEA; sistema de presión 100 bares, 50 mL/min; t_r

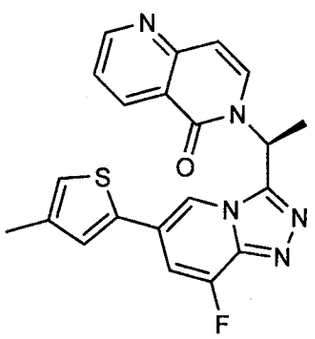
:6.0 min). En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *S*. M/Z = 420.2 [M+H], calc 419.15 para $C_{21}H_{18}FN_7O_2$.



Ejemplo 511

(R)–6–(1–(8–fluor–6–(4–metiltiofen–2–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona

El compuesto se preparó de acuerdo con el Método General N. La hidrazina se preparó de manera análoga a 1–(3–fluor–5–(1–metil–1H–pirazol–4–il)piridin–2–il)hidrazina. La separación quiral mediante SFC preparativa (Chiralpak® AD–H (20 x 250 mm 5m), 40% MeOH 0.2% DEA, 80 mL/min y sistema de retropresión de 100 bares, tiempo de retención = 5.1 minutos. En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *R*. MS m/z = 406.0 $[M+1]^+$. Calc. para $C_{21}H_{16}FN_5OS$: 405.5.

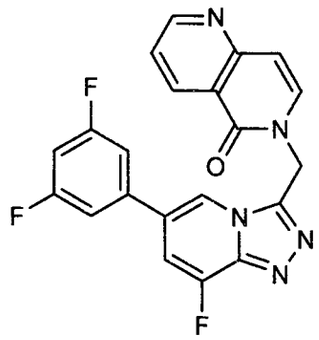


Ejemplo 512

(S)–6–(1–(8–fluor–6–(4–metiltiofen–2–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona

El compuesto se preparó de acuerdo con el Método General N. La hidrazina se preparó de manera análoga a 1–(3–fluor–5–(1–metil–1H–pirazol–4–il)piridin–2–il)hidrazina. La separación quiral mediante SFC preparativa (Chiralpak® AD–H (20 x 250 mm 5m), 40% MeOH 0.2% DEA, 80 mL/min y sistema de retropresión de 100 bares, tiempo de retención = 6.1 minutos. En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *S*. MS m/z = 406.0 $[M+1]^+$. Calc. para $C_{21}H_{16}FN_5OS$: 405.5.

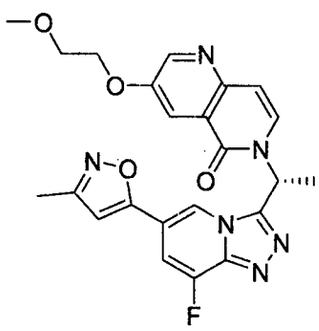
000402



Ejemplo 513

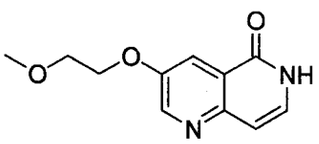
6–((6–(3,5–difluorfenil)–8–fluor–[1,2,4]triazol[4,3–a]piridin–3–il)metil)–1,6–naftiridin–5(6H)–ona

Se sintetizó el compuesto del título del mismo modo general tal como se ha descrito previamente para el Ejemplo 503 usando 1–(5–(3,5–difluorfenil)–3–fluorpiridin–2–il)hidrazina. MS *m/z* = 408.2 [M+H], calc 407.4para $C_{21}H_{12}F3N_5O$.

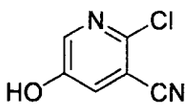


Ejemplo 514

(R)–6–(1–(8–fluor–6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–3–((2–metoxietoxi)metil)–1,6–naftiridin–5(6H)–ona



1. **3–(2–metoxietoxi)–1,6–naftiridin–5(6H)–ona**

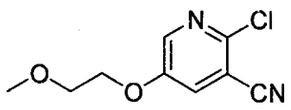


a. 2–cloro–5–hidroxinicotinonitrilo.

En un tubo sellado de 300 mL bajo N_2 se disolvió acetato de potasio (20 g, 207 mmol), 5–bromo–2–cloronicotinonitrilo (15 g, 69 mmol), 4,4,5,5–tetrametil–2–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1,3,2–dioxaborolano (21 g, 83 mmol) y Aducto $PdCl_2$(dppf)–CH_2Cl_2 (1.7 g, 2.1 mmol) en 150 mL de p–dioxano luego se agitó y calentó a 85

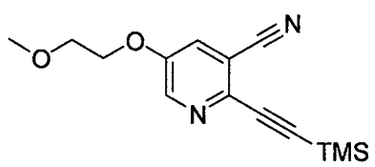
000403

°C durante 2 hrs. Después del completamiento, la reacción se enfrió a 0 °C y se trató con peróxido de hidrógeno (31.5%) (22 ml, 207 mmol) luego se agitó a temperatura ambiente durante 1 hr. La mezcla de reacción se diluyó con DCM (100 mL) luego se agregó agua (200 mL). La fase acuosa se extrajo 3 veces con DCM (100 mL), luego la capa orgánica se lavó con una solución tiosulfato de sodio saturado (300 mL). Los orgánicos luego se secaron sobre Na_2SO_4, se filtraron y concentraron bajo presión reducida. El 2–cloro–5–hidroxinicotinonitrilo crudo (7.5 g, 70% de rendimiento) se dejó crudo para la etapa siguiente.



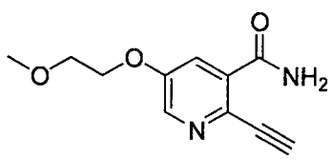
b. <u>2–cloro–5–(2–metoxietoxi)nicotinonitrilo.</u>

En un frasco de fondo redondo de 100 mL bajo N_2 se disolvieron trifenilfosfina (19 g, 73 mmol), 2–cloro–5–hidroxinicotinonitrilo (7.5 g, 49 mmol), y 2–metoxietanol (5.7 ml, 73 mmol) en THF (130 mL) seguido de una lenta adición de DEAD (27 ml, 68 mmol), y luego se agitó a temperatura ambiente. Después de 2 hs la reacción mostró la conversión completa del compuesto deseado. La mezcla cruda se purificó mediante MPLC eluyendo con 100% de DCM a 90% DCM:10% MeOH para proporcionar 2–cloro–5–(2–metoxietoxi)nicotinonitrilo (6.46 g, 63% de rendimiento) en forma de un sólido de color castaño.



c. <u>5–(2–metoxietoxi)–2–(2–(trimetilsilil)etinil)nicotinonitrilo.</u>

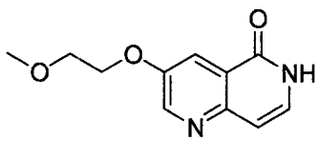
En un tubo sellado, se disolvieron diclorobis(trifenil–fosfina)paladio (ii) (0.17 g, 0.24 mmol), trimetilacetileno (2.0 ml, 14 mmol), 2–cloro–5–(2–metoxietoxi)nicotinonitrilo (2.50 g, 12 mmol), y yoduro de cobre(I) (0.11 g, 0.59 mmol) en acetonitrilo (0.5 M, 24 mL) y a la reacción se agregó trietilamina (3.3 ml, 24 mmol). La mezcla de reacción se calentó a 85 °C durante 12 hrs. La reacción se concentró y purificó directamente a través de MPLC, eluyendo con 0–100% de EtOAc en hexanos para proporcionar 5–(2–metoxietoxi)–2–(2–(trimetilsilil)etinil)nicotinonitrilo (1.9 g, 59% de rendimiento).



d. <u>2–etinil–5–(2–metoxietoxi)nicotinamida.</u>

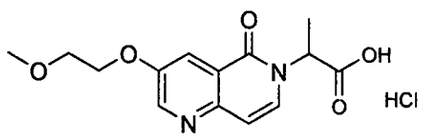
Se disolvió 5–(2–metoxietoxi)–2–(2–(trimetilsilil)etinil)nicotinonitrilo (4.23 g, 15 mmol) en acetona (60 mL). A la solución se agregó por goteo carbonato de sodio 3 M (62 ml, 185

mmol) e hidrógeno de peróxido (31 ml, 308 mmol), y se agitó a temperatura ambiente durante 4 h. Después de completarse, la reacción se enfrió a 0 °C y a esto se agregó lentamente tiosulfato de sodio (200 mL) con agitamiento. La capa acuosa se extrajo con DCM (x3, 200 mL), y los orgánicos combinados se concentraron y purificaron mediante MPLC eluyendo con 100% DCM a 90% DCM:10% MeOH:1% NH_4OH para proporcionar 2–etinil–5–(2–metoxietoxi)nicotinamida (2.0 g, 59% de rendimiento).



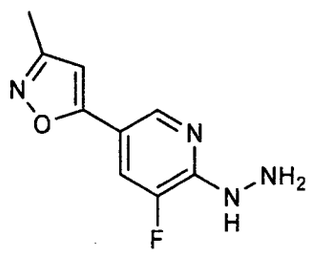
e. 3–(2–metoxietoxi)–1,6–naftiridin–5(6H)–ona.

Se disolvió 2–etinil–5–(2–metoxietoxi)nicotinamida (2.04 g, 9 mmol) en dimetilamina 1M (en metanol o etanol) (46 ml, 93 mmol). La reacción se calentó a 85 °C durante 12 hrs. La reacción se concentró y purificó mediante MPLC eluyendo con 100% de DCM a 90% de DCM:10% de MeOH:1% de NH_4OH para proporcionar 3–(2–metoxietoxi)–1,6–naftiridin–5(6H)–ona (0.900 g, 44% de rendimiento).

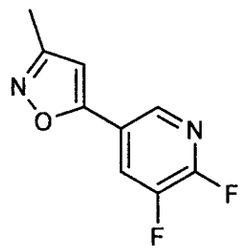


2. Clorhidrato de ácido2–(3–(2–metoxietoxi)–5–oxo–1,6–naftiridin–6(5H)–il)propanoico.

Se sintetizó el compuesto a partir de 3–(2–metoxietoxi)–1,6–naftiridin–5(6H)–ona similar a la síntesis de clorhidrato de ácido 2–(5–oxo–1,6–naftiridin–6(5H)–il)propanoico en el Método N (Ejemplo 503).



3. 1–(3–fluor–5–(3–metilisoxazol–5–il)piridin–2–il)hidrazina



a. 2,3–difluor–5–(3–metilisoxazol–5–il)piridina.

Organizacion y Digitalizacion CSA Ltd

Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD
PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 10-98383

54. **TÍTULO** 3/3

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE**

DOMICILIO

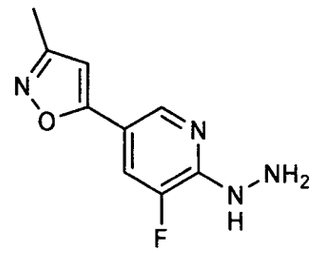
74. **APODERADO**

22. **BOGOTÁ, D.C.,**

(FORMA P-10)

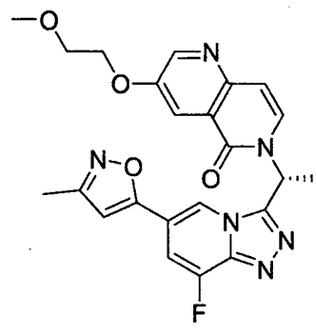
000405

Un recipiente de presión de 330 mL se cargó con 5–cloro–2,3–difluorpiridina (5.00 g, 33.4 mmol), 3–metil–5–(tributilestanilo)isoxazol (14.9 g, 40.1 mmol), Xfos (2.23 g, 4.68 mmol), $PdOAc_2$ (0.526 g, 2.34 mmol), y 1,4–dioxano (167 ml, 33.4 mmol), se inundó con argón, se selló, luego se calentó a 100°C durante 16 horas. La mezcla se concentró, el aceite negro se absorbió sobre gel de sílice y se purificó mediante MPLC, eluyendo con 20% de EtOAc en hexanos isocráticos para proporcionar un sólido naranja; esto se trituró con hexanos para proporcionar 2,3–difluor–5–(3–metilisoxazol–5–il)piridina (3.6278 g, 55.3% de rendimiento) en forma de un sólido amarillo.



b. <u>1–(3–fluor–5–(3–metilisoxazol–5–il)piridin–2–il)hidrazina.</u>

Un recipiente de presión de 330 mL se cargó con 4,5–difluor–2–(3–metilisoxazol–5–il)piridina (3.6695 g, 18.7 mmol), hidrazina (3.53 ml, 112 mmol), e IPA (93.5 ml, 18.7 mmol), se selló, luego se calentó a 65°C durante 3 horas. La mezcla se filtró, el sólido se trituró con una solución de $NaHCO_3$ acuosa y se lavó con agua (2 x 20 mL). Se aisló 1–(4–fluor–6–(3–metilisoxazol–5–il)piridin–3–il)hidrazina (3.5668 g, 91.6% de rendimiento) en forma de un polvo blanco.

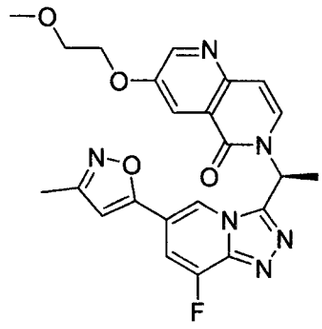


4. <u>(R)–6–(1–(8–fluor–6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–3–((2–metoxietoxi)metil)–1,6–naftiridin–5(6H)–ona.</u>

Usando 3–(2–metoxietoxi)–1,6–naftiridin–5(6H)–ona y 1–(3–fluor–5–(3–metilisoxazol–5–il)piridin–2–il)hidrazina, se sintetizó el compuesto del título usando el Método General N para proporcionar (R)–6–(1–(8–fluor–6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–3–((2–metoxietoxi)metil)–1,6–naftiridin–5(6H)–ona. La separación quiral mediante SFC preparativa (Chiralpak® AD–H (20 x 150 mm, 5µm), 25% MeOH, 75% CO_2, 0.2% DEA; sistema de presión de 100 bares; 75 mL/min; t_r 5.78 min). En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *R*. M/Z = 465.2 [M+H], calc 464.16 para $C_{23}H_{21}FN_6O_4$. ^1H RMN (400 MHz, CLOROFORMO–*d*) δ ppm 2.17 (d, *J*=7.14 Hz,

CC0406

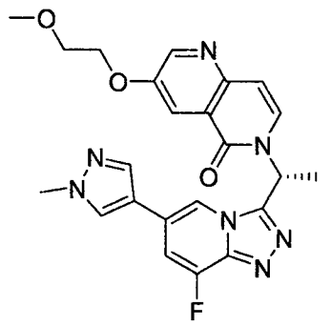
3 H) 2.39 (s, 3 H) 3.49 (s, 3 H) 3.78 – 3.94 (m, 2 H) 4.23 – 4.43 (m, 2 H) 6.43 (s, 1 H) 6.85 (d, *J*=7.82 Hz, 1 H) 7.08 (q, *J*=7.11 Hz, 1 H) 7.29 (dd, *J*=10.07, 1.17 Hz, 1 H) 7.43 (d, *J*=7.82 Hz, 1 H) 8.17 (d, *J*=2.93 Hz, 1 H) 8.58 – 8.81 (m, 2 H).



Ejemplo 515

(S)–6–(1–(8–fluor–6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–3–((2–metoxietoxi)metil)–1,6–naftiridin–5(6H)–ona

Se sintetizó del mismo modo general tal como se ha descrito previamente para el Ejemplo 509 usando el Método General N. La separación quiral mediante SFC preparativa (Chiralpak® AD–H (20 x 150 mm, 5µm), 25% MeOH, 75% CO_2, 0.2% DEA; sistema de presión de 100 bares; 75 mL/min; t_r 4.75min). En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *S*. M/Z = 465.2 [M+H], calc 464.16 para $C_{23}H_{21}FN_6O_4$

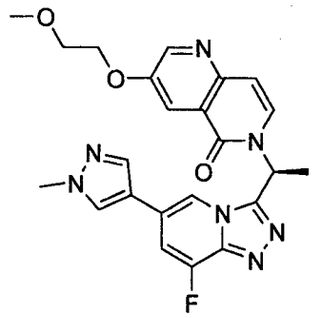


Ejemplo 516

(*R*)–6–(1–(8–fluor–6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–3–(2–metoxietoxi)–1,6–naftiridin–5(6H)–ona

Se sintetizó el compuesto del título usando el Método General N. La separación quieral mediante SFC preparativa Chiralpak® AS–H (20 x 150 mm, 5 µm), 20% iPrOH, 80% CO_2; sistema de presión de 100 bares, 50 mL/min; t_r 1.67 min). En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *R*. M/Z = 464.2 [M+H], calc 463.18 para $C_{23}H_{22}FN_7O_3$. ^{1}H RMN (400 MHz, CLOROFORMO–*d*) δ ppm 2.15 (d, *J*=7.14 Hz, 3 H) 3.49 (s, 3 H) 3.80 – 3.90 (m, 2 H) 3.97 (s, 3 H) 4.27 – 4.39 (m, 2 H) 6.83

(d, *J*=7.73 Hz, 1 H) 7.00 – 7.13 (m, 2 H) 7.42 (d, *J*=7.82 Hz, 1 H) 7.61 (s, 1 H) 7.72 (s, 1 H) 8.15 (d, *J*=2.84 Hz, 1 H) 8.31 (s, 1 H) 8.72 (d, *J*=3.03 Hz, 1 H).

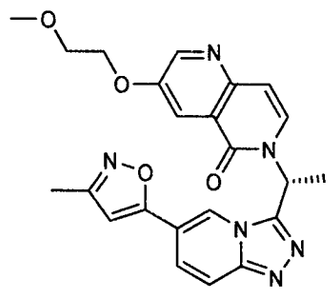


000408

Ejemplo 517

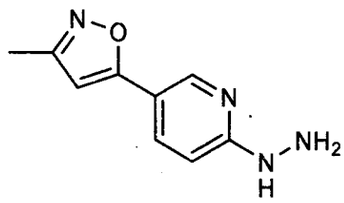
(S)–6–(1–(8–fluor–6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–3–(2–metoxietoxi)–1,6–naftiridin–5(6H)–ona

Se sintetizó el compuesto del mismo modo general tal como se ha descrito para el Ejemplo 516 de acuerdo con el Método General N. La separación quiral mediante SFC preparativa (Chiralpak® AS–H (20 x 150 mm, 5 µm), 20% iPrOH, 80% CO_2; sistema de presión de 100 bares, 50 mL/min; t_r : 2.02 min). En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *S*. M/Z = 464.2 [M+H], calc 463.18 para $C_{23}H_{22}FN_7O_3$.

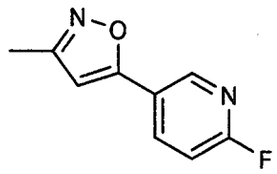


Ejemplo 518

(R)–3–(2–metoxietoxi)–6–(1–(6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona

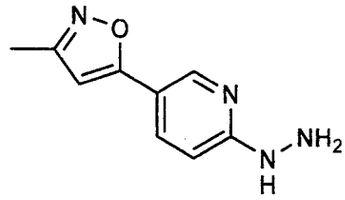


1. **1–(5–(3–metilisoxazol–5–il)piridin–2–il)hidrazina**



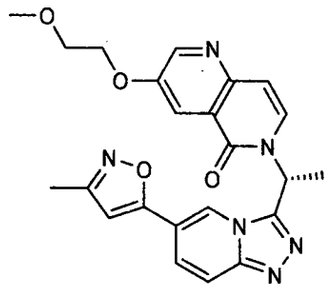
a. **2–fluor–5–(3–metilisoxazol–5–il)piridina.**

Un tubo de 48 mL se cargó con 5–bromo–2–fluorpiridina (1.17 ml, 11.4 mmol), 3–metil–5–(tributilestanilo)isoxazol (5.29 g, 14.2 mmol), ciclohexilo JohnPhos (0.398 g, 1.14 mmol), Pd_2dba_3 (0.312 g, 0.341 mmol), y DMF (12.4 ml, 159 mmol), se inundó con argón, se selló, luego se calentó a 90°C durante 16 horas. Se agregaron 3–metil–5–(tributilestanilo)isoxazol adicional (5.29 g, 14.2 mmol) (2 g), Pd_2dba_3 (0.312 g, 0.341 mmol), y ciclohexilo JohnPhos (0.398 g, 1.14 mmol) y la mezcla se agitó a 90°C durante 10 horas más. Esto se concentró y el residuo marrón se purificó mediante MPLC, eluyendo con 15% de acetato de etilo en hexanos isocráticos. Se aisló 2–fluor–5–(3–metilisoxazol–5–il)piridina (1.1029 g, 54.5% de rendimiento) en forma de un sólido amarillo claro.



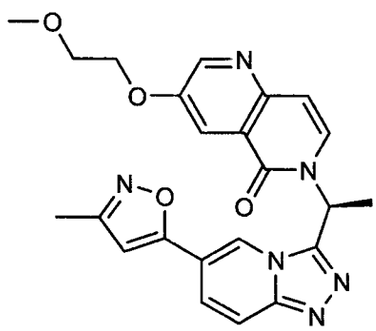
b. 1–(5–(3–metilisoxazol–5–il)piridin–2–il)hidrazina.

Se sintetizó la hidrazina de manera similar a 1–(3–fluor–5–(3–metilisoxazol–5–il)piridin–2–il)hidrazina (excepto que se calentó a 60°C) (84.2% de rendimiento).



2. (R)–3–(2–metoxietoxi)–6–(1–(6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona.

Se sintetizó el compuesto del título de acuerdo con el Método General N. La separación quiral mediante SFC preparativa (Chiralcel OH–H (2 cm ID x 25 cm longitud, 5 µ), 35 – 65% MeOH 0.2% DEA en CO_2, 80 mL/min; t_r = 4.95 min). En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *R*. EM m/z = 447.2 $[M+1]^+$. Calc. para $C_{23}H_{22}N_6O_4$: 446.5. 1H RMN (400 MHz, DMSO–d_6) δ ppm 8.89 (t, 1 H), 8.68 (d, *J*=3.03 Hz, 1 H), 8.01 – 8.02 (m, 1 H), 7.96 (dd, *J*=9.59, 1.08 Hz, 1 H), 7.79 (dd, *J*=9.54, 1.61 Hz, 1 H), 7.60 (d, *J*=7.82 Hz, 1 H), 7.01 – 7.05 (m, 1 H), 6.99 (s, 1 H), 6.75 (d, *J*=7.63 Hz, 1 H), 4.29 – 4.32 (m, 2 H), 3.70 – 3.73 (m, 2 H), 3.32 (s, 3 H), 2.31 (s, 3 H), 1.99 (d, *J*=7.04 Hz, 3 H).



Ejemplo 519

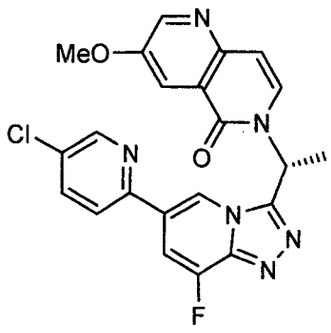
(S)–3–(2–metoxietoxi)–6–(1–(6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona

El compuesto se sintetizó del mismo modo general que ha sido descrito para el Ejemplo 518 de acuerdo con el Método General N. La separación quiral mediante SFC

CC0410

preparativa (Chiralcel OH–H (2 cm ID x 25 cm de longitud, 5 µ), 35 – 65% MeOH 0.2% DEA en CO_2, 80 mL/min; t_r = 7.05 min). En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *S*. EM m/z = 447.2 $[M+1]^+$. Calc. para $C_{23}H_{22}N_6O_4$: 446.5.

5

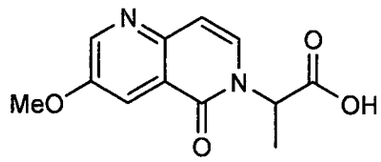


CC0411

Ejemplo 520

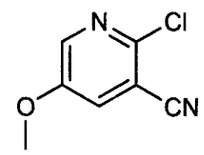
***(R)*–6–(1–(6–(5–cloropiridin–2–il)–8–fluor–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–3–metoxi–1,6–naftiridin–5(6H)–ona**

HCl



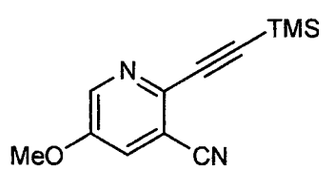
1. Clorhidrato de ácido 2–(3–metoxi–5–oxo–1,6–naftiridin–6(5H)–il)propanoico

Todas las etapas para la síntesis de este ácido son las mismas que para clorhidrato de ácido 2–(3–(2–metoxietoxi)–5–oxo–1,6–naftiridin–6(5H)–il)propanoico (Ejemplo 514) con las siguientes excepciones:



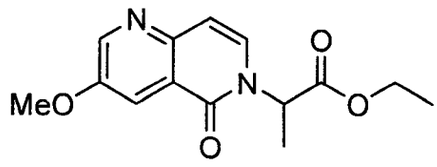
a. 2–cloro–5–metoxinicotinonitrilo.

Se colocó 2–cloro–5–hidroxinicotinonitrilo (18.0 g, 116 mmol) en un tubo resistente a presión re–sellable y suspendido en DMF (146 ml, 116 mmol). A esto se agregó carbonato de cesio (76 g, 233 mmol) y yoduro de metilo (36 mL, 582 mmol). El recipiente se selló y la mezcla se agitó a 65 ^{0}C durante 17 h. La mezcla de reacción se diluyó con agua (250 mL) y el producto se extrajo con DCM (3 X400mL). Las capas orgánicas se combinaron, se secaron sobre sulfato de sodio y se concentraron para proporcionar 40 g del aceite marrón espeso. Esto se pasó a través de un tapón de sílice para proporcionar 13 g del 85% del material puro. Esto se trituró en 10% de DCM/Hexanos (caliente ~ 40^{0}C) y los sólidos se filtraron, se enjuagaron con hexanos y se secaron para proporcionar 2–cloro–5–metoxinicotinonitrilo en forma de un sólido marrón (10.0 g, 51%). EM m/z = 169[M+1]$^{+}$. Calc. para $C_7H_5ClN_2O$: 168.6.



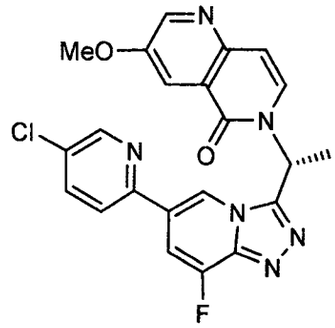
b. 5–metoxi–2–(2–(trimetilsilil)etinil)nicotinonitrilo.

Esta etapa se llevó a cabo a 65°C en vez de 85°C.



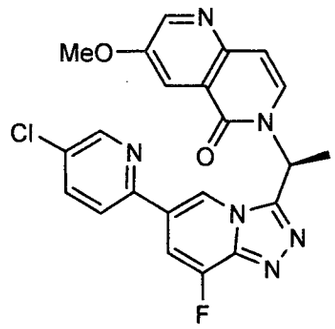
c. 2–(3–metoxi–5–oxo–1,6–naftiridin–6(5H)–il)propanoato de etilo.

Se usó 2–bromopropanoato de etilo en vez de yoduro y la temperatura de reacción fue también inferior (60°C).



2. (R)–6–(1–(6–(5–cloropiridin–2–il)–8–fluor–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–3–metoxi–1,6–naftiridin–5(6H)–ona.

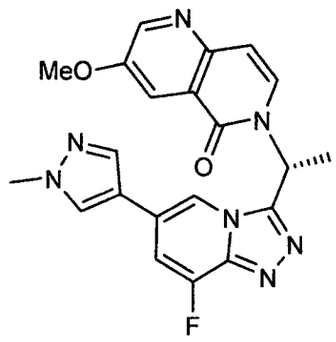
Se sintetizó el compuesto del título de acuerdo con el Método General N. La separación quiral mediante SFC preparativa (ChiralCel® OD–H (20 x 250 mm 5m), 35% MeOH 0.2% DEA, 70 mL/min y sistema de retropresión de 100 bares (t_r: 6.3 mins). En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *R*. EM m/z = 450.8 $[M+1]^+$. Calc. para $C_{22}H_{16}ClFN_6O_2$: 450.8.



Ejemplo 521

(S)–6–(1–(6–(5–cloropiridin–2–il)–8–fluor–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–3–metoxi–1,6–naftiridin–5(6H)–ona

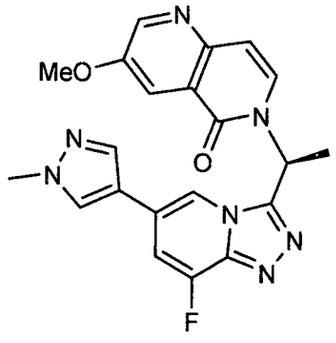
Preparado de acuerdo con el Método General N. La separación quiral mediante SFC preparativa (ChiralCel® OD–H (20 x 250 mm 5m), 35% MeOH 0.2% DEA, 70 mL/min y sistema de retropresión de 100 bares (t_r: 8.0 mins). En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *S*. m/z = 450.8 $[M+1]^+$. Calc. para $C_{22}H_{16}ClFN_6O_2$: 450.8.



Ejemplo 522

***(R)*–6–(1–(8–fluor–6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–3–metoxi–1,6–naftiridin–5(6H)–ona**

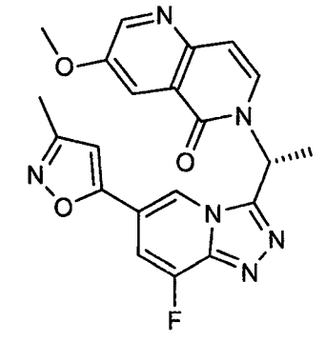
Preparado de acuerdo con el Método General N. La separación quiral mediante SFC (ChiralCel® OD–H (20 x 250 mm 5m), 40% EtOH 0.2% DEA, 70 mL/min y sistema de retropresión de 100 bares (t_r : 5.2 mins). En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *R*. EM m/z = 419.8 $[M+1]^+$. Calc. para $C_{21}H_{18}FN_7O_2$: 419.4.



Ejemplo 523

***(S)*–6–(1–(8–fluor–6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–3–metoxi–1,6–naftiridin–5(6H)–ona**

Preparado de acuerdo con el Método General N. La separación quiral mediante SFC preparativa (ChiralCel® OD–H (20 x 250 mm 5m), 40% EtOH 0.2% DEA, 70 mL/min y sistema de retropresión de 100 bares (t_r : 6.8 mins). En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *S*. EM m/z = 419.8 $[M+1]^+$. Calc. para $C_{21}H_{18}FN_7O_2$: 419.4.

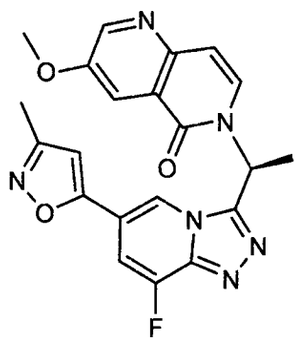


000415

Ejemplo 524

(*R*)–6–(1–(8–fluor–6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–3–metoxi–1,6–naftiridin–5(6H)–ona

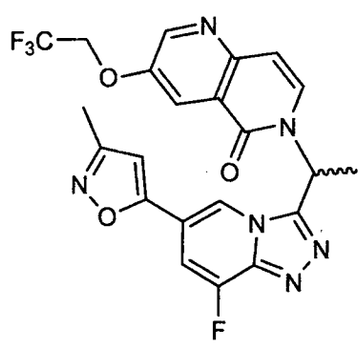
Preparado de acuerdo con el Método General N. Separación quiral mediante SFC preparativa (ChiralPak® AD–H (20 x 250 mm 5m), 40% MeOH 0.2% DEA, 70 mL/min y sistema de retropresión de 100 bares (t_r: 4.7 mins). En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *R*. EM m/z = 420.8 $[M+1]^+$. Calc. para $C_{21}H_{17}FN_6O_3$: 420.4. 1H RMN (400 MHz, DMSO–d_6) δ ppm 2.00 (d, *J*=7.04 Hz, 3 H) 2.31 (s, 3 H) 3.94 (s, 3 H) 6.77 (dd, *J*=7.78, 0.54 Hz, 1 H) 6.94 – 7.05 (m, 2 H) 7.64 (d, *J*=7.82 Hz, 1 H) 7.76 – 7.89 (m, 1 H) 7.98 (dd, *J*=3.08, 0.54 Hz, 1 H) 8.68 (d, *J*=3.03 Hz, 1 H) 8.80 (d, *J*=1.08 Hz, 1 H).



Ejemplo 525

(*S*)–6–(1–(8–fluor–6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–3–metoxi–1,6–naftiridin–5(6H)–ona

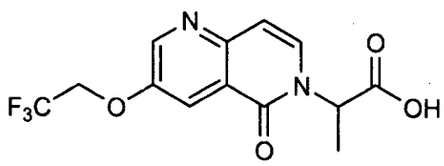
Preparado de acuerdo con el Método General N. Separación quiral mediante SFC preparativa (ChiralPak® AD–H (20 x 250 mm 5m), 40% MeOH 0.2% DEA, 70 mL/min y sistema de retropresión de 100 bares (t_r: 3.9 mins). En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *S*. EM m/z = 420.8 $[M+1]^+$. Calc. para $C_{21}H_{17}FN_6O_3$: 420.4.



Ejemplo 526

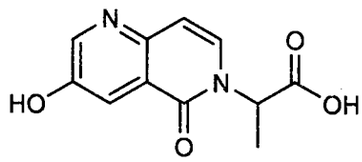
6–(1–(8–fluor–6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–3–(2,2,2–trifluoretoxi)–1,6–naftiridin–5(6H)–ona

HCl



1. **Clorhidrato de ácido 2–(5–oxo–3–(2,2,2–trifluoretoxi)–1,6–naftiridin–6(5H)–il)propanoico**

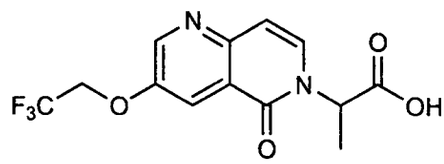
HBr



a. **Bromhidrato de ácido 2–(3–hidroxi–5–oxo–1,6–naftiridin–6(5H)–il)propanoico**

Una botella resistente a presión re–sellable se cargó con 2–(3–metoxi–5–oxo–1,6–naftiridin–6(5H)–il)propanoato de etilo (0.83 g, 3.0 mmol) (Ejemplo 515) **y** HBr conc. (0.16 ml, 3.0 mmol). El recipiente se selló y la mezcla se agitó a 130°C durante 20 horas. La mezcla de reacción luego se concentró para proporcionar bromhidrato de ácido 2–(3–hidroxi–5–oxo–1,6–naftiridin–6(5H)–il)propanoico (0.95 g, 100% de rendimiento) en forma de un sólido marrón. Esto se dejó en crudo para la etapa siguiente. Material de base libre EM m/z = 235.0 $[M+1]^+$. Calc. para $C_{11}H_{11}BrN_2O_4$: 315.1.

HCl

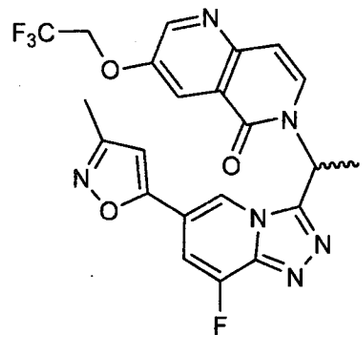


b. **Clorhidrato de ácido 2–(5–oxo–3–(2,2,2–trifluoretoxi)–1,6–naftiridin–6(5H)–il)propanoico.**

Un frasco presurizado re–sellable se cargó con bromhidrato de ácido 2–(3–hidroxi–5–oxo–1,6–naftiridin–6(5H)–il)propanoico (0.54 g, 2 mmol), carbonato de cesio (2 g, 7 mmol), trifluormetansulfonato de 2,2,2–trifluoretilo (2 g, 7 mmol), y N,N–dimetilformamida (6 mL, 0.3M). El recipiente se selló y la mezcla se agitó a 60°C durante 1 hr. La mezcla de reacción se diluyó con EtOAc y se lavó con agua. Se recogió la capa orgánica, se secó sobre sulfato de sodio, y se concentró bajo presión reducida para proporcionar un aceite marrón. Esto se purificó a través de MPLC (10–50% EtOAC/Hexanos) para proporcionar un sólido de color castaño de material bis alquilado. Esto se suspendió y se reflujó en 5 mL de HCl 6N durante 2 horas. La mezcla de reacción se concentró y se secó bajo presión reducida para proporcionar clorhidrato de ácido 2–(5–oxo–3–(2,2,2–trifluoretoxi)–1,6–naftiridin–6(5H)–il)propanoico (0.3 g, 50% de rendimiento). Esto se concentró bajo presión reducida hasta

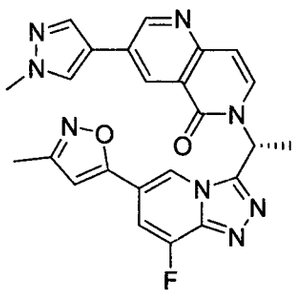
C00417

sequedad para proporcionar clorhidrato de ácido 2–(5–oxo–3–(2,2,2–trifluoretoxi)–1,6–naftiridin–6(5H)–il)propanoico (0.3 g, 50% de rendimiento) en forma de un sólido amarillo. Material de base libre EM m/z = 317.0 $[M+1]^+$. Calc. para $C_{13}H_{12}ClF_3N_2O_4$: 352.7.



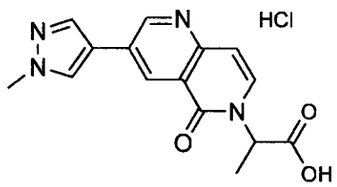
2. 6–(1–(8–fluor–6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–3–(2,2,2–trifluoretoxi)–1,6–naftiridin–5(6H)–ona.

Preparado de acuerdo con el Método General N. EM m/z = 488.8 $[M+1]^+$. Calc. para $C_{22}H_{16}F_4N_6O_3$: 488.4. 1H RMN (400 MHz, DMSO–d_6) δ ppm 2.01 (d, *J*=7.04 Hz, 3 H) 2.25 – 2.38 (m, 3 H) 5.05 (q, *J*=8.77 Hz, 2 H) 6.74 – 6.83 (m, 1 H) 6.96 – 7.07 (m, 2 H) 7.71 (d, *J*=7.82 Hz, 1 H) 7.86 (dd, *J*=11.49, 1.12 Hz, 1 H) 8.20 (d, *J*=2.74 Hz, 1 H) 8.78 (d, *J*=3.03 Hz, 1 H) 8.83 (d, *J*=1.08 Hz, 1 H)



Ejemplo 527

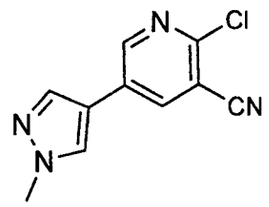
6–((R)–1–(8–fluor–6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–3–(1–metil–1H–pirazol–4–il)–1,6–naftiridin–5(6H)–ona



1. Clorhidrato de ácido 2–(3–(1–metil–1H–pirazol–4–il)–5–oxo–1,6–naftiridin–6(5H)–il)propanoico

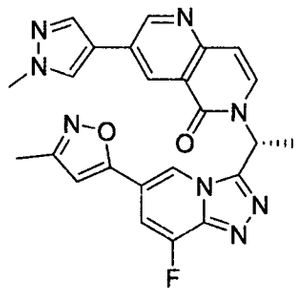
Todas las etapas para la síntesis de este ácido son iguales que para clorhidrato de ácido 2–(3–(2–metoxietoxi)–5–oxo–1,6–naftiridin–6(5H)–il)propanoico (Ejemplo 514) con la siguiente excepción:

CO0418



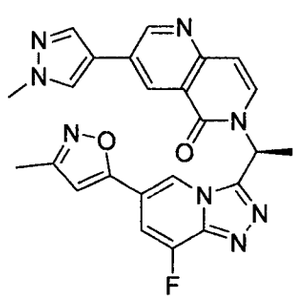
a. 2–cloro–5–(1–metil–1H–pirazol–4–il)nicotinonitrilo.

Un tubo de 48 mL se cargó con 1–metil–4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–1H–pirazol (8.42 g, 40.5 mmol), 5–bromo–2–cloronicotinonitrilo (8.00 g, 36.8 mmol), carbonato de potasio (15.3 g, 110 mmol), $PdCl_2$(dppf) (2.69 g, 3.68 mmol), 1,4–dioxano (135 mL, 1582 mmol) y agua (23.9 mL, 1324 mmol), se inundó con argón, se selló y luego se calentó a 60°C durante 8 h. La mezcla de reacción se concentró, se absorbió sobre gel de sílice, y se purificó mediante MPLC eluyendo con 3% de MeOH en DCM. Se obtuvo 2–cloro–5–(1–metil–1H–pirazol–4–il)nicotinonitrilo (4.962 g, 61.7%) (con una pequeña impureza). El material se extrajo en adelante crudo.



2. 6–((R)–1–(8–fluor–6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–3–(1–metil–1H–pirazol–4–il)–1,6–naftiridin–5(6H)–ona.

Se sintetizó usando el Método General N. La separación quiral mediante SFC preparativa (Chiralpak® OJ–H 5 µm (20 x 250 mm, 5 µm), 45% MeOH, 55%, CO_2, 0.2% DEA, 70 mL/min; sistema de presión de 120 bares; t_r : 8.3 min). En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *R*. M/Z = 471.2 [M+H], calc 470.16 para $C_{24}H_{19}FN_8O_2$. ^{1}H RMN (400 MHz, DMSO–d_6) δ ppm 2.01 (d, *J*=7.04 Hz, 3 H) 2.31 (s, 3 H) 3.89 (s, 3 H) 6.78 (d, *J*=8.41 Hz, 1 H) 6.95 – 7.09 (m, 2 H) 7.72 (d, *J*=7.82 Hz, 1 H) 7.85 (d, *J*=12.62 Hz, 1 H) 8.12 (s, 1 H) 8.46 (s, 1 H) 8.67 (dd, *J*=2.35, 0.68 Hz, 1 H) 8.83 (d, *J*=1.08 Hz, 1 H) 9.20 (d, *J*=2.45 Hz, 1 H).



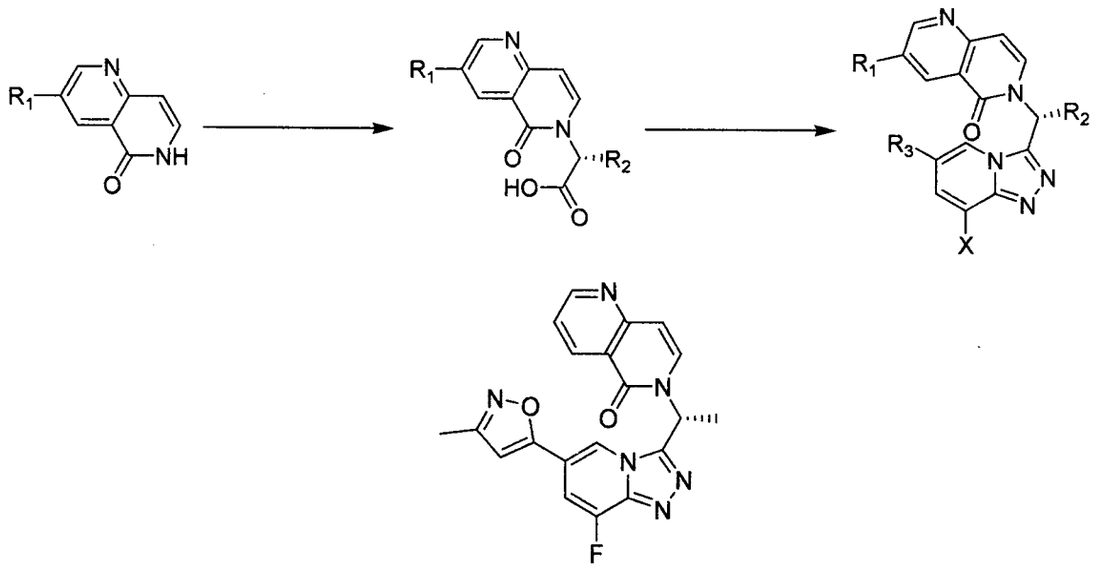
C00419

Ejemplo 528

6-((*S*)-1-(8-fluor-6-(3-metilisoxazol-5-il)-[1,2,4]triazol[4,3-a]piridin-3-il)etil)-3-(1-metil-1H-pirazol-4-il)-1,6-naftiridin-5(6H)-ona

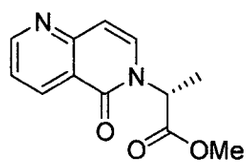
Preparado del mismo modo general tal como ha sido descrito para el Ejemplo 527 de acuerdo con Método General N. Separación quiral mediante SFC preparativa (Chiralpak® OJ-H 5 µm (20 x 250 mm, 5 µm), 45% MeOH, 55%, CO_2, 0.2% DEA, 70 mL/min; sistema de presión de 120 bares; t_r : 7.2 min). En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *S*. M/Z = 471.2 [M+H], calc 470.16 para $C_{24}H_{19}FN_8O_2$.

Método General O.



Ejemplo 529

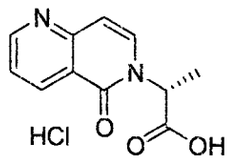
(R)-6-(1-(8-fluor-6-(3-metilisoxazol-5-il)-[1,2,4]triazol[4,3-a]piridin-3-il)etil)-1,6-naftiridin-5(6H)-ona



1. 2-(5-oxo-1,6-naftiridin-6(5H)-il)propanoato de (R)-metilo.

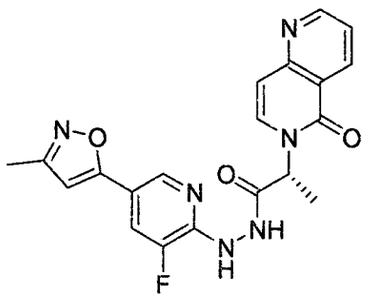
Se disolvió 1,6-naftiridin-5(6H)-ona (10.6 g, 73 mmol), 2-hidroxipropanoato de (S)-metilo (8.6 ml, 91 mmol) y trifenilfosfina (30 g, 116 mmol) en 144 mL THF (0.5M) y se enfrió a 0 °C. Luego se agregó por goteo DEAD (17 ml, 109 mmol), monitoreando la temperatura de modo tal que no exceda los 5 °C. Luego se calentó a temperatura ambiente durante 1 hr, donde la reacción se completó mediante LCMS. La reacción se concentró sobre sílice y se purificó mediante MPLC, primero con un gradiente de Hexanos:EtOAc (remueve la mayor cantidad de PPh_3O); luego el gradiente de 100% de DCM a 90% de DCM:10% MeOH:1% NH_4OH para proporcionar 2-(5-oxo-1,6-naftiridin-6(5H)-il)propanoato de (R)-metilo (16 g, 95% de rendimiento) donde el ee se confirmó para ser >95%.

000420



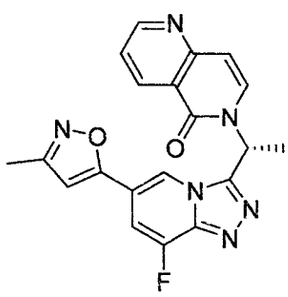
2. Clorhidrato de ácido (R)–2–(5–oxo–1,6–naftiridin–6(5H)–il)propanoico

Se disolvió 2–(5–oxo–1,6–naftiridin–6(5H)–il)propanoato de (R)–metilo (3.20 g, 14 mmol) en 70 mL de THF y se agregó HCl 6M (23 ml, 138 mmol) y se calentó a 80 °C durante 3 hrs hasta que se completó la reacción mediante LCMS. La reacción se concentró para remover agua, y se azeotropeó 3 veces con benceno para remover el exceso de agua, para proporcionar clorhdirato de ácido (R)–2–(5–oxo–1,6–naftiridin–6(5H)–il)propanoico (3.4 g, 95% de rendimiento) que fue de >95% ee de acuerdo con HPLC (conditciones: 25/75 EtOH–TFA (0.1%):Heptano, Columna ChiralPak AD–H, 1.0 mL/min, 20 min, 4.6X150 mm. Se obtuvo clorhidrato de ácido (R)–2–(5–oxo–1,6–naftiridin–6(5H)–il)propanoico en forma de un sólido amarillo, que se extrajo en crudo para la etapa siguiente.



3. (2R)–N'–(3–fluor–5–(3–metilisoxazol–5–il)piridin–2–il)–2–(5–oxo–1,6–naftiridin–6(5H)–il)propanhidrazida.

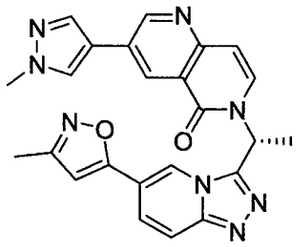
Se extrajeron HATU (9.0 g, 24 mmol), clorhidrato de ácido (R)–2–(5–oxo–1,6–naftiridin–6(5H)–il)propanoico y 1–(3–fluor–5–(3–metilisoxazol–5–il)piridin–2–il)hidrazina (3.6 g, 17 mmol) en acetonitrilo (52 ml, 0.3 M) y se enfrió a 0 °C. Se agregó por goteo DIPEA (8.2 ml, 47 mmol) y la reacción se dejó agitar a temperatura ambiente durante 30 minutos hasta completarla mediante LCMS. El material crudo se concentró sobre gel de sílice y luego se purificó a través de MPLC eluyendo con 100% de DCM a 90% de DCM:10% MeOH:1% NH_4OH para proporcionar (2R)–N'–(3–fluor–5–(3–metilisoxazol–5–il)piridin–2–il)–2–(5–oxo–1,6–naftiridin–6(5H)–il)propanhidrazida (4.927 g, 77% de rendimiento).



4. (R)–6–(1–(8–fluor–6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona.

C00421

Se extrajeron (2R)–N'–(3–fluor–5–(3–metilisoxazol–5–il)piridin–2–il)–2–(5–oxo–1,6–naftiridin–6(5H)–il)propanhidrazida (1.9 g, 4.7 mmol) y trifenilfosfina (1.8 g, 7.0 mmol) en THF (47 ml, 4.7 mmol). Se agregó azida TMS (0.93 ml, 7.0 mmol), seguido de lenta adición de DEAD (1.1 ml, 7.0 mmol) y la reacción se agitó a temperatura ambiente durante 50 minutos (se monitoreó la temperatura de modo tal que no excediera demasiado los 30–40 °C) hasta completar la reacción. La mezcla de reacción se concentró, se removió aproximadamente ½ volumen de THF. El material luego se redisolvió en EtOAc (~100 mL), y se agregó HCl 2M (~30 mL). La mezcla se agitó vigorosamente, y se apartó la capa acuosa (sin producto). La capa EtOAc se extrajo x2 con HCl (30 mL) y se combinaron todas las capas acuosas. La capa acuosa se enfrió a 0 °C, y a esto se agregó por goteo NaOH 6M hasta que el pH fue de 7–8 (el producto deseado surgió en forma de un sólido blancuzco). El sólido se filtró al vacío para remover el producto deseado a partir de agua. el sólido se disolvió luego a través del fritado en un nuevo frasco con DCM/MeOH, y se secó sobre $NaSO_4$ (para secado extra). El producto luego se recristalizó a partir de EtOH con calor, sonicación y luego enfriamiento o raspado para promover una rápida cristalización. (R)–6–(1–(8–fluor–6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona (1.5 g, 60–80% de rendimiento) se aisló en forma de un sólido blanco con >95% ee mediante HPLC (condiciones: 50/50 EtOH:Heptano, columna ChiralPak® AD–H, 1.0 mL/min, 20 min, 4.6X150 mm, tr 6.61 min). En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *R*. M/Z = 391.2 [M+H], calc 390.12 para $C_{20}H_{15}FN_6O_2$. ^{1}H RMN (400 MHz, DMSO–d_6) δ ppm 2.00 (d, *J*=7.04 Hz, 3 H) 2.31 (s, 3 H) 6.78 (d, *J*=7.92 Hz, 1 H) 6.95 – 7.12 (m, 2 H) 7.54 (dd, *J*=8.22, 4.50 Hz, 1 H) 7.77 (d, *J*=7.73 Hz, 1 H) 7.85 (d, *J*=11.54 Hz, 1 H) 8.62 (d, *J*=9.59 Hz, 1 H) 8.82 (s, 1 H) 8.92 (dd, *J*=4.55, 1.71 Hz, 1 H).

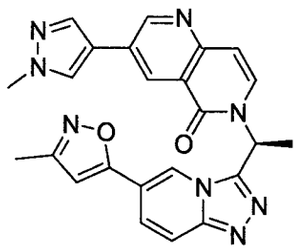


Ejemplo 530

3–(1–metil–1H–pirazol–4–il)–6–((R)–1–(6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona

Preparado del mismo modo general tal como ha sido descrito para el Ejemplo 527 de acuerdo con Método General N. Separación quiral mediante SFC preparativa (ChiralCel OD–H (20 x 250 mm 5μ), 35:65:0.2 MeOH:CO_2:DEA, 80 mL/min y sistema de retropresión de 100 bares (t_r : 12 mins).. En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *R* M/Z = 453.0 [M+H], calc 452.5 para $C_{24}H_{20}N_8O_2$.

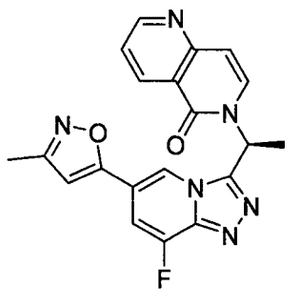
000422



Ejemplo 531

3–(1–metil–1H–pirazol–4–il)–6–((S)–1–(6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona

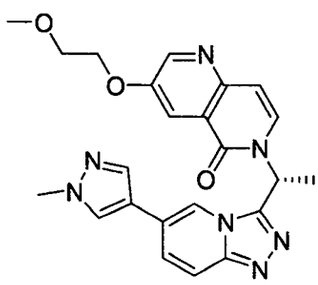
Preparado del mismo modo general tal como ha sido descrito para el Ejemplo 527 de acuerdo con Método General N. Separación quiral mediante SFC preparativa (ChiralCel OD–H (20 x 250 mm 5µ), 35:65:0.2 MeOH:CO_2:DEA, 80 mL/min y sistema de retropresión de 100 bares (t_r : 18 mins). En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *S*. M/Z = 453.0 [M+H], calc 452.5 para $C_{24}H_{20}N_8O_2$.



Ejemplo 532

(S)–6–(1–(8–fluor–6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona

Se sintetizó de acuerdo con el Método General N. Separación mediante HPLC preparativa (ChiralPak® IA, (50 x 250 mm, 5 µm), 50% Heptano, 50% EtOH; 100 mL/min; t_r : 14.0 min) para proporcionar (S)–6–(1–(8–fluor–6–(3–metilisoxazol–5–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona. En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *S*. M/Z = 391.2 [M+H], calc 390.12 para $C_{20}H_{15}FN_6O_2$.

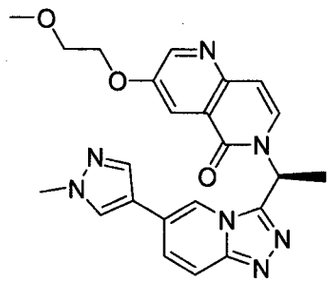


C00424

Ejemplo 533

(R)–3–(2–metoxietoxi)–6–(1–(6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona

Se sintetizó usando el Método General N. Separación quiral mediante SFC preparativa (Chiralpak® OD–H (20 x 250 mm, 5 µm), 30% MeOH, 70%, CO_2, 0.2% DEA, 70 mL/min; sistema de presión de 100 bares; t_r : 6.8 min). En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *R*. M/Z = 446.2 [M+H], calc 445.19 para $C_{23}H_{23}N_7O_3$.

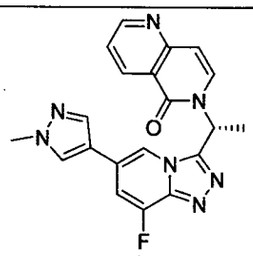
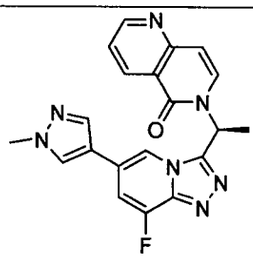
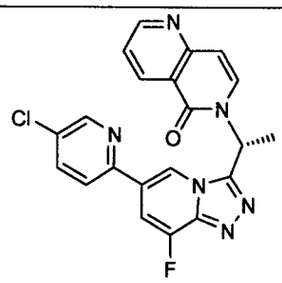
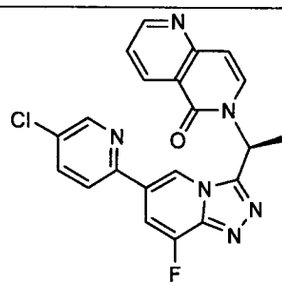
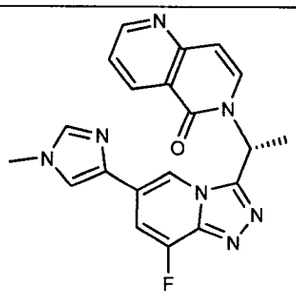
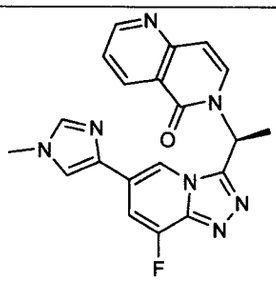


Ejemplo 534

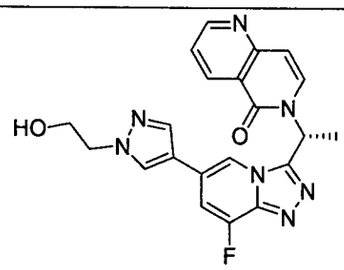
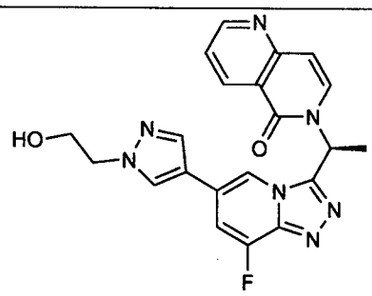
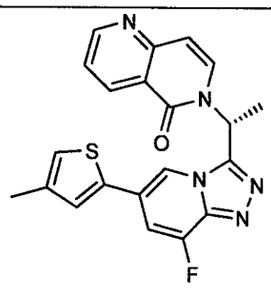
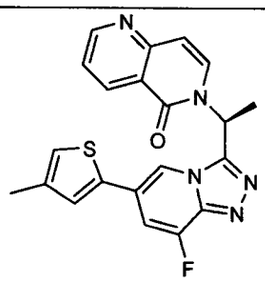
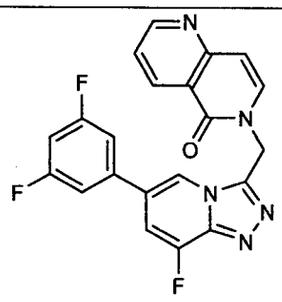
(S)–3–(2–metoxietoxi)–6–(1–(6–(1–metil–1H–pirazol–4–il)–[1,2,4]triazol[4,3–a]piridin–3–il)etil)–1,6–naftiridin–5(6H)–ona

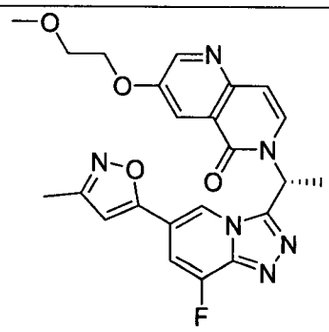
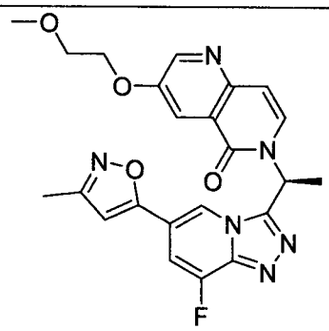
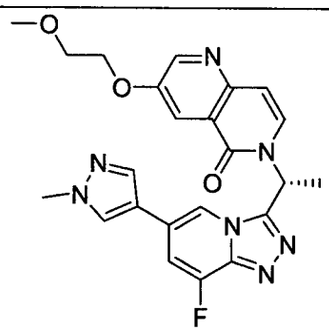
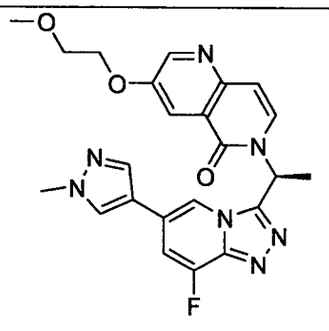
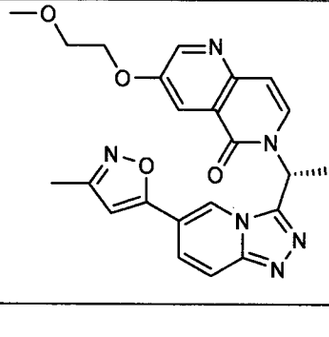
Preparado del mismo modo general tal como ha sido descrito para el Ejemplo 533 de acuerdo con Método General N. Separación quiral mediante SFC preparativa (Chiralpak® OD–H (20 x 250 mm, 5 µm), 30% MeOH, 70%, CO_2, 0.2% DEA, 70 mL/min; sistema de presión de 100 bares; t_r : 9.9 min). En base a datos cristalográficos previos y potencia registrada para el compuesto relacionado en el mismo programa, la estereoquímica absoluta ha sido asignada al enantiómero *S*. M/Z = 446.2 [M+H], calc 445.19 para $C_{23}H_{23}N_7O_3$.

C00425

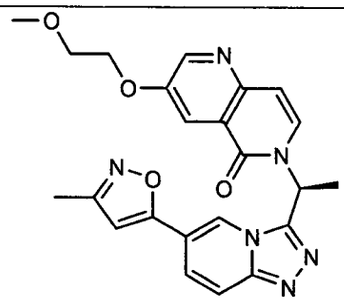
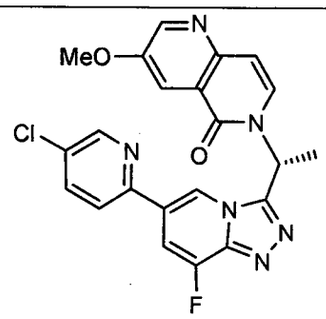
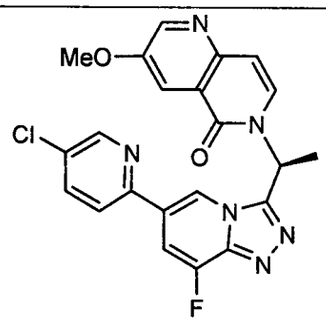
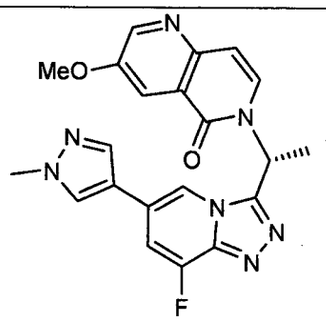
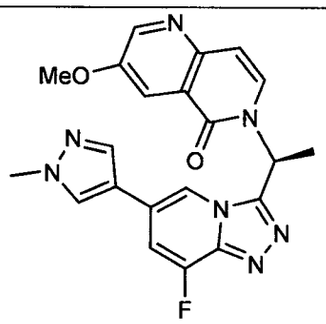
Ej	Estructura	MW	Masa Hallada	Método General
503		389,4	390,2	N
504		389,4	390,2	N
505		420,8	420,8	N
506		420,8	420,8	N
507		389,4	389,8	N
508		389,4	389,8	N

000426

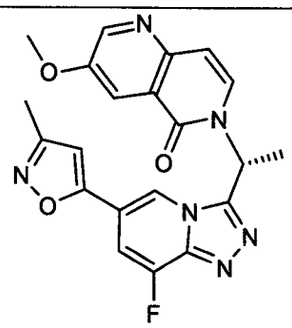
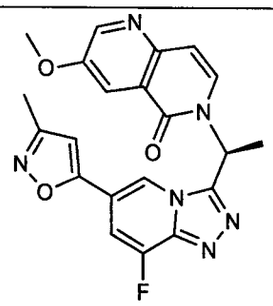
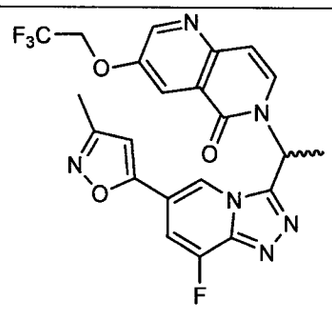
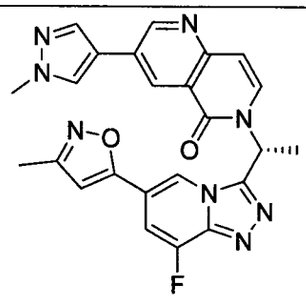
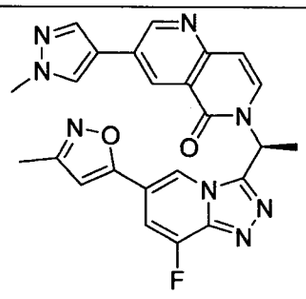
Ej	Estructura	MW	Masa Hallada	Método General
509		419,4	420,2	N
510		419,4	420,2	N
511		405,5	406,0	N
512		405,5	406,0	N
513		407,4	408,2	N

Ej	Estructura	MW	Masa Hallada	Método General
514		464,5	465,2	N
515		464,5	465,2	N
516		463,2	464,2	N
517		463,2	464,2	N
518		446,5	447,2	N

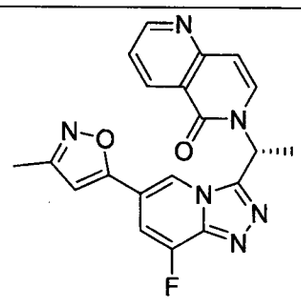
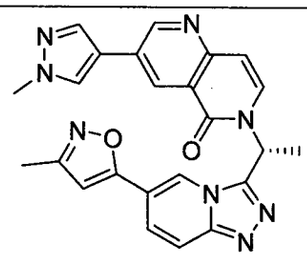
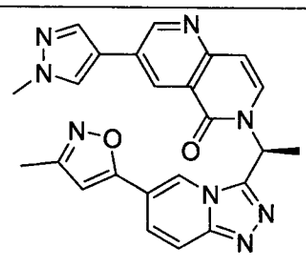
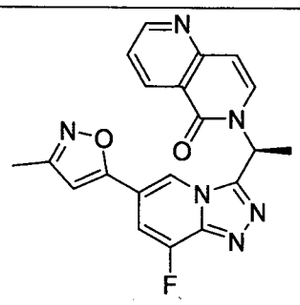
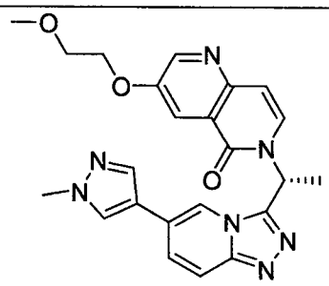
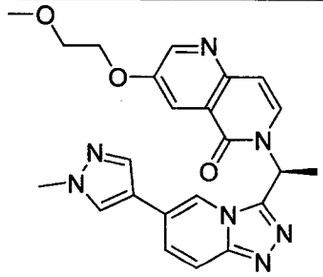
000428

Ej	Estructura	MW	Masa Hallada	Método General
519		446,5	447,2	N
520		450,8	450,8	N
521		450,8	450,8	N
522		419,4	419,8	N
523		419,4	419,8	N

C00429

Ej	Estructura	MW	Masa Hallada	Método General
524		420,4	420,8	N
525		420,4	420,8	N
526		488,4	488,8	N
527		470,2	471,2	N
528		470,2	471,2	N

C00490

Ej	Estructura	MW	Masa Hallada	Método General
529		390,1	391,2	O
530		452,5	453,0	N
531		452,5	453,0	N
532		390,1	391,2	N
533		445,2	446,2	N
534		445,2	446,2	N

C00491

Ejemplo	Dato 1H RMN
348	1H RMN (400 MHz, DMSO–d_6) δ ppm 8,70 (d, *J*=2,74 Hz, 1 H), 8,53 (s, 1 H), 8,50 (d, *J*=5,28 Hz, 1 H), 8,35 (d, *J*=9,68 Hz, 1 H), 8,21 (d, *J*=0,78 Hz, 1 H), 8,17 (s, 1 H), 7,94 (d, *J*=2,64 Hz, 1 H), 7,69 – 7,73 (m, 1 H), 6,94 (d, *J*=5,38 Hz, 1 H), 5,15 (d, *J*=6,16 Hz, 2 H), 3,94 (s, 3 H)
351	1H RMN (400 MHz, CLOROFORMO–*d*) d ppm 8,66 (d, *J*=1,56 Hz, 1 H), 8,08 (d, *J*=8,51 Hz, 1 H), 7,83 – 7,93 (m, 2 H), 7,61 (s, 1 H), 7,53 (d, *J*=8,61 Hz, 1 H), 7,42 (d, *J*=9,78 Hz, 1 H), 7,33 (s, 1 H), 6,80 – 6,95 (m, 3 H), 4,78 (s, 2 H), 3,93 (s, 3 H),
352	1H RMN (400 MHz, CLOROFORMO–*d*) d ppm 8,67 (d, *J*=2,84 Hz, 1 H), 8,15 (d, *J*=8,51 Hz, 1 H), 7,94 – 7,99 (m, 1 H), 7,86 (dd, *J*=9,59 Hz, 1 H), 7,62 (s, 1 H), 7,56 (dd, *J*=8,61 Hz, 1 H), 7,34 – 7,43 (m, 2 H), 7,07 (s, 1 H), 4,77 (s, 2 H), 3,95 (s, 3 H), 2,51 (s, 3 H),
355	1H RMN (400 MHz, DMSO–d_6) δ ppm 2,52 (s, 3 H) 5,19 (d, *J*=6,26 Hz, 2 H) 6,95 (d, *J*=5,38 Hz, 1 H) 7,71 (dd, *J*=8,51, 4,11 Hz, 1 H) 7,94 (d, *J*=9,78 Hz, 1 H) 8,04 (t, *J*=6,21 Hz, 1 H) 8,09 (s, 1 H) 8,21 (dd, *J*=8,51, 1,56 Hz, 1 H) 8,50 (d, *J*=5,28 Hz, 1 H) 8,54 (d, *J*=9,78 Hz, 1 H) 8,79 (dd, *J*=4,11, 1,56 Hz, 1 H),
359	1H RMN (400 MHz, DMSO–d_6) δ ppm 2,51 (s, 3 H) 5,19 (d, *J*=6,06 Hz, 2 H) 6,96 (d, *J*=5,48 Hz, 1 H) 7,94 (d, *J*=9,68 Hz, 1 H) 8,05 (dd, *J*=10,03, 2,49 Hz, 1 H) 8,09 (s, 1 H) 8,22 (s, 1 H) 8,48 – 8,59 (m, 2 H) 8,85 (d, *J*=2,64 Hz, 1 H)
364	1H RMN (400 MHz, DMSO–d_6) δ ppm 2,51 (s, 3 H) 5,17 (d, *J*=6,16 Hz, 2 H) 6,94 (d, *J*=5,38 Hz, 1 H) 7,53 (t, *J*=73,21 Hz, 1 H) 7,89 – 7,99 (m, 2 H) 8,09 (s, 1 H) 8,12 (t, *J*=6,26 Hz, 1 H) 8,51 (d, *J*=5,28 Hz, 1 H) 8,54 (d, *J*=9,68 Hz, 1 H) 8,70 (d, *J*=2,74 Hz, 1 H),
365	1H RMN (400 MHz, DMSO–d_6) δ ppm 2,52 (s, 3 H) 3,33 (s, 3 H) 3,71 – 3,76 (m, 2 H) 4,27 – 4,31 (m, 2 H) 5,14 (d, *J*=6,16 Hz, 2 H) 6,82 (d, *J*=5,38 Hz, 1 H) 7,59 (d, *J*=2,74 Hz, 1 H) 7,94 (d, *J*=9,78 Hz, 2 H) 8,09 (s, 1 H) 8,41 (d, *J*=5,28 Hz, 1 H) 8,49 – 8,57 (m, 2 H)
370	1H RMN (400 MHz, MeOH) δ ppm 3,44 (s, 3 H) 3,82 – 3,87 (m, 2 H) 4,29 – 4,34 (m, 2 H) 5,40 (s, 2 H) 7,02 (d, *J*=5,97 Hz, 1 H) 7,19 – 7,27 (m, 1 H) 7,51 (d, *J*=2,64 Hz, 1 H) 7,75 – 7,86 (m, 2 H) 7,95 (d, *J*=9,88 Hz, 1 H) 8,33 (d, *J*=9,88 Hz, 1 H) 8,39 (d, *J*=6,26 Hz, 1 H) 8,59 (s, 1 H)

Ejemplo	Dato 1H RMN
371	1H RMN (400 MHz, DMSO–d_6) δ ppm 5,02 (q, *J*=8,80 Hz, 2 H) 5,22 (d, *J*=6,26 Hz, 2 H) 6,91 (d, *J*=5,48 Hz, 1 H) 7,53 (t, *J*=9,15 Hz, 1 H) 7,79 (d, *J*=2,64 Hz, 1 H) 7,99 – 8,10 (m, 3 H) 8,21 (t, *J*=5,97 Hz, 1 H) 8,44 (d, *J*=5,28 Hz, 1 H) 8,51 (d, *J*=9,78 Hz, 1 H) 8,61 (d, *J*=2,64 Hz, 1 H)
372	1H RMN (400 MHz, DMSO–d_6) δ ppm 2,52 (s, 3 H) 5,02 (q, *J*=8,90 Hz, 2 H) 5,15 (d, *J*=6,16 Hz, 2 H) 6,87 (d, *J*=5,38 Hz, 1 H) 7,80 (d, *J*=2,84 Hz, 1 H) 7,94 (d, *J*=9,78 Hz, 1 H) 8,01 (t, *J*=6,11 Hz, 1 H) 8,09 (s, 1 H) 8,45 (d, *J*=5,28 Hz, 1 H) 8,54 (d, *J*=9,78 Hz, 1 H) 8,62 (d, *J*=2,84 Hz, 1 H),
383	1H RMN (400 MHz, DMSO–d_6) δ ppm 3,94 (s, 3 H) 4,50 – 4,62 (m, 2 H) 5,14 (d, *J*=6,16 Hz, 2 H) 6,30 – 6,64 (m, 1 H) 6,87 (d, *J*=5,48 Hz, 1 H) 7,66 – 7,74 (m, 2 H) 8,06 (t, *J*=6,11 Hz, 1 H) 8,21 (d, *J*=0,68 Hz, 1 H) 8,34 (d, *J*=9,68 Hz, 1 H) 8,44 (d, *J*=5,38 Hz, 1 H) 8,52 (s, 1 H) 8,59 (d, *J*=2,84 Hz, 1 H),
390	(400 MHz, DMSO–*d6)* δ ppm 8,64 (s, 1H), 8,51 (d, J = 2,8 Hz, 1H), 8,40 (d, J = 5,2 Hz, 1H), 8,35 (d, J = 9,6 Hz, 1Hz), 8,19 (s, 1H), 7,99 (t, J = 6,0 Hz, 1H), 7,72 (d, J = 10 Hz, 1H), 7,57 (d J = 2,8 Hz, 1H), 6,83 (d, J = 5,2 Hz, 1H), 5,12 (d, J = 6,0 Hz, 2H), 3,93 (s, 3H), 3,80–3,86 (m, 1H), 1,10–1015 (m, 2H), 1,00–1,08 (m, 2H),
399	1H RMN (400 MHz, DMSO–d_6) d ppm 8,49 – 8,55 (m, 2 H), 8,41 (d, *J*=5,38 Hz, 1 H), 8,24 (s, 1 H), 8,03 (d, *J*=9,68 Hz, 1 H), 7,94 (t, *J*=6,16 Hz, 1 H), 7,58 (d, *J*=2,84 Hz, 1 H), 6,83 (d, *J*=5,38 Hz, 1 H), 5,67 (t, *J*=5,77 Hz, 1 H), 5,15 (d, *J*=6,16 Hz, 2 H), 4,63 (d, *J*=5,67 Hz, 2 H), 3,93 (s, 3 H),
400	1H RMN (400 MHz, DMSO–d_6) δ ppm 5,26 (d, *J*=6,36 Hz, 2 H) 7,02 (d, *J*=5,38 Hz, 1 H) 7,96 – 8,10 (m, 2 H) 8,22 – 8,32 (m, 2 H) 8,48 – 8,57 (m, 3 H) 8,85 (d, *J*=2,84 Hz, 1 H)
405	1H RMN (400 MHz, DMSO–d_6) δ ppm 3,43 – 3,53 (m, 4 H) 3,70 – 3,80 (m, 4 H) 3,94 (s, 3 H) 5,16 (d, *J*=6,16 Hz, 2 H) 6,85 (d, *J*=5,28 Hz, 1 H) 7,57 (d, *J*=2,74 Hz, 1 H) 7,87 (s, 1 H) 7,90 (d, *J*=9,68 Hz, 1 H) 8,01 – 8,08 (m, 1 H) 8,35 – 8,45 (m, 2 H) 8,52 (d, *J*=2,64 Hz, 1 H)
406	1H RMN (400 MHz, DMSO–d_6) δ ppm 3,94 (s, 3 H) 5,19 (d, *J*=6,26 Hz, 2 H) 6,85 (d, *J*=5,38 Hz, 1 H) 7,57 (d, *J*=2,93 Hz, 1 H) 7,97 – 8,02 (m, 1 H) 8,05 (d, *J*=9,78 Hz, 1 H) 8,42 (d, *J*=5,28 Hz, 1 H) 8,45 (d, *J*=9,68 Hz, 1 H) 8,52 (d, *J*=2,84 Hz, 1 H) 8,71 (d, *J*=1,96 Hz, 1 H) 9,36 (d, *J*=1,96 Hz, 1 H)

Ejemplo	Dato 1H RMN
408	1H RMN (400 MHz, DMSO–d_6) δ ppm 1,90 (d, *J*=7,04 Hz, 3 H) 2,44 (s, 3 H) 5,24 (q, *J*=7,01 Hz, 1 H) 7,51 (dd, *J*=8,27, 4,16 Hz, 1 H) 7,64 – 7,73 (m, 2 H) 7,81 (dd, *J*=8,75, 2,01 Hz, 1 H) 7,94 (d, *J*=1,96 Hz, 1 H) 8,00 (d, *J*=8,61 Hz, 1 H) 8,32 (d, *J*=8,41 Hz, 1 H) 8,64 (d, *J*=1,17 Hz, 1 H) 8,86 (dd, *J*=4,16, 1,71 Hz, 1 H)
409	1H RMN (400 MHz, DMSO–d_6) δ ppm 1,92 (d, *J*=7,14 Hz, 3 H) 5,26 (q, 1 H) 7,31 (t, *J*=9,29 Hz, 1 H) 7,49 (dd, *J*=8,36, 4,16 Hz, 2 H) 7,55 (d, *J*=8,61 Hz, 1 H) 7,77 – 7,86 (m, *J*=8,22 Hz, 2 H) 7,95 (s, 1 H) 7,99 (d, *J*=8,71 Hz, 1 H) 8,31 (d, *J*=7,24 Hz, 1 H) 8,68 (s, 1 H) 8,85 (dd, *J*=4,11, 1,66 Hz, 1 H)
411	1H RMN (400 MHz, DMSO–d_6) δ ppm 1,89 (d, *J*=7,04 Hz, 3 H) 2,27 (s, 3 H) 3,88 (s, 3 H) 5,22 (q, *J*=6,98 Hz, 1 H) 6,99 (s, 1 H) 7,63 (dd, *J*=8,71, 2,05 Hz, 1 H) 7,67 – 7,70 (m, 1 H) 7,72 (d, *J*=1,86 Hz, 1 H) 7,76 (dd, *J*=11,54, 1,17 Hz, 1 H) 7,93 (d, *J*=8,61 Hz, 1 H) 8,58 (d, *J*=2,93 Hz, 1 H) 8,64 (d, *J*=1,08 Hz, 1 H)
413	1H RMN (400 MHz, DMSO–d_6) δ ppm 2,40 (s, 3 H) 2,44 (d, *J*=23,28 Hz, 3 H) 7,56 – 7,61 (m, 2 H) 7,75 (dd, *J*=8,90, 2,15 Hz, 1 H) 7,80 (dd, *J*=11,49, 1,22 Hz, 1 H) 8,02 (d, *J*=0,88 Hz, 1 H) 8,09 (d, *J*=8,90 Hz, 1 H) 8,12 (d, *J*=2,05 Hz, 1 H) 8,43 – 8,47 (m, 1 H) 8,95 (dd, *J*=4,21, 1,76 Hz, 1 H)
418	1H RMN (400 MHz, DMSO–d_6) δ ppm 3,89 (s, 3 H) 4,88 (s, 2 H) 7,61 (dd, *J*=8,56, 2,01 Hz, 1 H) 7,68 (d, *J*=2,74 Hz, 1 H) 7,70 – 7,75 (m, 1 H) 7,83 (s, 1 H) 7,89 (dd, *J*=11,44, 1,08 Hz, 1 H) 7,93 (d, *J*=8,61 Hz, 1 H) 8,59 (d, *J*=2,84 Hz, 1 H) 9,17 (d, *J*=1,08 Hz, 1 H)
430	1H RMN (400 MHz, DMSO–d_6) δ ppm 8,84 (dd, *J*=4,25, 1,71 Hz, 1 H), 8,42 – 8,46 (m, 1 H), 8,26 (d, *J*=2,05 Hz, 1 H), 8,15 (d, *J*=9,49 Hz, 1 H), 7,94 (s, 1 H), 7,90 (d, *J*=8,80 Hz, 1 H), 7,67 – 7,76 (m, 4 H), 7,52 (dd, *J*=8,26, 4,25 Hz, 1 H), 7,38 – 7,44 (m, 1 H), 7,32 – 7,37 (m, 2 H), 6,17 (s, 1 H), 2,17 (s, 3 H)
431	1H RMN (400 MHz, DMSO–d_6) δ ppm 8,85 (dd, *J*=4,21, 1,76 Hz, 1 H), 8,31 – 8,35 (m, 1 H), 8,21 (d, *J*=9,59 Hz, 1 H), 8,04 – 8,08 (m, 2 H), 7,95 – 7,99 (m, 2 H), 7,75 – 7,83 (m, 3 H), 7,49 – 7,58 (m, 4 H), 4,62 (s, 2 H)
433	1H RMN (400 MHz, DMSO–d_6) δ ppm 9,01 (dd, *J*=4,21, 1,66 Hz, 1 H), 8,54 – 8,59 (m, 1 H), 8,47 (s, 1 H), 8,44 (d, *J*=9,59 Hz, 1 H), 8,16 (d, *J*=8,80 Hz, 1 H), 8,13 (s, 1 H), 8,00 (dd, *J*=8,90, 2,05 Hz, 1 H), 7,88 (d, *J*=9,59 Hz, 1 H), 7,64 (dd, *J*=8,31, 4,21 Hz, 1 H), 7,11 (s, 1 H), 2,33 (s, 3 H)

Ejemplo	Dato 1H RMN
436	1H RMN (400 MHz, DMSO–d_6) δ ppm 8,46 (d, *J*=2,74 Hz, 1 H), 8,38 (d, *J*=5,38 Hz, 1 H), 8,29 (d, *J*=9,39 Hz, 1 H), 8,00 (s, 1 H), 7,76 – 7,82 (m, 3 H), 7,54 (d, *J*=2,84 Hz, 1 H), 6,79 (d, *J*=5,38 Hz, 1 H), 4,98 (d, *J*=6,36 Hz, 2 H), 3,91 (s, 3 H)
437	^{1}H RMN (400 MHz, CLOROFORMO–*d*) δ ppm 4,80 (s, 2 H) 7,19 (dd, *J*=10,76, 1,17 Hz, 1 H) 7,31 – 7,35 (m, 2 H) 7,38 – 7,43 (m, 4 H) 7,65 – 7,71 (m, 3 H) 8,07 (dd, *J*=8,31, 0,88 Hz, 1 H) 8,11 (d, *J*=8,41 Hz, 1 H) 8,91 (dd, *J*=4,21, 1,66 Hz, 1 H),
438	^{1}H RMN (400 MHz, DMSO–d_6) δ ppm 3,88 (s, 3 H) 4,76 (s, 2 H) 7,52 – 7,59 (m, 1 H) 7,61 (s, 1 H) 7,65 (d, J=12,32 Hz, 1 H) 7,80 (s, 1 H) 7,91 (d, J=8,80 Hz, 1 H) 8,01 (s, 1 H) 8,27 (s, 1 H) 8,57 – 8,66 (m, 2 H) 10,59 (br, s,, 1 H)
439	1H RMN (400 MHz, DMF) δ ppm 7,69 (tt, *J*=9,32, 2,27 Hz, 3 H) 7,99 (dd, *J*=8,31, 4,21 Hz, 1 H) 8,01 – 8,09 (m, 2 H) 8,43 (dd, *J*=8,90, 2,15 Hz, 1 H) 8,54 (d, *J* = 8,8 Hz 1 H) 8,83 – 8,95 (m, 2 H) 9,19 (d, *J*=2,25 Hz, 1 H) 9,37 (dd, *J*=4,25, 1,71 Hz, 1 H) 9,53 (d, *J*=2,25 Hz, 1 H), MS m/z = 410,0 $[M+1]^+$ Calc, para $C_{22}H_{11}F_4N_3O$: 409,3,
442	1H RMN (400 MHz, DMSO–d_6) δ ppm 4,00 (s, 3 H) 5,24 (d, *J*=5,97 Hz, 2 H) 5,76 (d, *J*=46,46 Hz, 2 H) 7,64 (d, *J*=2,74 Hz, 1 H) 7,77 (s, 1 H) 8,01 (d, *J*=9,68 Hz, 1 H) 8,10 (t, *J*=6,26 Hz, 1 H) 8,48 (d, *J*=5,28 Hz, 1 H) 8,59 (d, *J*=2,74 Hz, 1 H) 8,64 (d, *J*=9,68 Hz, 1 H),
443	1H RMN (400 MHz, DMSO–d_6) δ ppm 2,40 – 2,40 (m, 1 H) 7,58 (dd, *J*=8,31, 4,21 Hz, 1 H) 7,81 (s, 1 H) 8,00 (dd, *J*=8,90, 2,25 Hz, 1 H) 8,12 (d, *J*=8,90 Hz, 1 H) 8,44 (d, *J*=1,27 Hz, 1 H) 8,47 (dd, *J*=8,46, 1,03 Hz, 1 H) 8,70 (d, *J*=2,25 Hz, 1 H) 8,95 (dd, *J*=4,26, 1,71 Hz, 1 H) 9,07 (d, *J*=2,15 Hz, 1 H) ,
444	1H RMN (400 MHz, DMSO–d_6) δ ppm 7,44 – 7,53 (m, 1 H) 7,68 (dd, *J*=8,31, 4,21 Hz, 1 H) 8,00 (td, *J*=7,78, 1,76 Hz, 1 H) 8,11 (dd, *J*=8,90, 2,05 Hz, 1 H) 8,25 (dd, *J*=15,60, 8,36 Hz, 2 H) 8,55 (s, 1 H) 8,58 (dd, *J*=8,41, 0,78 Hz, 1 H) 8,75 (dq, *J*=4,77, 0,82 Hz, 1 H) 9,01 – 9,11 (m, 2 H) 9,53 (d, *J*=2,15 Hz, 1 H),
450	1H RMN (400 MHz, DMSO–d_6) δ ppm 7,35 – 7,45 (m, 1 H) 7,67 (dd, *J*=8,31, 4,21 Hz, 1 H) 7,73 – 7,85 (m, 2 H) 8,11 (dd, *J*= 8,9, 2,0 Hz, 1 H) 8,21 (d, *J*=8,90 Hz, 1 H) 8,48 (d, *J*=9,10 Hz, 1 H) 8,57 (s, 1 H) 8,60 (m, 2 H) 9,04 (dd, *J*=4,11, 1,56 Hz, 1 H),

Ejemplo	Dato 1H RMN
460	1H RMN (400 MHz, DMSO–d_6) δ ppm 3,89 (s, 3H); 3,89 (s, 3 H); 4,01 – 4,02 (m, 1 H); 7,86 (dd, *J*=8,8, 2,2 Hz, 1 H); 7,91 (dd, *J*=12,0, 1,0 Hz, 1 H); 7,95 (d, *J*=2,7 Hz, 1 H); 8,11 (d, *J*=0,7 Hz, 1 H); 8,15 (d, *J*=8,7 Hz, 1 H); 8,32 (d, *J*=1,5 Hz, 1 H); 8,56 (d, *J*=0,7 Hz, 1 H); 8,78 (d, *J*=2,9 Hz, 1 H)
462	1H RMN (400 MHz, DMSO–d_6) δ ppm 1,93 – 2,07 (m, 2 H) 2,30 – 2,42 (m, 4 H) 2,43 – 2,49 (m, 2 H) 3,50 – 3,65 (m, 4 H) 3,89 (s, 3 H) 4,20 (t, *J*=6,41 Hz, 2 H) 7,86 (dd, *J*=8,75, 1,91 Hz, 1 H) 7,96 (s, 1 H) 7,98 (d, *J*=2,64 Hz, 1 H) 8,13 (s, 1 H) 8,15 (d, *J*=8,90 Hz, 1 H) 8,32 (s, 1 H) 8,46 (s, 1 H) 8,57 (s, 1 H) 8,78 (d, *J*=2,84 Hz, 1 H)
468	1H RMN (400 MHz, CLOROFORMO–*d*) δ ppm 2,41 (s, 3 H); 3,97 (s, 3 H); 6,54 (s, 1 H); 7,39 (dd, *J*=9,8, 1,2 Hz, 1 H); 7,47 (d, *J*=2,8 Hz, 1 H); 7,83 (dd, *J*=8,8, 2,1 Hz, 1 H); 8,17 (d, *J*=1,1 Hz, 1 H); 8,21 (d, *J*=8,7 Hz, 1 H) 8,75 – 8,84 (m, 2 H)
469	1H RMN (400 MHz, DMSO–d_6) □ ppm 3,95 (s, 3 H); 7,83 – 7,92 (m, 2 H); 7,93 – 8,03 (m, 2 H); 8,18 (d, *J*=5,6 Hz, 1 H); 8,34 (s, 1 H); 8,69 (s, 1 H); 8,80 (d, *J*=2,93 Hz, 1 H)
470	1H RMN (400 MHz, DMSO–d_6) δ ppm 2,34 (s, 3 H); 7,26 (s, 1 H); 7,69 (dd, *J*=8,3, 4,2 Hz, 1 H); 8,05 (dd, *J*=8,8, 2,2 Hz, 1 H); 8,09 (dd, *J*=11,3, 1,1 Hz, 1 H); 8,25 (d, *J*=8,9 Hz, 1 H); 8,50 (d, *J*=1,7 Hz, 1 H); 8,60 (s, 1 H); 8,80 (d, *J*=1,0 Hz, 1 H); 9,08 (dd, *J*=4,3, 1,7 Hz, 1 H)
471	1H RMN (400 MHz, DMSO–d_6) δ ppm 3,70 (s, 3 H); 7,57 – 7,67 (m, 1 H); 7,72 (s, 1 H); 7,87 – 8,16 (m, 3 H); 8,29 (s, 1 H); 8,55 (s, 1 H); 8,70 (s, 1 H)
473	1H RMN (400 MHz, DMSO–d_6) δ ppm 2,32 (s, 3 H); 3,47 (s, 1 H); 3,55 (dd, *J*=11,4, 2,01 Hz, 1 H); 3,67 (s, 2 H); 3,80 (s, 1 H); 3,89 (s, 1 H); 3,98 (s, 1 H); 4,16 (d, *J*=5,0 Hz, 2 H); 7,22 (s, 1 H); 7,87 (dd, *J*=8,9, 2,0 Hz, 1 H); 7,98 (d, *J*=2,8 Hz, 1 H); 8,05 (dd, *J*=11,3, 0,6 Hz, 1 H); 8,16 (d, *J*=8,8 Hz, 1 H); 8,31 (s, 1 H); 8,74 (s, 1 H); 8,81 (d, *J*=2,9 Hz, 1 H)
474	1H RMN (400 MHz, DMSO–d_6) δ ppm 2,35 (s, 3 H); 3,94 (s, 3 H); 4,79 (d, *J*=5,97 Hz, 2 H); 6,76 (d, *J*=5,4 Hz, 1 H); 7,01 (s, 1 H); 7,57 (d, *J*=2,7 Hz, 1 H); 7,89 – 7,94 (m, 1 H); 7,93 (d, *J*=8,6 Hz, 1 H); 8,21 (d, *J*=8,6 Hz, 1 H); 8,34 (s, 1 H); 8,40 (d, *J*=5,4 Hz, 1 H); 8,51 (d, *J*=2,7 Hz, 1 H)

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Ejemplo	Dato 1H RMN
475	^{1}H RMN (400 MHz, DMSO–d_6) ppm 3,89 (s, 3 H) 7,68 (dd, J=8,28, 4,27 Hz, 1 H) 7,93 (d, J=12,05 Hz, 1 H) 8,04 (d, J=8,53 Hz, 1 H) 8,13 (s, 1 H) 8,23 (d, J=8,53 Hz, 1 H) 8,43 – 8,52 (m, 2 H) 8,55 – 8,63 (m, 2 H) 9,07 (d, J=4,02 Hz, 1 H),
476	^{1}H RMN (400 MHz, DMSO–d_6) d ppm 7,56 – 7,74 (m, 2 H) 7,99 (d, J=9,03 Hz, 1 H) 8,21 (d, J=8,53 Hz, 1 H) 8,40 (s, 1 H) 8,57 (d, J=8,03 Hz, 1 H) 8,63 (d, J=10,04 Hz, 1 H) 9,05 (d, J=4,02 Hz, 1 H)
477	^{1}H RMN (400 MHz, DMSO–d_6) d ppm 3,92 (s, 3 H) 3,94 (s, 3 H) 7,80 – 7,87 (m, 2 H) 8,01 – 8,07 (m, 1 H) 8,11 (d, J=9,04 Hz, 1 H) 8,37 (s, 1 H) 8,46 – 8,51 (m, 2 H) 8,75 (d, J=3,01 Hz, 1 H)
478	^{1}H RMN (400 MHz, DMSO–d_6) d ppm 7,67 (dd, J=8,03, 4,02 Hz, 1 H) 7,80 – 7,89 (m, 2 H) 8,17 (dd, J=13,05, 9,54 Hz, 2 H) 8,54 (s, 1 H) 8,60 (d, J=8,53 Hz, 1 H) 8,69 (d, J=10,04 Hz, 1 H) 9,04 (d, J=3,51 Hz, 1 H)
484	^{1}H RMN (400 MHz, DMSO–d_6) d ppm 2,94 (t, J=7,78 Hz, 2 H) 3,03 – 3,14 (m, 2 H) 7,44 (d, J=8,03 Hz, 2 H) 7,68 (dd, J=8,28, 4,27 Hz, 1 H) 7,85 (br, s,, 2 H) 7,95 (d, J=8,03 Hz, 2 H) 8,05 (d, J=8,53 Hz, 1 H) 8,12 (d, J=9,54 Hz, 1 H) 8,21 (d, J=8,53 Hz, 1 H) 8,49 (s, 1 H) 8,57 – 8,66 (m, 2 H) 9,05 (d, J=4,02 Hz, 1 H),
490	^{1}H RMN (300 MHz, CLOROFORMO–d) d ppm 2,10 (d, J=7,16 Hz, 3 H) 2,55 (s, 3 H) 5,04 (q, J=6,87 Hz, 1 H) 7,27 – 7,52 (m, 3 H) 7,82 (d, J=8,62 Hz, 1 H) 7,93 (s, 1 H) 8,05 (d, J=8,62 Hz, 1 H) 8,15 (d, J=9,21 Hz, 2 H) 8,85 (d, J=2,63 Hz, 1 H),
496	^{1}H RMN (300 MHz, CLOROFORMO–d)ppm 3,58 (s, 3 H) 4,78 (s, 2 H) 7,48 – 7,63 (m, 4 H) 7,66 (d, J=8,48 Hz, 1 H) 7,87 (d, J=7,16 Hz, 1 H) 7,91 – 8,06 (m, 3 H) 8,14 (d, J=9,65 Hz, 1 H) 8,47 (s, 1 H),
499	^{1}H RMN (300 MHz, CLOROFORMO–d) δ ppm 3,94 (s, 3 H) 4,73 (s, 2 H) 7,10 (d, J=9,65 Hz, 1 H) 7,33 (d, J=2,78 Hz, 1 H) 7,63 (d, J=10,67 Hz, 1 H) 7,76 (s, 1 H) 8,00 (d, J=8,48 Hz, 1 H) 8,07 (d, J=9,65 Hz, 1 H) 8,64 (d, J=2,92 Hz, 1 H),
501	^{1}H RMN (300 MHz, MeOH) d ppm 4,05 (s, 11 H) 4,82 (s, 7 H) 7,40 (dd, J=10,08, 1,46 Hz, 4 H) 7,81 (dd, J=8,77, 1,90 Hz, 4 H) 7,96 (d, J=0,88 Hz, 4 H) 8,05 (d, J=8,77 Hz, 4 H) 8,21 (d, J=2,78 Hz, 4 H) 8,50 (d, J=0,73 Hz, 3 H) 8,85 (d, J=2,92 Hz, 4 H),
502	^{1}H RMN (400 MHz, CLOROFORMO–*d*) δ ppm 2,59 (s, 3 H) 3,93 (s, 3 H) 4,77 (s, 2 H) 7,34 (d, *J*=2,74 Hz, 1 H) 7,38 (d, *J*=9,68 Hz, 1 H) 7,46 (s, 1 H) 7,66 (dd, *J*=8,61, 2,05 Hz, 1 H) 7,84 (d, *J*=1,96 Hz, 1 H) 7,98 (d, *J*=8,61 Hz, 1 H) 8,16 (d, *J*=9,59 Hz, 1 H) 8,61 (d, *J*=2,93 Hz, 1 H),

Ejemplo	Dato ^{1}H RMN
503	^{1}H RMN (400 MHz, CLOROFORMO–*d*) δ ppm 2.16 (d, *J*=5.18 Hz, 3 H) 3.97 (s, 3 H) 6.82 (d, *J*=6.55 Hz, 1 H) 7.01 – 7.13 (m, 2 H) 7.41 – 7.49 (m, 1 H) 7.54 (d, *J*=6.26 Hz, 1 H) 7.61 (s, 1 H) 7.71 (s, 1 H) 8.33 (s, 1 H) 8.78 (d, *J*=7.73 Hz, 1 H) 8.93 (s, 1 H).
505	1H RMN (400 MHz, DMSO–d_6) δ ppm 2.01 (d, *J*=7.04 Hz, 3 H) 6.78 (d, *J*=7.82 Hz, 1 H) 7.03 (d, *J*=6.94 Hz, 1 H) 7.54 (dd, *J*=8.07, 4.55 Hz, 1 H) 7.78 (d, *J*=7.82 Hz, 1 H) 7.97 – 8.09 (m, 2 H) 8.16 (dd, *J*=8.56, 2.49 Hz, 1 H) 8.61 (dd, *J*=7.97, 1.71 Hz, 1 H) 8.70 – 8.78 (m, 1 H) 8.92 (dd, *J*=4.55, 1.81 Hz, 1 H) 9.03 (d, 1 H).
507	1H RMN (400 MHz, DMSO–d_6) δ ppm 1.97 (d, *J*=6.94 Hz, 3 H) 3.68 (s, 3 H) 6.75 (d, *J*=7.73 Hz, 1 H) 6.94 (d, *J*=6.85 Hz, 1 H) 7.52 – 7.59 (m, 1 H) 7.64 (dd, *J*=7.78, 0.54 Hz, 1 H) 7.69 – 7.75 (m, 3 H) 8.46 (s, 1 H) 8.63 (dt, *J*=8.12, 0.88 Hz, 1 H) 8.90 – 8.94 (m, 1 H)
509	^{1}H RMN (400 MHz, CLOROFORMO–*d*) δ ppm 2.17 (d, *J*=7.14 Hz, 3 H) 4.00 – 4.09 (m, 2 H) 4.29 – 4.33 (m, 2 H) 6.91 (d, *J*=7.92 Hz, 1 H) 7.04 (dd, 1 H) 7.10 (dd, *J*=10.56, 1.17 Hz, 1 H) 7.51 (dd, *J*=8.17, 4.74 Hz, 1 H) 7.59 (d, *J*=7.82 Hz, 1 H) 7.72 (d, *J*=0.68 Hz, 1 H) 7.76 (d, *J*=0.78 Hz, 1 H) 8.34 (d, *J*=1.17 Hz, 1 H) 8.84 (dd, *J*=8.07, 1.22 Hz, 1 H) 8.92 (dd, *J*=4.74, 1.81 Hz, 1 H)
514	^{1}H RMN (400 MHz, CLOROFORMO–*d*) δ ppm 2.17 (d, *J*=7.14 Hz, 3 H) 2.39 (s, 3 H) 3.49 (s, 3 H) 3.78 – 3.94 (m, 2 H) 4.23 – 4.43 (m, 2 H) 6.43 (s, 1 H) 6.85 (d, *J*=7.82 Hz, 1 H) 7.08 (q, *J*=7.11 Hz, 1 H) 7.29 (dd, *J*=10.07, 1.17 Hz, 1 H) 7.43 (d, *J*=7.82 Hz, 1 H) 8.17 (d, *J*=2.93 Hz, 1 H) 8.58 – 8.81 (m, 2 H).
516	^{1}H RMN (400 MHz, CLOROFORMO–*d*) δ ppm 2.15 (d, *J*=7.14 Hz, 3 H) 3.49 (s, 3 H) 3.80 – 3.90 (m, 2 H) 3.97 (s, 3 H) 4.27 – 4.39 (m, 2 H) 6.83 (d, *J*=7.73 Hz, 1 H) 7.00 – 7.13 (m, 2 H) 7.42 (d, *J*=7.82 Hz, 1 H) 7.61 (s, 1 H) 7.72 (s, 1 H) 8.15 (d, *J*=2.84 Hz, 1 H) 8.31 (s, 1 H) 8.72 (d, *J*=3.03 Hz, 1 H).
518	1H RMN (400 MHz, DMSO–d_6) δ ppm 8.89 (t, 1 H), 8.68 (d, *J*=3.03 Hz, 1 H), 8.01 – 8.02 (m, 1 H), 7.96 (dd, *J*=9.59, 1.08 Hz, 1 H), 7.79 (dd, *J*=9.54, 1.61 Hz, 1 H), 7.60 (d, *J*=7.82 Hz, 1 H), 7.01 – 7.05 (m, 1 H), 6.99 (s, 1 H), 6.75 (d, *J*=7.63 Hz, 1 H), 4.29 – 4.32 (m, 2 H), 3.70 – 3.73 (m, 2 H), 3.32 (s, 3 H), 2.31 (s, 3 H), 1.99 (d, *J*=7.04 Hz, 3 H).

Ejemplo	Dato ^{1}H RMN
524	1H RMN (400 MHz, DMSO–d_6) δ ppm 2.00 (d, *J*=7.04 Hz, 3 H) 2.31 (s, 3 H) 3.94 (s, 3 H) 6.77 (dd, *J*=7.78, 0.54 Hz, 1 H) 6.94 – 7.05 (m, 2 H) 7.64 (d, *J*=7.82 Hz, 1 H) 7.76 – 7.89 (m, 1 H) 7.98 (dd, *J*=3.08, 0.54 Hz, 1 H) 8.68 (d, *J*=3.03 Hz, 1 H) 8.80 (d, *J*=1.08 Hz, 1 H).
526	1H RMN (400 MHz, DMSO–d_6) δ ppm 2.01 (d, *J*=7.04 Hz, 3 H) 2.25 – 2.38 (m, 3 H) 5.05 (q, *J*=8.77 Hz, 2 H) 6.74 – 6.83 (m, 1 H) 6.96 – 7.07 (m, 2 H) 7.71 (d, *J*=7.82 Hz, 1 H) 7.86 (dd, *J*=11.49, 1.12 Hz, 1 H) 8.20 (d, *J*=2.74 Hz, 1 H) 8.78 (d, *J*=3.03 Hz, 1 H) 8.83 (d, *J*=1.08 Hz, 1 H)
527	^{1}H RMN (400 MHz, DMSO–d_6) δ ppm 2.01 (d, *J*=7.04 Hz, 3 H) 2.31 (s, 3 H) 3.89 (s, 3 H) 6.78 (d, *J*=8.41 Hz, 1 H) 6.95 – 7.09 (m, 2 H) 7.72 (d, *J*=7.82 Hz, 1 H) 7.85 (d, *J*=12.62 Hz, 1 H) 8.12 (s, 1 H) 8.46 (s, 1 H) 8.67 (dd, *J*=2.35, 0.68 Hz, 1 H) 8.83 (d, *J*=1.08 Hz, 1 H) 9.20 (d, *J*=2.45 Hz, 1 H)
529	^{1}H RMN (400 MHz, DMSO–d_6) δ ppm 2.00 (d, *J*=7.04 Hz, 3 H) 2.31 (s, 3 H) 6.78 (d, *J*=7.92 Hz, 1 H) 6.95 – 7.12 (m, 2 H) 7.54 (dd, *J*=8.22, 4.50 Hz, 1 H) 7.77 (d, *J*=7.73 Hz, 1 H) 7.85 (d, *J*=11.54 Hz, 1 H) 8.62 (d, *J*=9.59 Hz, 1 H) 8.82 (s, 1 H) 8.92 (dd, *J*=4.55, 1.71 Hz, 1 H)

Aunque las propiedades farmacológicas de los compuestos de la presente invención varían con cambio estructural, en general, la actividad que poseen estos compuestos puede demostrarse *in vivo*. Las propiedades farmacológicas de los compuestos de esta invención pueden ser confirmadas por una cantidad de ensayos farmacológicos *in vitro*. Los ensayos farmacológicos ejemplificados, que siguen, se han llevado a cabo con los compuestos de acuerdo con la invención. Los compuestos ejemplificados de la presente invención demostraron un K_i comprendido entre 20 μM y 0,1 nM. Se proveen valores ilustrativos de la actividad, en la tabla siguiente.

Ej.	cMet K_i (μM)
373	0.0001
430	0.3480
437	0.0364
439	0.2531
440	0.1716
441	0.0286
447	0.0121
450	0.1823
466	0.6351

Ej.	cMet Ki (μM)
503	0.0015
505	0.0015
508	1.3438
509	0.0032
511	0.0005
514	0.0007
516	0.0061
518	0.0015
520	0.0011
522	0.0011
524	0.0009
525	0.0257
527	0.0003
529	0.0021

ENSAYO BIOLÓGICO

La eficacia de los compuestos de la invención como inhibidores de actividad relacionada con HGF se demuestra de la manera siguiente:

Ensayo del receptor c–Met

Clonación, Expresión y Purificación del Dominio c–Met Quinasa

1) Un producto PCR que cubre los residuos 1058–1365 (dominio C–Met quinasa es generado por ADNc QuickClone™ de Hígado Humano (Invitrogen) tal como se describió en WO 08/008539.

2). El producto PCR es clonado en un vector de expresión pFastBac1 modificado (que aloja al gen para *S. japonicum* glutationa S–transferasa inmediatamente cadena arriba del sitio de clonación múltiple) mediante el uso de técnicas biológicas moleculares convencionales. El gen de fusión de dominio GST–c–Met quinasa (GST–Met) es transpuesto a un ADN de baculovirus de longitud total usando el sistema BacToBac™ (Invitrogen). Células High5 son infectadas con el baculovirus recombinante durante 72 h a 27°C. Las células infectadas son cosechadas por centrifugación y el pellet se almacena a –80°C. El pellet es resuspendido en buffer A (50 mM HEPES, pH 8,0, 0,25 M NaCl, 10 mM de 2–mercaptoetanol), 10% (p/v) de glicerol, 0,5 % (v/v) de cóctel inhibidor de proteasa (Sigma P8340), agitado a 4°C hasta homogeneidad y las células son disgregadas por microfluidificación (Microfluidics) a 10,000 psi. El lisado resultante es centrifugado a 50,000 x *g* durante 90 min. a 4 °C, y el sobrenadante es adsorbido sobre 10 mL de glutationa sepharose™ 4B (Amersham) por el método de lotes. La suspensión es sacudida suavemente

durante la noche a 4°C. La resina de glutationa es cosechada por centrifugación y es lavada 3 veces con 40 mL de buffer A mediante el método de lotes. La resina se lava tres veces con buffer B (el buffer A se ajusta a NaCl 0,1 M, sin inhibidores de proteasa). La proteína es eluida con buffer B que contiene 25 mM de glutationa reducida. Las fracciones eluidas son analizadas con SDS–PAGE y concentradas hasta <10 mL (~10 mg/mL de proteína total). La proteína concentrada es separada por cromatografía de exclusión de tamaño Superdex™ 200 (Amersham en buffer C (25 mM Tris, pH 7.5, 0.1 M NaCl, 10 mM 2–mercaptoetanol, 10% glicerol). Las fracciones son analizadas mediante SDS–PAGE y las fracciones apropiadas son reunidas y concentradas hasta ~1 mg/mL. La proteína es almacenada en alícuotas a –80°C.

Purificación alternativa de GST–cMET humano de células de Baculovirus

Se disgregaron células de Baculovirus en 5x (volumen/ peso) de Buffer de Lisis (50 mM de HEPES, pH 8,0, 0,25 M NaCl, 5 mM de mercaptoetanol, 10% de glicerol, más Inhibidores de Proteasa Completos (Roche (#10019600), 1 tableta por 50 mL de buffer). La suspensión de células lisadas es centrifugada a 100.000 x g (29.300 rpm) en una ultracentrifugadora Beckman rotor Ti45 durante 1 h. El sobrenadante es incubado con 10 ml de Glutationa Sepharose 4B de Amersham Biosciences (#27–4574–01). La incubación se lleva a cabo durante la noche (aproximadamente 8°C). La resina y el sobrenadante se vertieron en una columna descartable del tamaño apropiado y se recogió el flujo a través del sobrenadante. La resina se lavó con volúmenes de 10 columna (100 mL) de Buffer de Lysis. ElGST–cMET es eluido con 45 mL de Glutationa 10 mM Sigma # G–4251) en Buffer de lisis. La elución es recogida en fracciones de 15 mL. Se pasa alícuotas de las fracción de elución sobre SDS PAGE (12% Tris Gell de glicina, Invitrogen, #EC6005BOX). El gel se tiñe con 0,25% de tinte Azul de Coomassie. Las fracciones con GST–cMET se concentran con un Concentrador Vivaspin 20 mL (#VS2002; 10,00 MW de corte hasta un volumen final inferior a 2,0 ml. La solución GST–cMET concentrada e es aplicada a una columna Superdex 75 16/60 (Amersham Biosciences #17–1068–01) equilibrada con 25 mM de Tris, pH 7.5, 100 mM NaCl, 10 mM de mercaptoetanol, 10% de glicerol. El GST–cMET es eluído con una serie isocrática del buffer anterior, recogiendo el eluyente en fracciones de 1,0 mL. Las fracciones con lecturas OD_{280} significativas se efectúan en otro gel de Tris Glicina al 12%. Se reúnen los tubos pico con GST–cMET y se lee el OD_{280} con la columna buffer mencionada anteriormente como buffer blanco.

La fosforilación del GST–cMET purificado se lleva a cabo por incubación de la proteína durante 3 h a RT con lo siguiente:

	Concentración final
a) 100 mM ATP (Sigma #A7699)	25 mM
b) 1,0 M $MgCl_2$ (Sigma #M–0250)	100 mM
c) 200 mM de Ortovanadato de Sodio (Sigma #S–6508)	15 mM

d) 1,0 M Tris–HCl, pH 7.00 (en casa
) 50 mM
e) H_20
f) GST–cMET 0.2 – 0.5 mg/mL

Después de la incubación, la solución es concentrada en un Concentrador Vivaspin 20 ml hasta un volumen de menos de 2,00 ml. La solución es aplicada a la misma columna Superdex 75 16/60 usada anteriormente después de re–equilibración. El GST–cMET es eluído tal como se describió anteriormente. Las fracciones de elución que corresponden al primer pico eluido en el cromatograma se efectúan al 12% de gel Tris Glicina, tal como, para identificar las fracciones con GST–cMET. Las fracciones son reunida y se lee el OD_{280} usando el buffer de columna como blanco.

Se prepara un Buffer de reacción de Quinasa de la siguiente manera:

			Por 1 L
60 mM HEPES $_p$H 7.4	carga 1 M	16.7 X	60 mL
50 mM NaCl	carga 5 M	100 X	10 mL
20 mM $MgCl_2$	carga 1 M	50 X	20 mL
5 mM $MnCl_2$	carga 1 M	200 X	5 mL

Mientras se lleva a cabo el ensayo, se agrega nuevamente:

2 mM DTT	carga 1 M	500 X
0.05 % BSA	carga 5 %	100 X
0.1 mM Na_3OV_4	carga 0,1 M	1000 X

El buffer HTRF contiene:
50 mM Tris–HCl ($_p$H 7.5), 100 mM NaCl, 0,1 % BSA, 0,05 % Tween 20,5 mM EDTA

Se agrega nuevo SA–APC (Conjugado de PJ25S Phycolink Estreptavidin–Aloficocianina, Prozyme Inc.) y Eu–PT66 (Eu–W1024 rotulado con anticuerpo anti–fosforotirosina PT66, AD0069, Lote 168465, Perkin–Elmer Inc.) para alcanzar la concentración final:

0,1 nM Eu–PT66 final
11 nM SA–APC final

Métodos:

1. Diluir enzima GST–cMet (P) en buffer quinasa de la manera siguiente:
Preparar 8 nM de solución de trabajo GST–cMet (P) (7,32 µM a 8 nM, 915 X, 10 µL a 9,15 mL). En una placa transparente de 96 receptáculos [Costar # 3365] se agregan 100 µL en once columnas, en una columna se agregan solo 100 µL de buffer de reacción quinasa.

2. Preparación de placa de ensayo:

Usar Biomek FX para transferir 10 µL de 8 nM de enzima GST–cMet (P), 48,4 µL de buffer de reacción de quinasa, 1,6 µL de compuesto en DMSO) (Concentración de inicio a 10 mM, 1 mM y 0,1 mM, dilución consecutiva 1:3 hasta alcanzar 10 puntos de ensayo) en una placa transparente costar de 96 receptáculos [Costar # 3365], mezclar varias veces. Incubar luego la placa a RT durante 30 min.

3. Preparar solución de trabajo Gastrin y ATP en buffer de reacción de quinasa, de la manera siguiente:

Preparar solución de trabajo de 4 µM de Gastrin y 16 µM de ATP

		Por 10 mL
carga de Gastrin 4 µM	(500 µM to 4 µM, 125 X)	80 µL
ATP 16 µM de carga	(1000 µM hasta 16 µM, 62.5 X)	160 µL

Usar Biomek FX para agregar una solución de trabajo de 20 µl de ATP y Gastrin a la placa de ensayo para in iniciar la reacción, incubar la placa a RT durante 1 h.

4. Transferir 5 µL de producto de reacción al cabo 1 h en 80 µL de buffer HTRF en una placa negra [Costar # 3356], leer en Discover después de 30 min. de incubación.

Resumen de Condición de Ensayo:

K_M ATP *	–	6 µM
[ATP]	–	4 µM
K_M Gastrin/p(EY)	–	3.8 µM
[gastrin]	–	1 µM
[enzima]	–	1 nM

K_M ATP, K_M gastrin para varias enzimas se determina mediante rotulación de HTRF/^{33}P y métodos HTRF.

Los ejemplos 1–28, 30, 33–34, 36–37, y 39–48 exhibieron actividad con valores CI_{50} de menos de 0,5 µM.

Ensayo de autofosforilación basado en células c–Met

Células PC3 humanas y CT26 de ratón son asequibles y obtenidas en ATCC. Las células fueron cultivadas en un medio de crecimiento que contenía RPMI 1640, penicilina/ estreptomicina/ glutamina (1X) y 5% FBS. 2 x 10^4 células de cada medio, fueron depositadas en cada receptáculo de una placa de 96 receptáculos y se incubaron a 37 °C durante la noche. Las células se privaron de suero, reemplazando el medio de crecimiento con un medio básico (DMEM de glucosa baja + 0,1 de BSA, 120 µL por receptáculo) a 37 °C durante 16 h. Los compuestos (tanto de 1 mM como de 0,2 mM) en 100% de DMSO, se diluyeron en forma seriada (1:3) 3333 veces en una placa de 96 receptáculos, diluyendo 1,3

con DMSO de la columna 1 hasta la columna 11 (las columnas 6 y 12 no reciben compuesto). Las muestras de compuesto (2,4 µL por receptáculo) se diluyeron en un medio básico (240 µL) en una placa de 96 receptáculos. Las células se lavaron una vez con un medio básico (GIBCO, DMEM 11885–076) y luego se agregó solución del compuesto (100 µL). Las células fueron incubadas a 37 °C durante 1 h. Una solución (2 mg/ mL) de CHO–HGF (7.5 µL) fue diluida con 30 mL de medio básico para proporcionar una concentración final de 500 ng/ mL. Este medio que contenía HGF (120 µL) fue transferido a una placa de 96 receptáculos. Se agregaron (1,2 µL) de compuesto al medio que contenía HGF y se mezcló bien. La mezcla de medio/ HG/ compuesto (100 µL) se agregó a las células (concentración final HGF – 250 ng/ mL) y luego se incubó a 37 °C durante 10 min. Se preparó un buffer de lisado de células (20 mL) que contenía 1% de Triton X–100, 50 mM de Tris a pH 8,0, 100 mM de NaCl, Inhibidor de proteasa (Sigma, #P–8340) 200 µL, inhibidor de Proteasa Roche (Completo, # 1–697–498) 2 tabletas, Inhibidor II de Fosfatasa (Sigma, #P–5726) 200 µL, y una solución de vanadato de sodio que contenía 900 µL de PBS, 100 µL de 300 mM de $NaVO_3$, 6 µL de H_2O_2 (carga al 30% y agitación a RT durante 15 min) (90 µL). Las células se lavaron una vez con 1X PBS enfriado con hielo (GIBCO, #14190–136), luego se agregó buffer de lisis (60 µL) y las células se incubaron en hielo durante 20 min.

El ensayo IGEN se llevó a cabo de la manera siguiente: Un granulado de estreptavidina, Dynabeads M–280 fue pre–incubado con HGFR anti–humano biotinilado (240 µL de HGFR anti–humano (sistema R&D, BAF527 o BAF328) @ 100 µg/mL + 360 µL de Granulado (IGEN #10029 + 5.4 µL buffer – PBS/ 1% BSA/0.1% Tween 20) por rotación durante 30 min a RT. El granulado de anticuerpos (25 µL) fue transferido a una placa de 96 receptáculos. Una solución de lisado de células (25 µL) fue agregada por transferencia y la placa se agitó a RT durante 1 h. Se agregó anti–fosfotirosina 4G10 (Upstate 05–321) (19,7 µL anticuerpo + 6 mL 1X PBS) (12.5 µL), a cada uno de los receptáculos y luego se incubó durante 1 h a RT. Se agregó IgG ORI–Tag nti–ratón (ORIGEN #110087) (24 µL de Anticuerpo + 6 mL buffer) (12,5 µL) a cada uno de los receptáculos y luego se incubó a RT durante 30 min. Se agregó 1X PBS (175 µL) a cada receptáculo y se leyó la electroquimioluminiscencia mediante IGEN M8. Los datos en bruto fueron analizados usando una ecuación de ajuste de 4 parámetros en XLFit. Luego se determinaron los valores de CI_{50} usando software Grafit. Los ejemplos 2, 4, 6–8, 11, 13, 15–21, 23–26, 36–37, 39, 41, y 43–44 exhibieron actividad en células PC3 con valores de CI_{50} de menos de 1,0 µM. Los ejemplos 2, 4, 6–8, 11–13, 15–21, 23–26, 36–37, 41, y 43–44 exhibieron actividad en células CT26 con valores de CI_{50} de menos de 1,0 µM.

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rHu–bFGF: Concentración de carga de 180 ng/ µL: R&D rHu– bFGF: Se agregaron 139 µL del vehículo apropiado anterior a un frasco de 25 µg. liofilizado. 13,3 µL del frasco de carga [180 ng/nµL] y 26,6 µL de vehículo agregado, para proporcionar una concentración final de 3,75 µM de concentración.

Preparación de disco de nitro–celulosa: La punta de una aguja de calibre 20 fue jaquelada y se biseló con papel esmeril para crear un punzón. Esta punto se usó luego para cortar discos de ≅ 0,5 mm de diámetro a partir de una hoja de papel filtro de nitrocelulosa (Gelman Sciences). Los discos preparados se colocaron luego en tubos microcentrifugadores Eppendorf que contenían soluciones de cualquiera de 0,1% de BSA en vehículo PBS, 10 µM de rHu–VEGF (R&D Systems, Minneapolis, MN), o bien 3,75 µM de rHu–bFGF (R&D Systems, Minneapolis, MN) y se dejaron en remojo durante 45–60 min. antes de usarlos Cada disco de filtro de nitrocelulosa absorbe aproximadamente 0,1 µL de solución.

En el ensayo de micro bolsa de rata, los compuestos de la presente invención inhibirán la angiogénesis a una dosis de menos de 50 mg/kg/día.

Modelo de tumor

Células A431 (ATCC) expandieron el cultivo, se cosecharon y se inyectaron subcutáneamente a ratones atímicos hembras de 5–8 semanas de vida (CD1 nu/nu, Charles River Labs) (n = 5–15). La administración subsiguiente del compuesto por introducción oral forzada (10 – 200 mpk/ dosis) comienza en cualquier momento desde el día 0 hasta el día 29 post desafío con células tumorales y generalmente continúa una vez o dos por día en toda la duración del experimento. El avance del crecimiento del tumor es seguido de tres mediciones de calibre dimensional y se registra como función del tiempo. El análisis estadístico inicial se efectúa por análisis de mediciones repetidas de variancia (RMANOVA), seguido de ensayos Scheffe post hoc para comparaciones múltiples. El vehículo solo (Ora–Plus, pH 2,0) es el control negativo. Los compuestos de la presente invención serán activos en dosis de menos de 150 mpk.

Modelos de tumor

Células tumorales de glioma humano (células U87MG, ATCC) se expandieron en cultivo, se cosecharon y se inyectaron subcutáneamente en ratones atímicos hembras, de 5–8 semanas de vida (CD1 nu/nu, Charles River Labs) (n=10). La administración subsiguiente del compuesto por introducción oral forzada o por IP (10 – 100 mpk/ dosis) comienza en cualquier momento desde el día 0 hasta el día 29 post desafío con células tumorales y generalmente continúa una vez o dos por día en toda la duración del experimento. El avance del crecimiento del tumor es seguido de tres mediciones de calibre dimensional y se registra como función del tiempo. El análisis estadístico inicial se efectúa por mediciones repetidas de análisis de variancia (RMANOVA), seguido de ensayos Scheffe post hoc para comparaciones múltiples. El vehículo solo (Claptisol o similares) es el control negativo. Los compuestos de la presente invención serán activos en dosis de menos de 150 mpk.

Células tumorales de adenocarcinoma gástrico humano (células MKN45, ATCC) son expandidas en cultivo, cosechadas e inyectadas subcutáneamente a ratones atímicos hembra de 5–8 semanas de vida (CD1 nu/nu, Charles River Labs) (n=10). La administración subsiguiente del compuesto por introducción oral forzada o por IP (10 – 100 mpk/ dosis)

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comienza desde el día 0 hasta el día 29 post desafío con células tumorales y generalmente continúa una vez o dos por día en toda la duración del experimento. El avance del crecimiento del tumor es seguido de tres mediciones de calibre dimensional y se registra como función del tiempo. El análisis estadístico inicial se efectúa por análisis de mediciones repetidas de variancia (RMANOVA), seguido de ensayos Scheffe post hoc para comparaciones múltiples. El vehículo solo (captisol, o similares) es el control negativo. Los compuestos de la presente invención serán activos en dosis de menos de 150 mpk.

FORMULACIONES

Está también abarcada en esta invención una clase de composiciones farmacéuticas que comprenden los compuestos activos de la presente invención en asociación con uno o más portadores y/o diluyentes y/ o coadyuvantes no tóxicos, (denominados colectivamente aquí como materiales "portadores") y, si se desea, otros ingredientes activos. Los compuestos activos de la presente invención pueden administrarse mediante cualquier vía apropiada, preferiblemente en forma de una composición farmacéutica adaptada a dicha vía, y en una dosis eficaz para el tratamiento propuesto. Los compuestos y composiciones de la presente invención pueden, administrarse por ejemplo, por vía oral, mucosal, tópica, rectal, pulmonar tal como por inhalación de rocío, o parenteralmente, intrravascularmente, intravenosamente, intraperitonealmente, subcutáneamente, intramuscularmente, intraesternalmente y por técnicas de infusión, en formulaciones de dosis unitaria que contienen portadores, coadyuvantes y vehículos farmacéuticamente aceptables convencionales.

Los compuestos farmacéuticamente activos de esta invención pueden procesarse de acuerdo con métodos convencionales de farmacia para producir agentes medicinales para la administración a pacientes, incluyendo seres humanos y otros mamíferos.

Para administración oral, la composición farmacéutica puede estar en forma de, por ejemplo, una tableta, cápsula, suspensión o líquido. La composición farmacéutica se prepara preferiblemente en forma de una unidad de dosificación que contiene una cantidad particular de ingrediente activo. Ejemplos de dichas unidades de dosificación son tabletas o cápsulas. Por ejemplo, éstas, pueden contener una cantidad de ingrediente activo comprendida entre aproximadamente 1 hasta 2000 mg, preferiblemente desde aproximadamente 1 hasta aproximadamente 1 hasta aproximadamente 500 mg. Una dosis diaria apropiada para seres humanos u otros mamíferos puede variar ampliamente dependiendo del estado del paciente y de otros factores, pero, una vez más, puede determinarse usando métodos rutinarios.

La cantidad de compuestos que se administran y el régimen de dosificación para tratar una enfermedad con los compuestos y/ o composiciones de esta invención depende de una variedad de factores, incluyendo la edad, el peso, el sexo y el estado de medicación del sujeto, el tipo de enfermedad, la gravedad de la enfermedad, la vía y frecuencia de administración, y el compuesto particular empleado. Por lo tanto, el régimen de dosificación puede variar ampliamente, pero puede ser determinado rutinariamente usando métodos convencionales. Una dosis diaria de aproximadamente 0,01 hasta 500 mg/ kg,

preferiblemente de entre aproximadamente 0,01 hasta aproximadamente 50 mg/ kg, y más preferiblemente aproximadamente 0,01 hasta aproximadamente 30 mg/kg de peso corporal, pueden ser apropiadas. La dosis diaria puede administrarse de una a cuatro dosis por día.

Para propósitos terapéuticos, los compuestos activos de la invención se combinan comúnmente con uno o más coadyuvantes apropiados para la vía de administración indicada. Si se administran per os, los compuestos pueden mezclarse con lactosa, sucrosa, polvo de almidón, ésteres de celulosa de ácidos alcanoicos, ésteres de alquil celulosa, talco, ácido esteárico, estearato de magnesio, óxido de magnesio, sales de sodio y calcio de ácidos fosfórico y sulfúrico, goma acacia, alginato de sodio, polivinil pirrolidona, y/ o alcohol polivinílico, y luego se forman tabletas o encapsulados para una administración conveniente. Dichas cápsulas o tabletas pueden contener una formulación de liberación controlada tal como la que puede ser provista en una dispersión de compuesto activo en hidroxipropilmetil celulosa, mezclada con lactosa, sucrosa, almidón en polvo, ésteres de celulosa de ácidos alcanoicos, alquil ésteres de celulosa, talco, ácido esteárico, estearato de magnesio, óxido de magnesio, sales de sodio y de calcio de ácidos fosfórico y sulfúrico, gelatina, goma acacia, alginato de sodio, polivinil pirrolidona y/ o alcohol polivinílico y luego se forman tabletas o se encapsulan para una administración conveniente. Dichas cápsulas o tabletas pueden contener una formulación de liberación controlada que puede proveerse en una dispersión de compuesto activo en hidroxipropil metil celulosa.

En el caso de psoriasis y otras enfermedades de la piel, puede ser preferible aplicar una preparación tópica apropiada para que penetre a través de la piel (por ejemplo linimentos, lociones, ungüentos, cremas o pastas) y gotas apropiadas para administración al ojo, oído o nariz. Una dosis tópica apropiada de ingrediente activo de un compuesto de la invención es de 0,1 mg hasta 150 mg administrado de una a cuatro, preferiblemente una o dos veces por día. Para administración tópica, el ingrediente activo puede comprender desde 0,001% hasta 10% p/p, por ejemplo, de 1% a 2% en peso de la formulación, aunque puede comprender tanto como 10% p/p, pero preferiblemente no más de 5% p/p, y más preferiblemente desde 0,1% hasta 1% de la formulación.

Cuando se formula como un ungüento, los ingredientes activos pueden emplearse tanto con una base de ungüento parafínico como con una base de ungüento miscible en agua. Alternativamente, los ingredientes activos pueden formularse en una crema con una base de crema de aceite en agua. Si se desea, la fase acuosa de la base de crema puede incluir, por ejemplo, por lo menos 30% p/p de un alcohol polihídrico tal como propilen glicol, butano–1,3–diol, manitol, sorbitol, glicerol, polietilen glicol y mezclas de los mismos. La formulación tópica puede incluir convenientemente un compuesto, que realza la absorción o penetración del ingrediente activo a través de la piel u otras áreas afectadas. Ejemplos de dichos realzadores de penetración dérmica incluyen DMSO y análogos relacionados.

Los compuestos de esta invención pueden administrarse también mediante un dispositivo transdérmico. Preferiblemente la administración transdérmica se llevará a cabo usando un parche, el cual puede ser del reservorio y del tipo de membrana porosa o de una

variedad de matriz sólida. En cualquier caso, el agente activo es liberado continuamente del reservorio o de las microcápsulas a través de una membrana dentro del adhesivo permeable al agente activo, el cual está en contacto con la piel o mucosa del receptor. Si el agente activo es absorbido a través de la piel, se administra al receptor un flujo controlado y predeterminado de agente activo. En el caso de microcápsulas, el agente encapsulante puede funcionar también como membrana.

La fase oleosa de las emulsiones de esta invención puede constituirse con ingredientes conocidos de manera conocida. Aunque la fase puede comprender simplemente un emulsionante, puede comprender una mezcla de por lo menos un emulsionante con una grasa o un aceite o con ambos, una grasa y un aceite. Preferiblemente, está incluido un emulsionante hidrofílico conjuntamente con un emulsionante lipofílico que actúa como estabilizador. También se prefiere incluir a ambos, un aceite y una grasa. Conjuntamente, los emulsionantes con o sin estabilizador constituyen lo que se denomina cera emulsionante, y la cera junto con el aceite y grasa constituyen lo que se denomina base de ungüento emulsionante, que forma la fase oleosa dispersada de las formulaciones de crema. Los emulsionantes y estabilizadores de emulsión apropiados para ser usados en la formulación de la presente invención incluyen Tween 60, Span 80, alcohol cetostearílico, alcohol miristílico, monoestearato de glicerilo, lauril sulfato de sodio, diestearato de glicerilo solo o con una cera, u otros materiales bien conocidos en la materia.

La elección de aceites o grasas apropiadas para la formulación se basa en lograr las propiedades cosméticas deseadas, debido a que la solubilidad del compuesto activo en la mayoría de los aceites, que probablemente se usarán en las formulaciones de emulsión farmacéutica es muy baja. Por lo tanto, la crema debería ser preferiblemente un producto no graso, que no manche y que sea lavable con consistencia apropiada para evitar fugas desde los tubos u otros contenedores. Pueden usarse ésteres de alquilo de cadena recta o ramificada, mono– o dibásicos, tales como diisoadipato, estearato de isocetilo, diéster de propilen glicol de ácidos grasos de coco, miristato de isopropilo, oleato de decilo, palmitato de isopropilo, estearato de butilo, palmitato de 2–etilhexilo o una mezcla de ésteres de cadena ramificada. Estos pueden usarse solos o en combinación, dependiendo de las propiedades requeridas. Alternativamente, pueden usarse lípidos de alto punto de fusión, tales como parafina blanda blanca y/ o parafina líquida u otros aceites minerales.

Formulaciones apropiadas para administración tópica al ojo incluyen también gotas para los ojos, donde los ingredientes activos están disueltos o suspendidos en un portador apropiado, especialmente un solvente acuoso para los ingredientes activos. Los ingredientes activos están presentes preferiblemente en dichas formulaciones en una concentración de 0,5 a 20%, ventajosamente 0,5 a 10% y particularmente aproximadamente 1,5% p/p.

Las formulaciones para administración parenteral pueden estar en forma de soluciones o suspensiones para inyección estéril isotónica acuosa o no acuosa. Estas soluciones y suspensiones pueden prepararse a partir de polvos o gránulos estériles usando uno o más de los portadores o diluyentes mencionados para uso en las formulaciones para

administración oral o mediante el uso de otros agentes dispersantes o humectantes apropiados y agentes de suspensión. Los compuestos pueden disolverse en agua, polietilen glicol, propilen glicol, etanol, aceite de maíz, aceite de semilla de algodón, aceite de maní, aceite de sésamo, alcohol bencílico, cloruro de sodio, goma tragacanto, y/ o varios buffers. Otros coadyuvantes y modos de administración son bien y ampliamente conocidos en la técnica farmacéutica. El ingrediente activo puede administrarse también por inyección en forma de una composición con portadores apropiados que incluyen solución salina, dextrosa o agua, o con ciclodextrina (por ejemplo, Captisol), solubilización cosolvente (por ejemplo propilen glicol) o solubilización micelar (por ejemplo Tween 80).

La preparación inyectable estéril puede ser también una solución o suspensión inyectable estéril en un diluyente o solvente no tóxico parenteralmente aceptable, por ejemplo como una solución en 1,3–butanodiol. Entre los vehículos y solventes aceptables que pueden emplearse están el agua, solución de Ringer y solución de cloruro de sodio isotónico. Además, convencionalmente se emplea aceites estériles, fijados, como medio solvente o de suspensión. Para ese propósito puede emplearse cualquier aceite blando fijado, incluyen mono– o diglicéridos sintéticos. Además, ácidos grasos tales como ácido oleico son útiles en la preparación de inyectables.

Para administración pulmonar, la composición farmacéutica puede administrarse en forma de un aerosol o con un inhalador incluyendo aerosol en polvo seco.

Los supositorios para administración rectal de la droga pueden prepararse mezclando la droga con un excipiente no irritante conocido, tal como manteca de cacao y polietilen glicoles que son sólidos a las temperaturas ordinarias pero líqudios a la temperatura rectal y por lo tanto se fundirán en el recto y liberarán la droga.

Las composiciones farmacéuticas pueden someterse a operaciones farmacéuticas convencionales tales como esterilización y/o pueden contener coadyuvantes convencionales, tales como preservadores, estabilizadores, agentes humectantes, emulsionantes, buffers etc. Adicionalmente pueden prepararse tabletas y pastillas con recubrimientos entéricos. Dichas composiciones pueden comprender también coadyuvantes, tales como agentes humectantes, edulcorantes, saborizantes y perfumantes.

Lo que antecede, es simplemente ilustrativo de la invención y no se considera limitativo de la invención para los compuestos descritos. Las variaciones y cambios, que son obvios para un experto en la materia, están destinados a entrar dentro del alcance y naturaleza de la invención, los cuales son definidos en las reivindicaciones anexas.

Con la descripción anterior, un experto en la materia podrá verificar fácilmente las características esenciales de esta invención, y sin apartarse del espíritu y alcance de la misma, pueden efectuar varios cambios y modificaciones en la invención para adaptarla a varios usos y condiciones.

No se esperan efectos toxicológicos inaceptables cuando los compuestos de la presente invención son administrados de acuerdo con la presente invención.

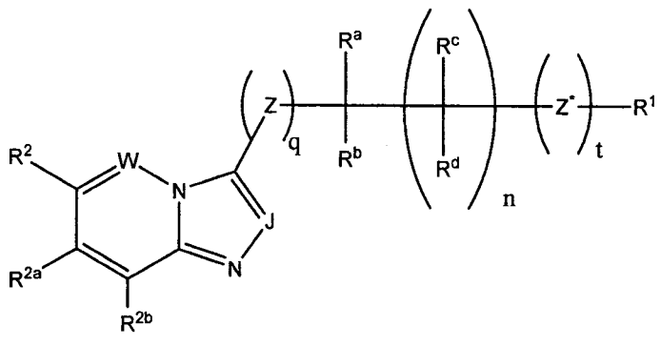
Todas las referencias, patentes, solicitudes y publicaciones mencionadas, se incorporan aquí como referencia en su totalidad, de la misma manera que si estuvieran escritas aquí.

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REIVINDICACIONES

1. Un compuesto de fórmula I



I

donde

J es N o CR^3;

W es CR^{2b} o N;

Z y Z* son independientemente –O–, $-S(O)_v-$, o $-NR^5-$;

R^a, R^b, R^c y R^d son cada uno independientemente H, halo, alquilo, alquenilo, alquinilo, haloalquilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, $-NO_2$, –CN, $-NR^5R^{5a}$, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$; $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-OC(=O)NR^5R^{5a}$, $-S(O)_vR^4$, $-S(O)_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$ cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia;

o R^a y R^b conjuntamente con el átomo de carbono al cual están unidos pueden combinarse para formar un cicloalquilo de 3–10 miembros, un anillo cicloalquenilo de 3–10 miembros, o un anillo heterociclo, cualquiera de los cuales puede estar opcionalmente sustituido con uno o más grupos R^{10} según lo permita la valencia.;

o R^c y R^d conjuntamente con el átomo de carbono al cual están unidos pueden combinarse para formar un cicloalquilo de 3–10 miembros, un anillo cicloalquenilo de 3–10 miembros, o un anillo heterociclo, cualquiera de los cuales puede estar opcionalmente sustituido con uno o más grupos R^{10} según lo permita la valencia.;

o R^a y/o R^b pueden combinarse con cualquiera de R^c o R^d para formar un anillo cicloalquilo de 3–8 miembros parcial o totalmente saturado o un anillo heterociclo, cualquiera de los cuales puede estar opcionalmente sustituido con uno o más grupos R^{10} según lo permita la valencia;

o R^a y R^b pueden combinarse para formar un grupo carbonilo;

o R^c y R^d unidos al mismo átomo de carbono pueden combinarse para formar un grupo carbonilo;

R^1 es arilo, heteroarilo o heterociclo cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia;

R^2 es

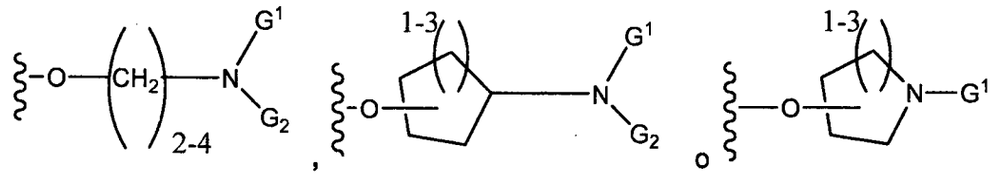
(i) H, halo, ciano, nitro, o

(ii) alquilo, haloalquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilo, $-OR^4$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más R^{10} según lo permita la valencia,

con la condición de que en los compuestos de fórmula I cuando W y J son ambos N, R^2 es distinto

(c) $-NR^5R^{5a}$ donde R^5 y R^{5a} son independientemente H, alquilo, haloalquilo, cicloalquilo, alquenilo, alquinilo, arilo, heteroarilo, heterociclo, arilalquilo, heteroarilalquilo, heterocicloalquilo, y cicloalquilalquilo; y

(d) fenilo sustituido con un grupo



donde G^1 y G^2 are independently alquilo, cicloalquilo, o G^1 y G^2 together with the nitrogen atom to which they are attached combine to form a 5– to 8–membered heterociclo ring;

R^{2a}, R^{2b} y R^3 están independientemente seleccionados en cada caso de H, halo, ciano, nitro, alquilo, haloalquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilo, $-OR^4$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más R^{10} groups según lo permita la valencia;

R^4 está independientemente seleccionado en cada caso de H, alquilo, haloalquilo, cicloalquilo, alquenilo, alquinilo, arilo, heteroarilo, heterociclo, arilalquilo, heteroarilalquilo, heterocicloalquilo, y cicloalquilalquilo, cada uno de los cuales puede

estar opcionalmente independientemente sustituido según lo permita la valencia con uno o más grupos R^{10};

R^5 y R^{5a} están independientemente seleccionados en cada caso de H, alquilo, haloalquilo, cicloalquilo, alquenilo, alquinilo, arilo, heteroarilo, heterociclo, arilalquilo, heteroarilalquilo, heterocicloalquilo, y cicloalquilalquilo, cualquiera de los cuales pueden estar opcionalmente sustituido según lo permita la valencia con uno o más R^{10};

o R^5 y R^{5a} pueden combinarse para formar un anillo heterociclo opcionalmente sustituido con uno o más R^{10};

R^{10} es independientemente en cada caso, halo, ciano, nitro, oxo, alquilo, haloalquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilo, $-(\text{alquileno})_m-OR^4$, $-(\text{alquileno})_m-S(O)_vR^4$, $-(\text{alquileno})_m-NR^5R^{5a}$, $-(\text{alquileno})_m-C(=O)R^4$, $-(\text{alquileno})_m-C(=S)R^4$, $-(\text{alquileno})_m-C(=O)OR^4$, $-(\text{alquileno})_m-OC(=O)R^4$, $-(\text{alquileno})_m-C(=S)OR^4$, $-(\text{alquileno})_m-C(=O)NR^5R^{5a}$, $-(\text{alquileno})_m-C(=S)NR^5R^{5a}$, $-(\text{alquileno})_m-N(R^5)C(=O)NR^5R^{5a}$, $-(\text{alquileno})_m-N(R^5)C(=S)NR^5R^{5a}$, $-(\text{alquileno})_m-N(R^5)C(=O)R^4$, $-(\text{alquileno})_m-N(R^5)C(=S)R^4$, $-(\text{alquileno})_m-OC(=O)NR^5R^{5a}$, $-(\text{alquileno})_m-OC(=S)NR^5R^{5a}$, $-(\text{alquileno})_m-SO_2NR^5R^{5a}$, $-(\text{alquileno})_m-N(R^5)SO_2R^4$, $-(\text{alquileno})_m-N(R^5)SO_2NR^5R^{5a}$, $-(\text{alquileno})_m-N(R^5)C(=O)OR^4$, $-(\text{alquileno})_m-N(R^5)C(=S)OR^4$, o $-(\text{alquileno})_m-N(R^5)SO_2R^4$;

donde dichos grupos alquilo, haloalquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilo pueden estar además independientemente sustituidos con uno o más $-(\text{alquileno})_m-OR^4$, $-(\text{alquileno})_m-S(O)_vR^4$, $-(\text{alquileno})_m-NR^5R^{5a}$, $-(\text{alquileno})_m-C(=O)R^4$, $-(\text{alquileno})_m-C(=S)R^4$, $-(\text{alquileno})_m-C(=O)OR^4$, $-(\text{alquileno})_m-OC(=O)R^4$, $-(\text{alquileno})_m-C(=S)OR^4$, $-(\text{alquileno})_m-C(=O)NR^5R^{5a}$, $-(\text{alquileno})_m-C(=S)NR^5R^{5a}$, $-(\text{alquileno})_m-N(R^5)C(=O)NR^5R^{5a}$, $-(\text{alquileno})_m-N(R^5)C(=S)NR^5R^{5a}$, $-(\text{alquileno})_m-N(R^5)C(=O)R^4$, $-(\text{alquileno})_m-N(R^5)C(=S)R^4$, $-(\text{alquileno})_m-OC(=O)NR^5R^{5a}$, $-(\text{alquileno})_m-OC(=S)NR^5R^{5a}$, $-(\text{alquileno})_m-SO_2NR^5R^{5a}$, $-(\text{alquileno})_m-N(R^5)SO_2R^4$, $-(\text{alquileno})_m-N(R^5)SO_2NR^5R^{5a}$, $-(\text{alquileno})_m-N(R^5)C(=O)OR^4$, $-(\text{alquileno})_m-N(R^5)C(=S)OR^4$, o $-(\text{alquileno})_m-N(R^5)SO_2R^4$;

y además donde cualquiera de los dos grupos R^{10} unidos al mismo átomo o unidos a átomos adyacentes pueden combinarse para formar un sistema de anillo de 3 a 8 miembros opcionalmente sustituido;

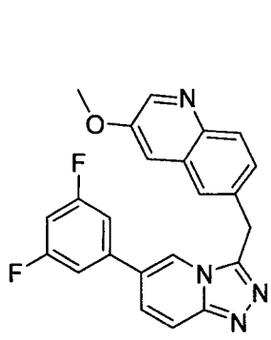
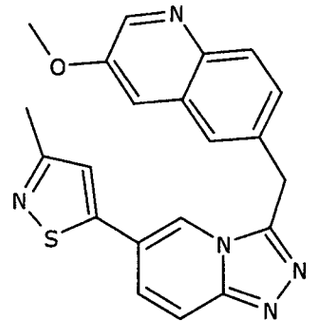
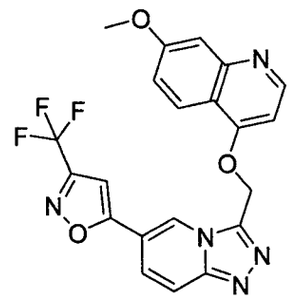
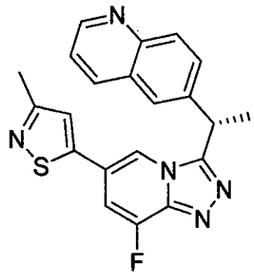
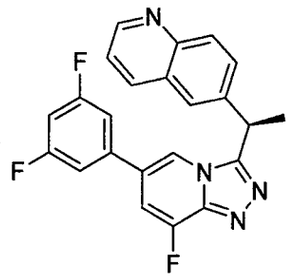
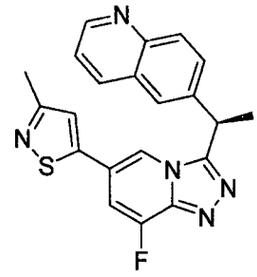
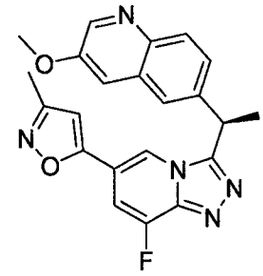
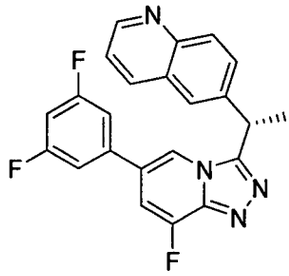
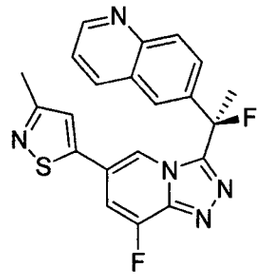
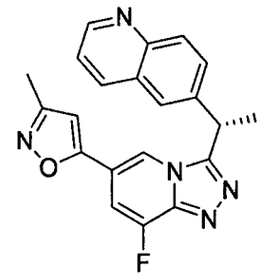
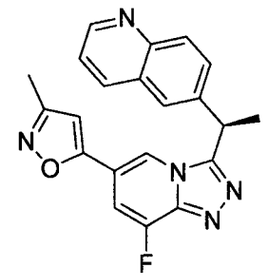
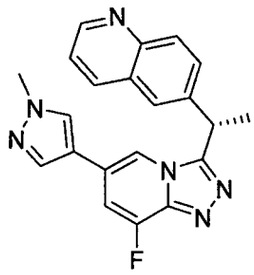
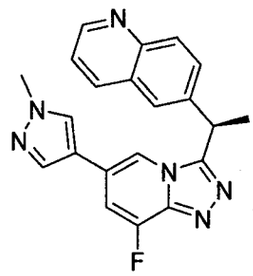
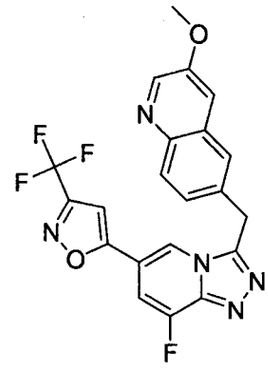
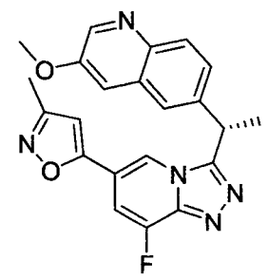
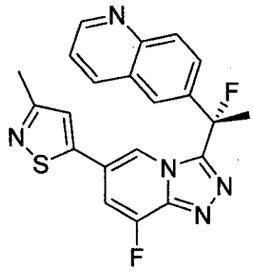
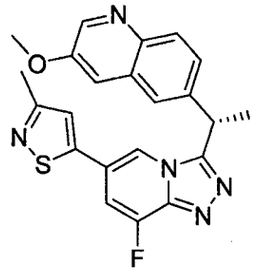
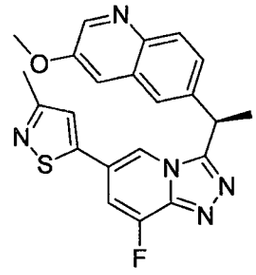
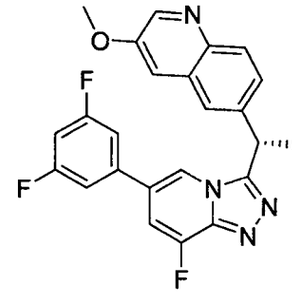
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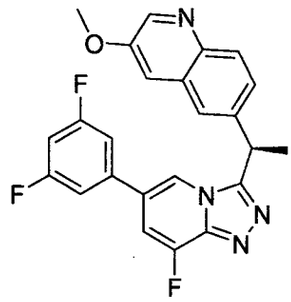
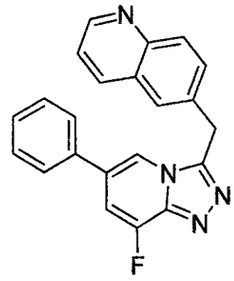
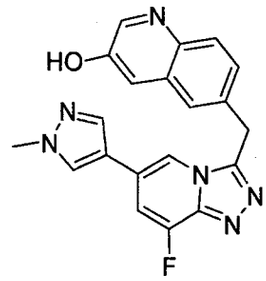
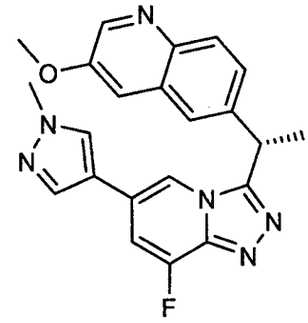
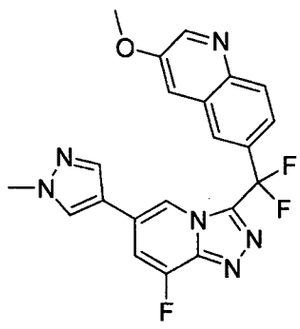
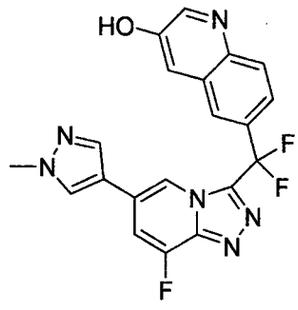
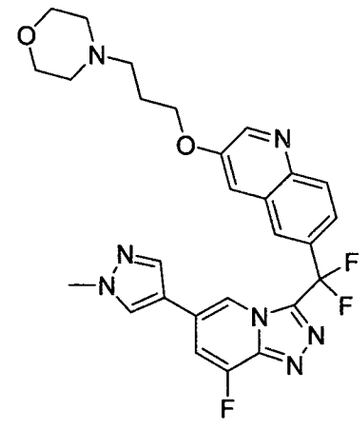
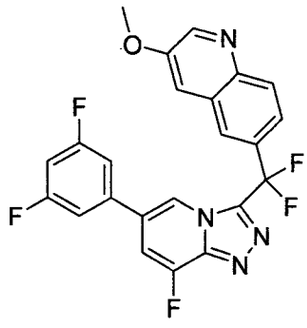
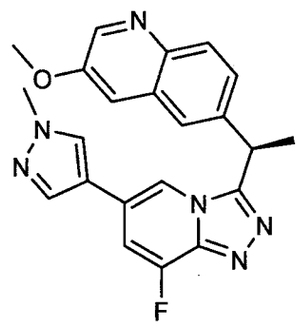
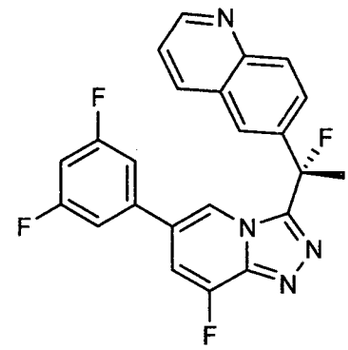
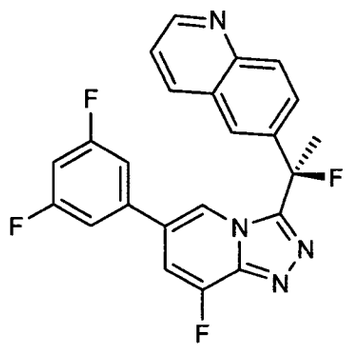
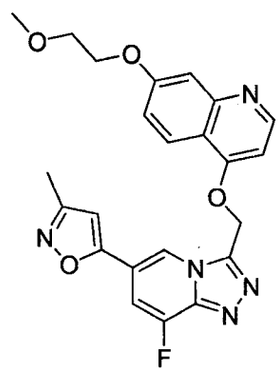
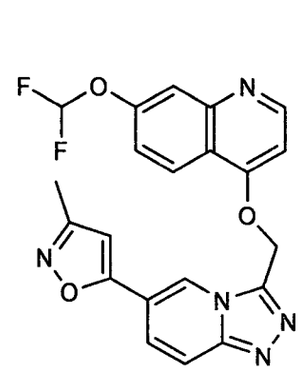
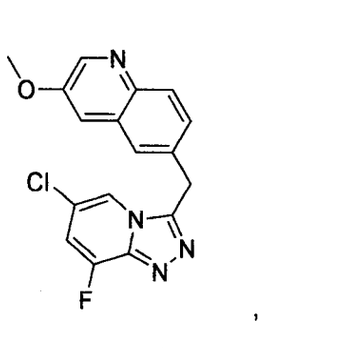
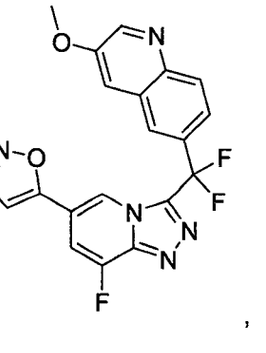
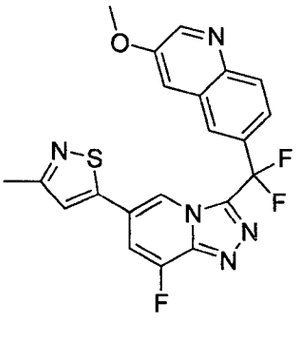
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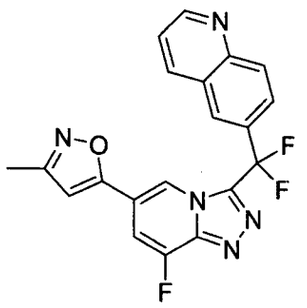
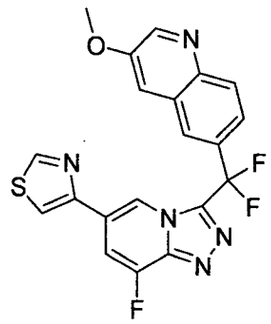
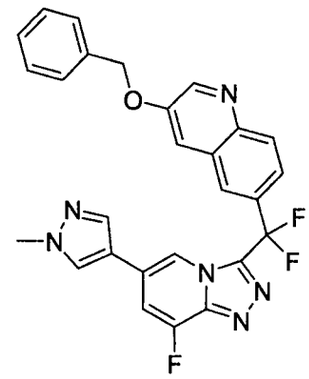
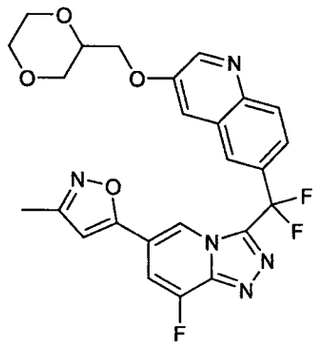
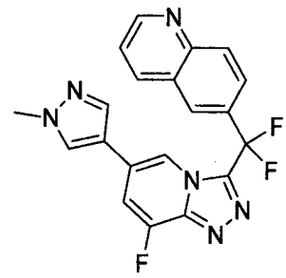
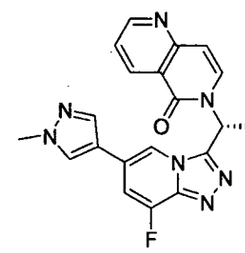
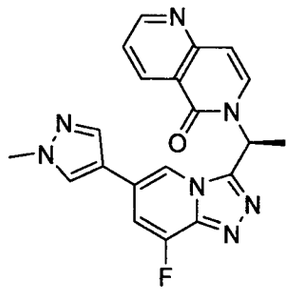
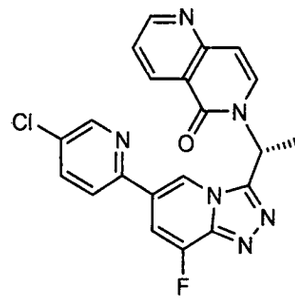
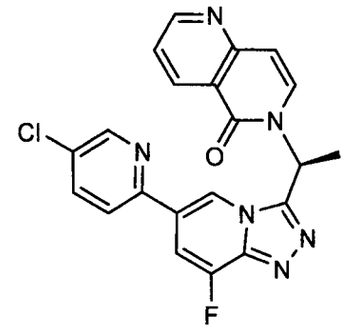
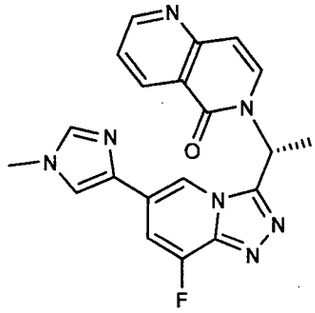
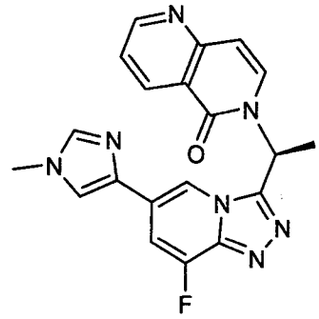
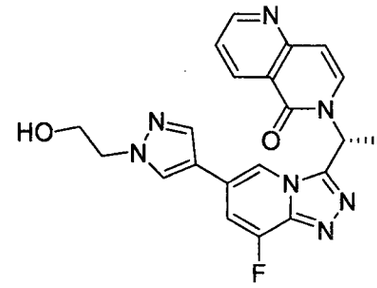
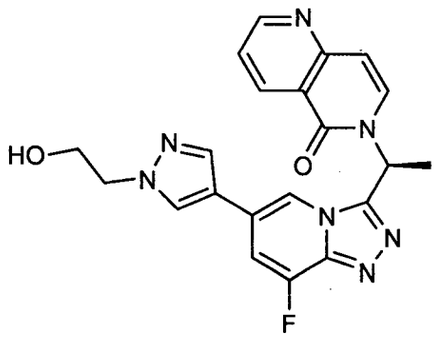
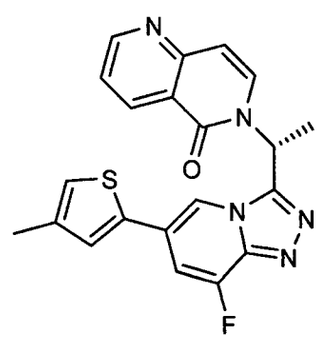
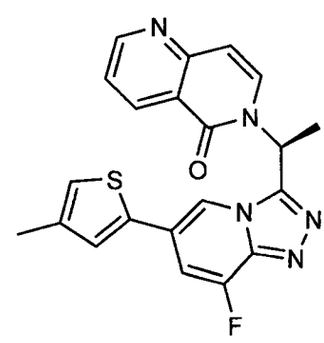

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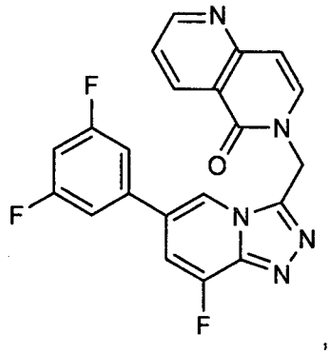
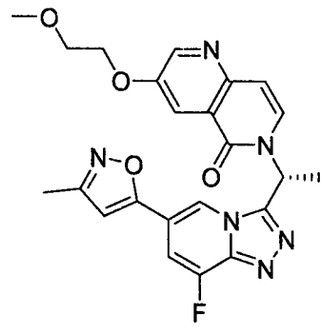
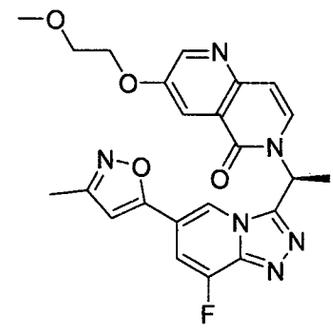
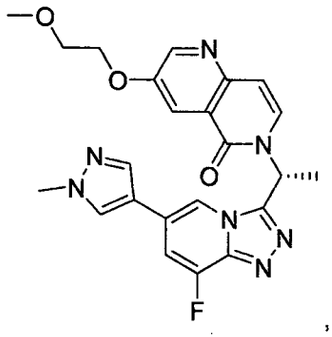
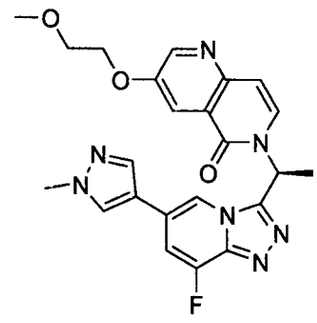
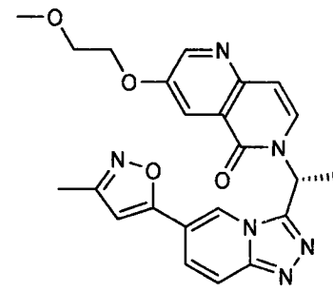
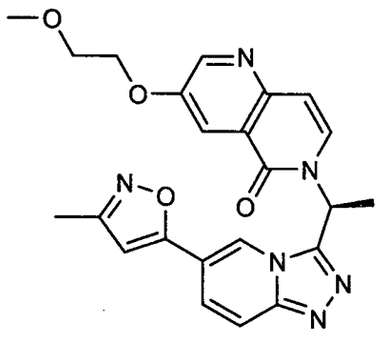
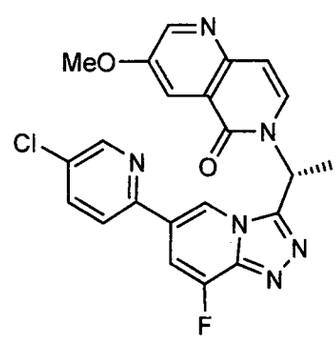
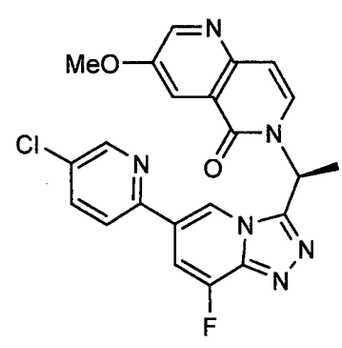
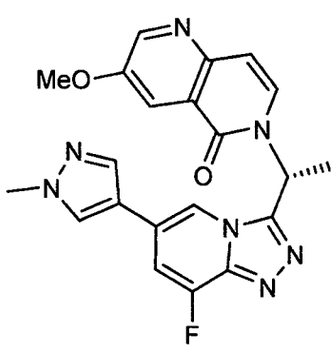
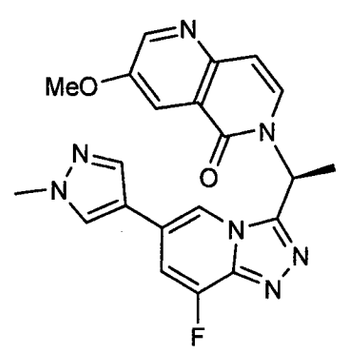
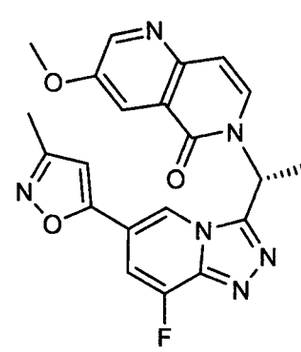
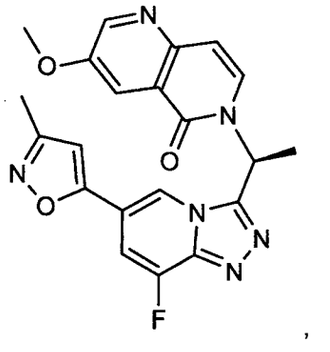
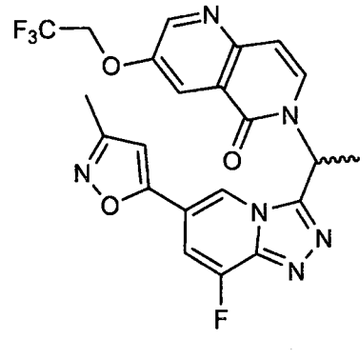
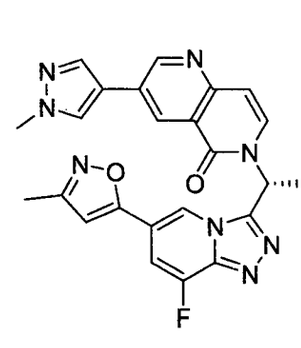
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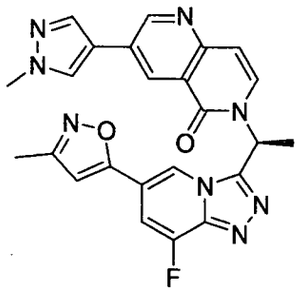
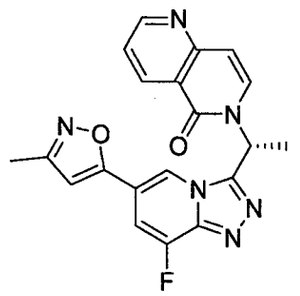
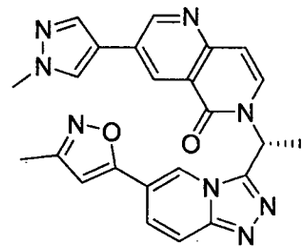
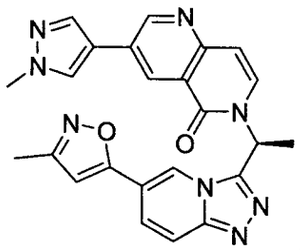
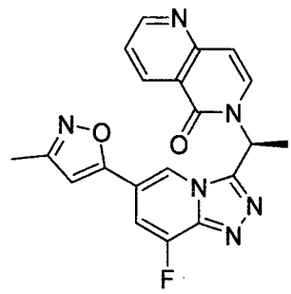
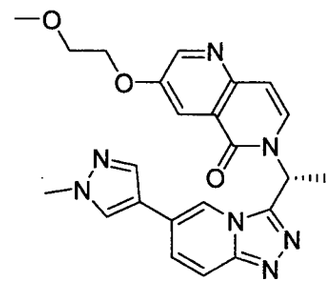
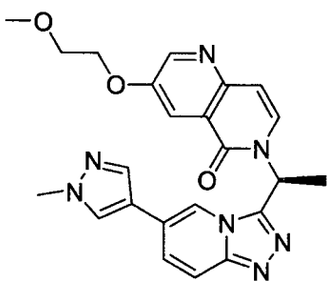
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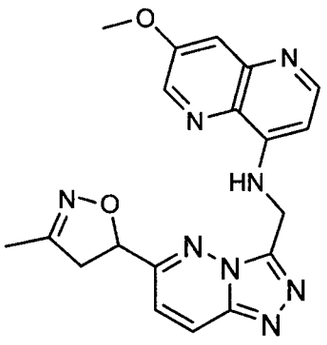
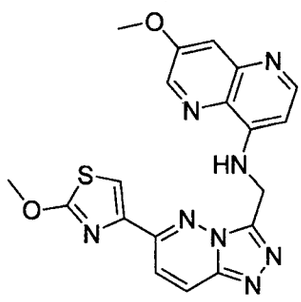
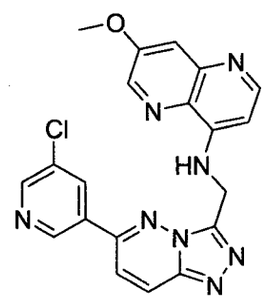
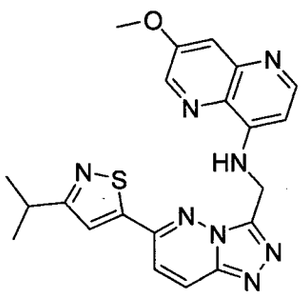
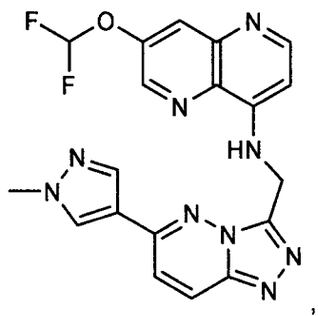
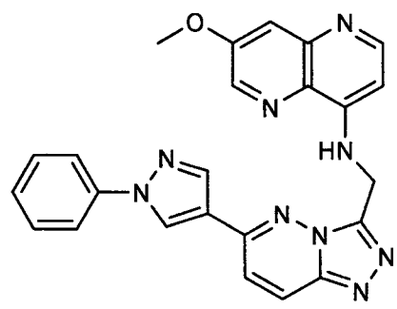
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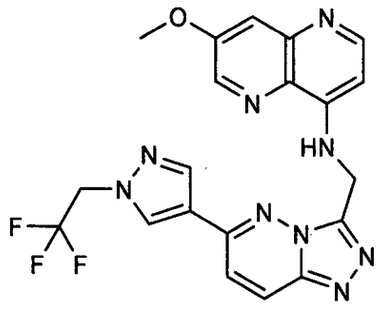
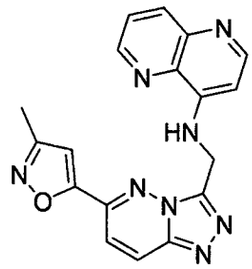
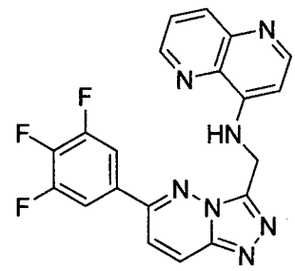
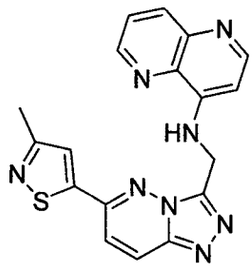
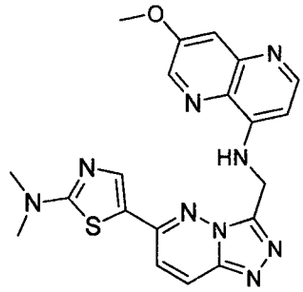
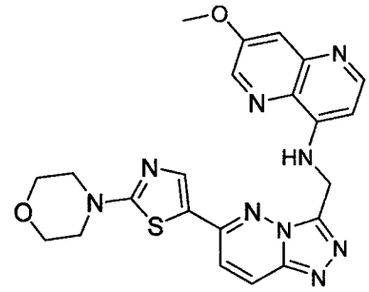
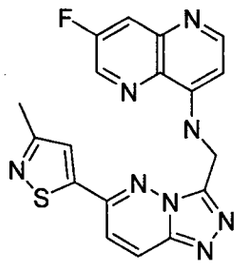
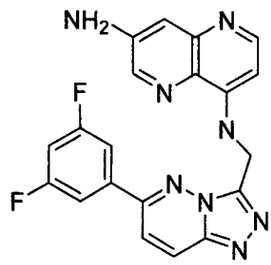
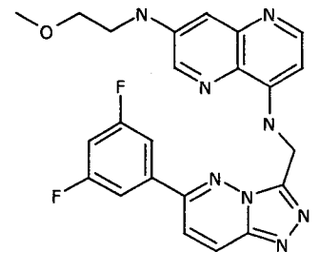
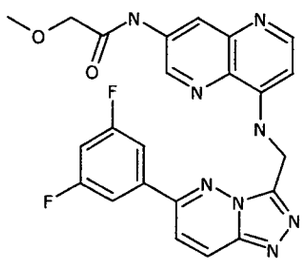
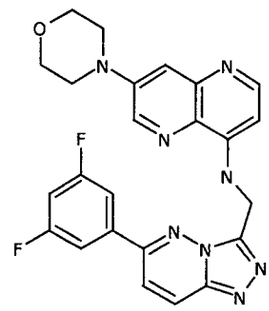
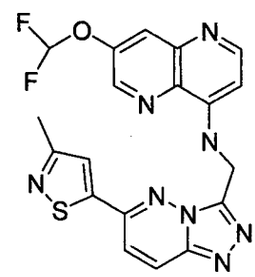
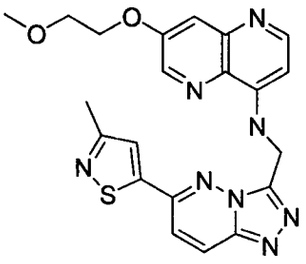
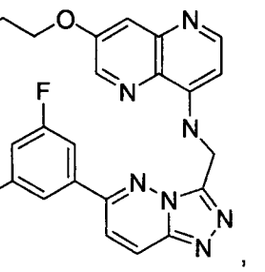
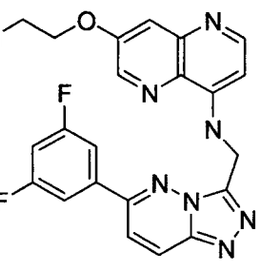
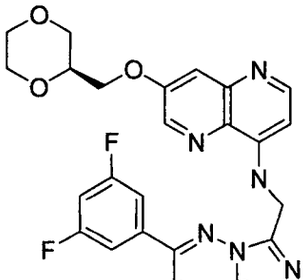
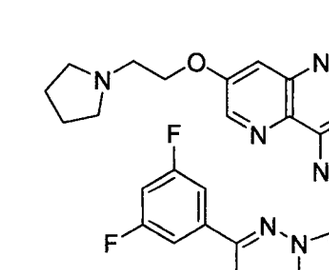
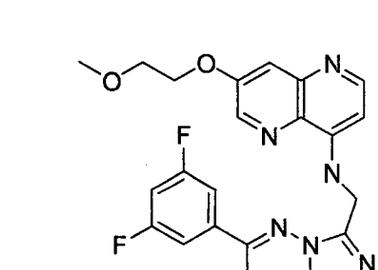
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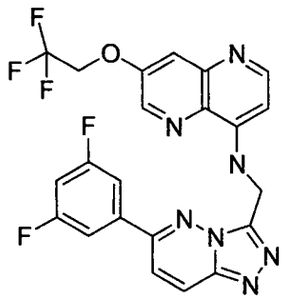
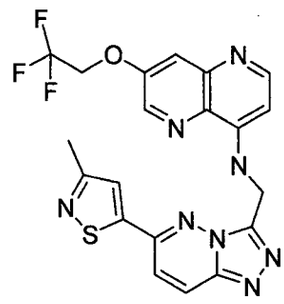
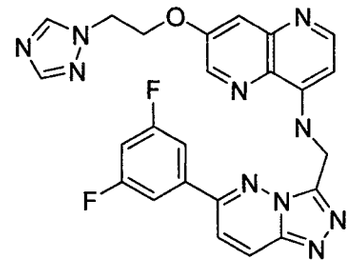
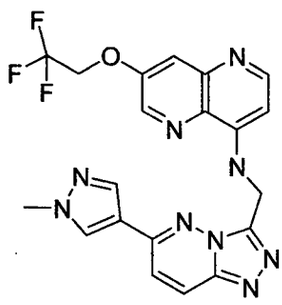
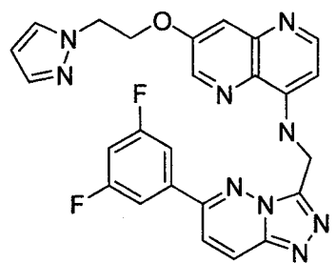
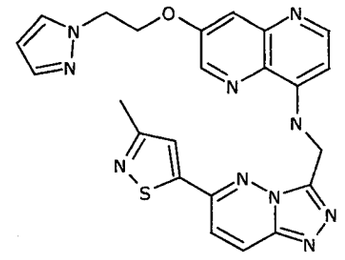
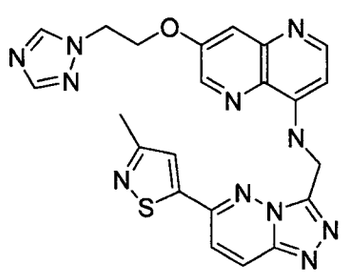
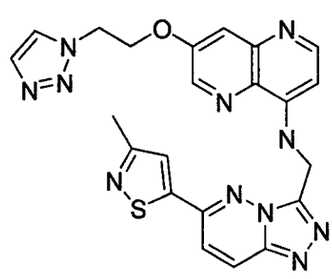
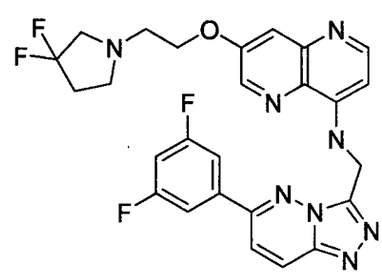
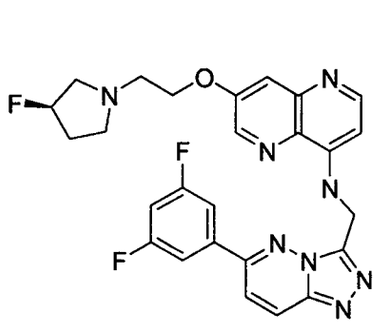
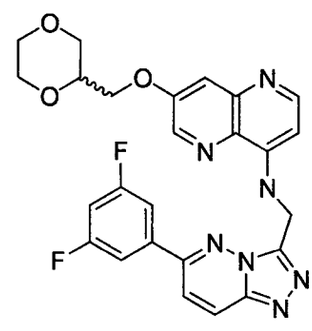
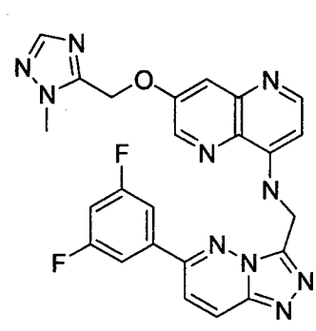

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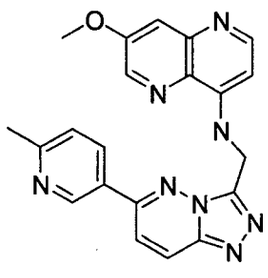
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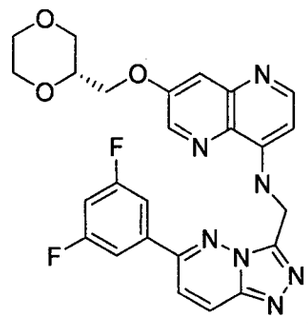
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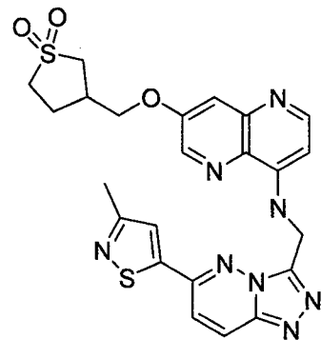
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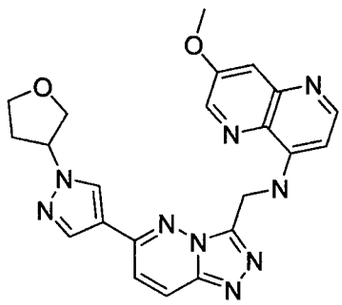
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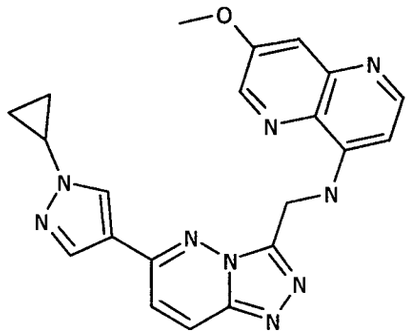
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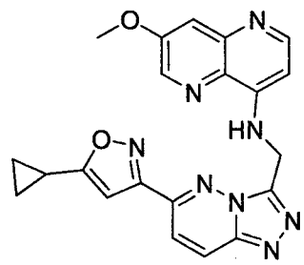


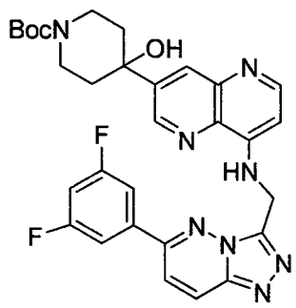


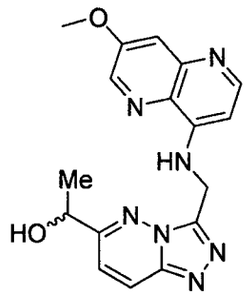


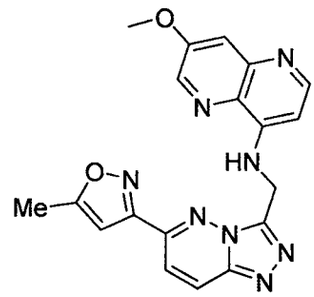


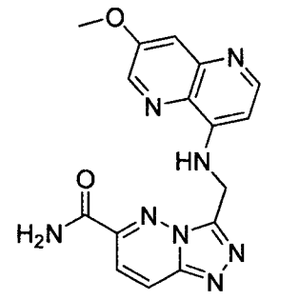


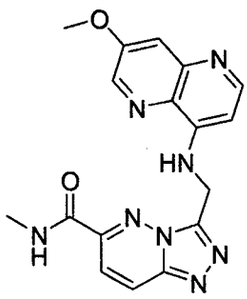


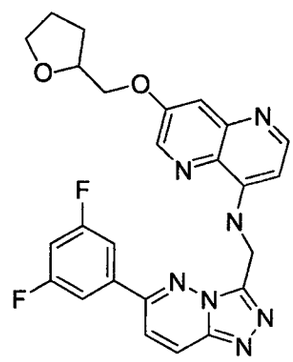


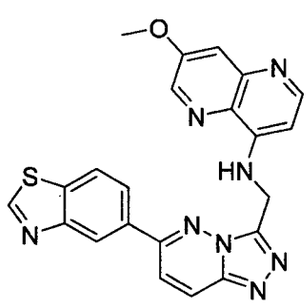


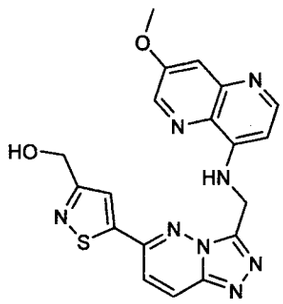


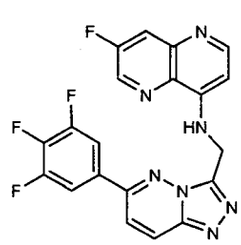


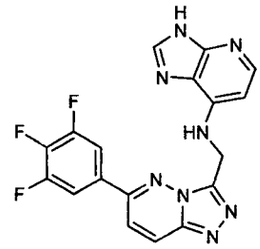






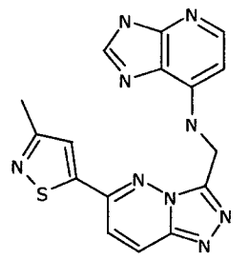
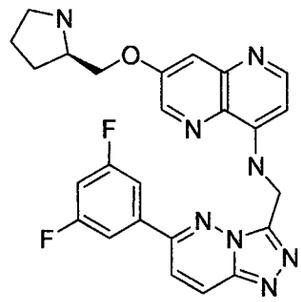
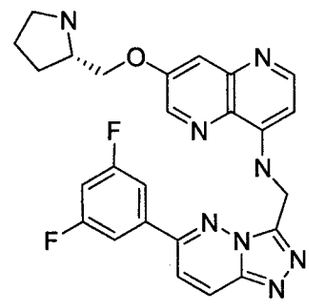
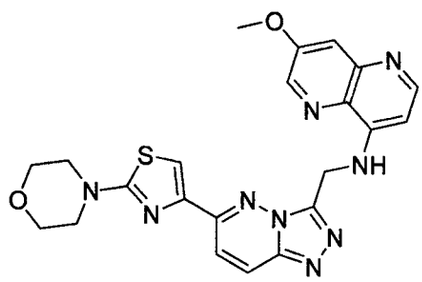
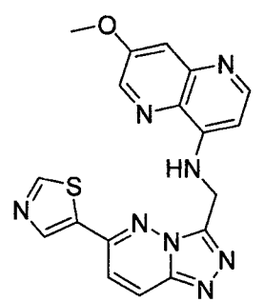
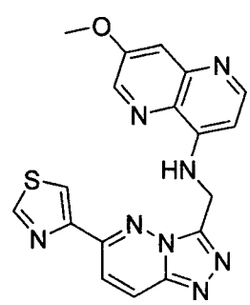
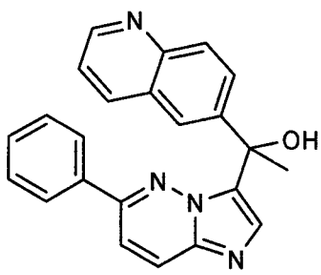
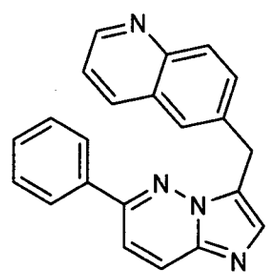
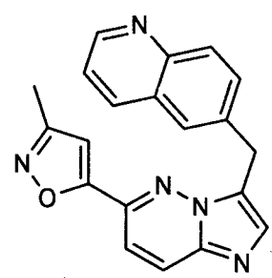
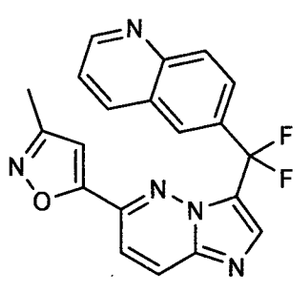
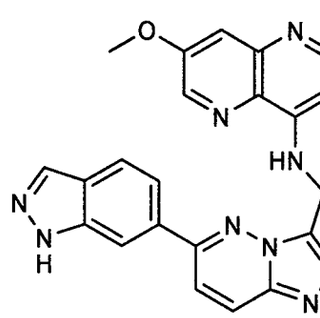
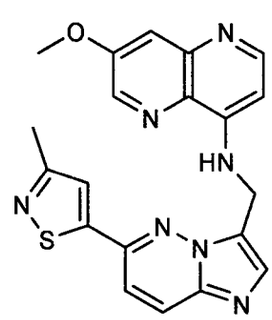
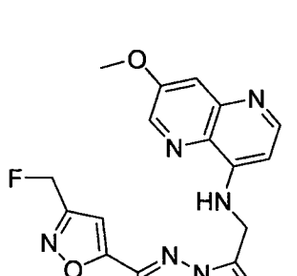
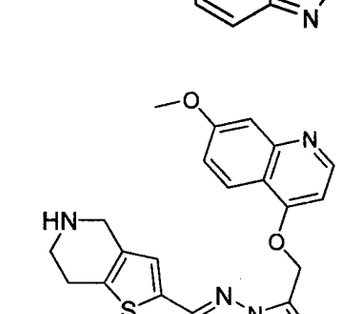
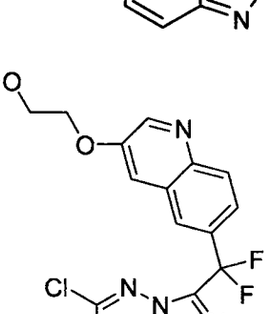
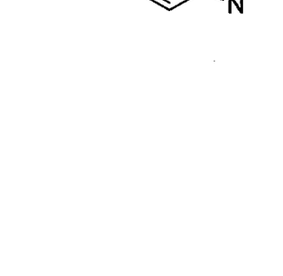






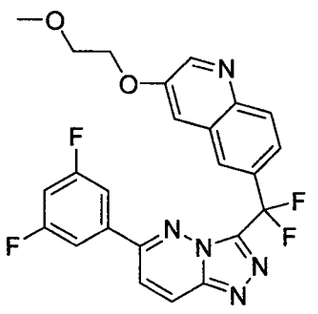
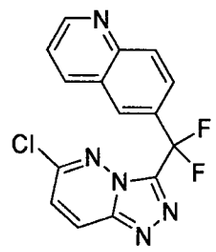
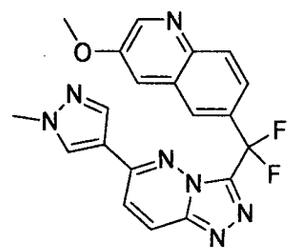
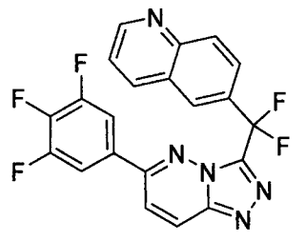
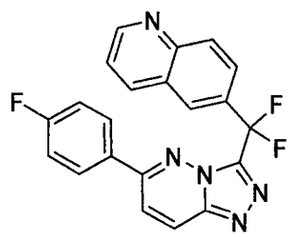
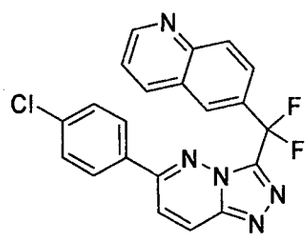
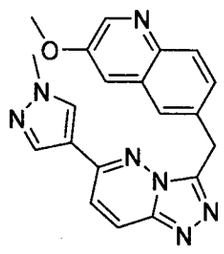
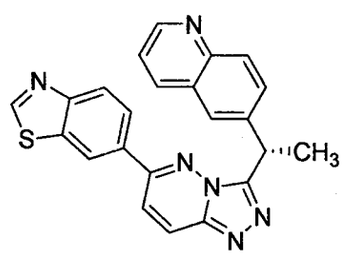
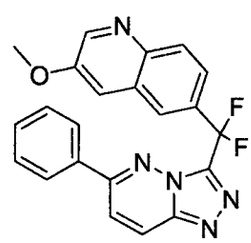
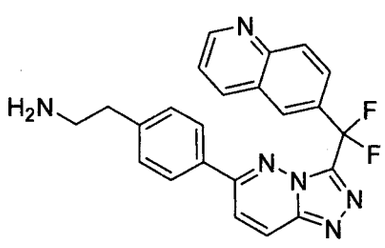
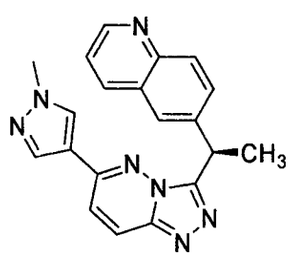
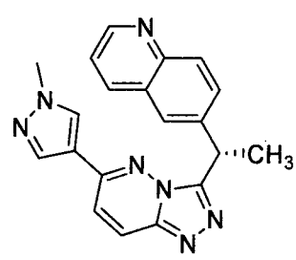
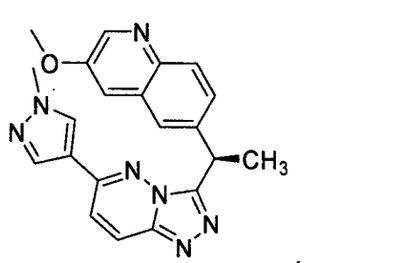
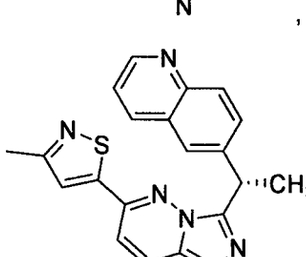
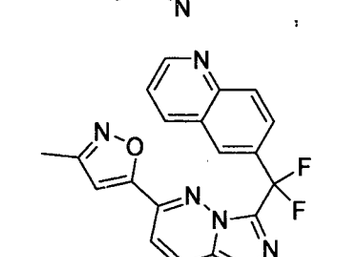
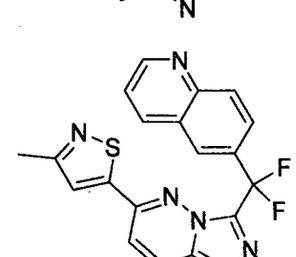
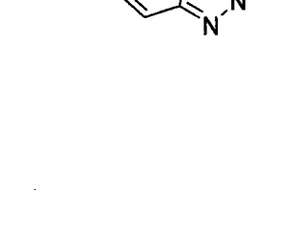
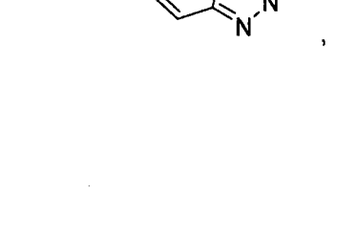
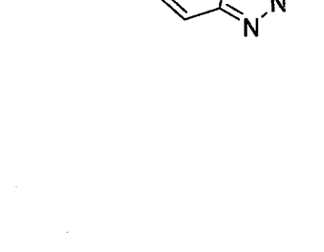
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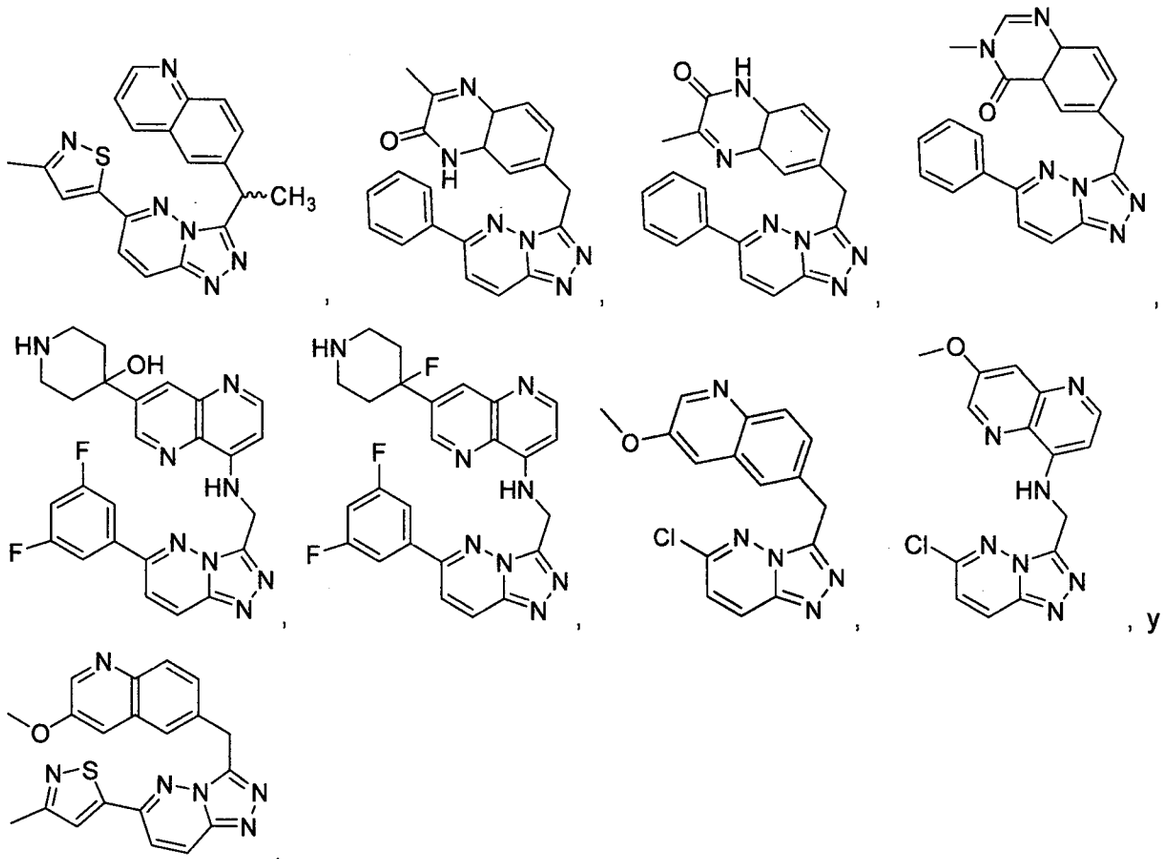
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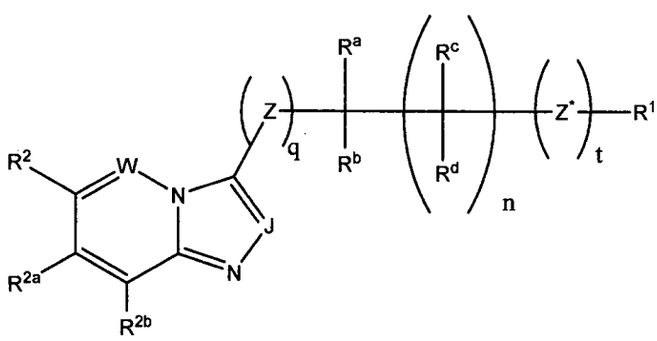
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y sales de los mismos.

2. Un compuesto de Fórmula I



I

enantiómeros, diaestereómeros, sales y solvatos de los mismos, donde

J es N o CR^3;

W es CR^{2b} o N;

Z y Z* son independientemente –O–, $–S(O)_v–$, o $–NR^5–$;

q es 0;

R^a, R^b, R^c y R^d son cada uno independientemente H, halo, alquilo, alquenilo, alquinilo, haloalquilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, $–NO_2$, –CN, $–NR^5R^{5a}$, $–OR^4$, $–C(=O)R^4$, $–C(=O)OR^4$; $–C(=O)NR^5R^{5a}$, $–N(R^5)C(=O)NR^5R^{5a}$, $–OC(=O)NR^5R^{5a}$, $–S(O)_vR^4$, $–S(O)_2NR^5R^{5a}$, $–N(R^5)SO_2R^4$ cada uno de los cuales puede estar opcionalmente

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independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia;

o R^a y R^b conjuntamente con el átomo de carbono al cual están unidos pueden combinarse para formar un cicloalquilo de 3–10 miembros, un anillo cicloalquenilo de 3–10 miembros o un anillo heterociclo, cualquiera de los cuales puede estar opcionalmente sustituido con uno o más grupos R^{10} según lo permita la valencia.;

or R^c y R^d conjuntamente con el átomo de carbono al cual están unidos pueden combinarse para formar un cicloalquilo de 3–10 miembros, un anillo cicloalquenilo de 3–10 miembros o un anillo heterociclo, cualquiera de los cuales puede estar opcionalmente sustituido con uno o más grupos R^{10} según lo permita la valencia.;

o R^a y/o R^b pueden combinarse con cualquiera de R^c o R^d para formar un anillo cicloalquilo de 3–8 miembros parcial o totalmente saturado o un anillo heterociclo, cualquiera de los cuales puede estar opcionalmente sustituido con uno o más grupos R^{10} según lo permita la valencia;

o R^a y R^b pueden combinarse para formar un grupo carbonilo;

o R^c y R^d unidos al mismo átomo de carbono pueden combinarse para formar un grupo carbonilo;

R^1 es un heteroarilo oxo–sustituido o un heterociclo oxo–sustituido seleccionado de naftiridinonilo, dihidronaftiridinonilo, piridopirimidinonilo, dihidropiridopirimidinonilo, imidazopiridinonilo, dihidroimidazopiridinonilo, oxazolopiridinonilo, dihidrooxazolopiridinonilo, tiazolopiridinonilo, dihidrotiazolopiridinonilo, pirazolpirazinonilo, dihidropirazolpirazinonilo, triazolopirazinonilo, dihidrotriazolopirazinonilo, triazolopiridinonilo o dihidrotriazolopiridinonilo cualquiera de los cuales puede estar además opcionalmente independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia.

R^2 es

(i) H, halo, ciano, nitro, o

(ii) alquilo, haloalquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilo, $-OR^4$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más R^{10} según lo permita la valencia,

R^{2a}, R^{2b} y R^3 están independientemente seleccionados en cada caso de H, halo, ciano, nitro, alquilo, haloalquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilo, $–OR^4$, –

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$S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más grupo R^{10} según lo permita la valencia;

R^4 está independientemente seleccionado en cada caso de H, alquilo, haloalquilo, cicloalquilo, alquenilo, alquinilo, arilo, heteroarilo, heterociclo, arilalquilo, heteroarilalquilo, heterocicloalquilo, y cicloalquilalquilo, cada uno de los cuales puede estar opcionalmente independientemente sustituido según lo permita la valencia con uno o más grupos R^{10};

R^5 y R^{5a} están independientemente seleccionados en cada caso de H, alquilo, haloalquilo, cicloalquilo, alquenilo, alquinilo, arilo, heteroarilo, heterociclo, arilalquilo, heteroarilalquilo, heterocicloalquilo, y cicloalquilalquilo, cualquiera de los cuales puede estar opcionalmente independientemente sustituido según lo permita la valencia con uno o más R^{10};

o R^5 y R^{5a} pueden combinarse para formar un anillo heterociclo opcionalmente sustituido con uno o más R^{10};

R^{10} es independientemente en cada caso, halo, ciano, nitro, oxo, alquilo, haloalquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilo, $-(alquileno)_m-OR^4$, $-(alquileno)_m-S(O)_vR^4$, $-(alquileno)_m-NR^5R^{5a}$, $-(alquileno)_m-C(=O)R^4$, $-(alquileno)_m-C(=S)R^4$, $-(alquileno)_m-C(=O)OR^4$, $-(alquileno)_m-OC(=O)R^4$, $-(alquileno)_m-C(=S)OR^4$, $-(alquileno)_m-C(=O)NR^5R^{5a}$, $-(alquileno)_m-C(=S)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=S)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)R^4$, $-(alquileno)_m-N(R^5)C(=S)R^4$, $-(alquileno)_m-OC(=O)NR^5R^{5a}$, $-(alquileno)_m-OC(=S)NR^5R^{5a}$, $-(alquileno)_m-SO_2NR^5R^{5a}$, $-(alquileno)_m-N(R^5)SO_2R^4$, $-(alquileno)_m-N(R^5)SO_2NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)OR^4$, $-(alquileno)_m-N(R^5)C(=S)OR^4$, o $-(alquileno)_m-N(R^5)SO_2R^4$;

donde dichos grupos alquilo, haloalquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilo pueden estar independientemente sustituidos con uno o más $-(alquileno)_m-OR^4$, $-(alquileno)_m-S(O)_vR^4$, $-(alquileno)_m-NR^5R^{5a}$, $-(alquileno)_m-C(=O)R^4$, $-(alquileno)_m-C(=S)R^4$, $-(alquileno)_m-C(=O)OR^4$, $-(alquileno)_m-OC(=O)R^4$, $-(alquileno)_m-C(=S)OR^4$, $-(alquileno)_m-C(=O)NR^5R^{5a}$, $-(alquileno)_m-C(=S)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=S)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)R^4$, $-(alquileno)_m-N(R^5)C(=S)R^4$, $-(alquileno)_m-$

$OC(=O)NR^5R^{5a}$, $-(alquileno)_m-OC(=S)NR^5R^{5a}$, $-(alquileno)_m-SO_2NR^5R^{5a}$, $-(alquileno)_m-N(R^5)SO_2R^4$, $-(alquileno)_m-N(R^5)SO_2NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)OR^4$, $-(alquileno)_m-N(R^5)C(=S)OR^4$, o $-(alquileno)_m-N(R^5)SO_2R^4$;

y además donde cualquiera de los dos grupos R^{10} unidos al mismo átomo o unidos a átomos adyacentes pueden combinarse para formar un sistema de anillo sustituido de 3–8 miembros;

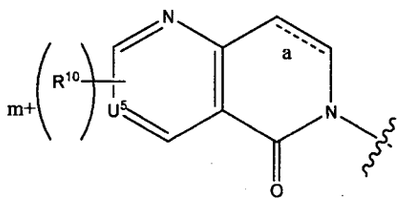
m es 0 o 1;

n es 0, 1 o 2;

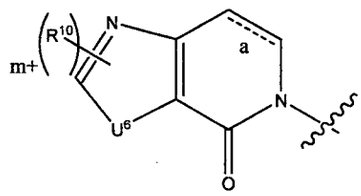
t es 0 o 1;

v es 0, 1 o 2.

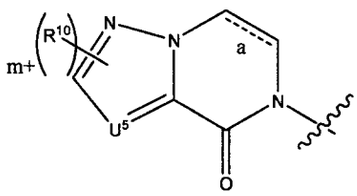
3. Un compuesto de la reivindicación 2 donde R^1 es

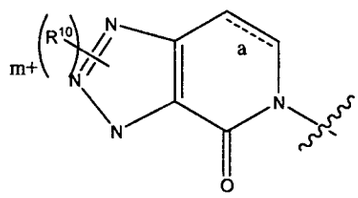


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,





, o

a es un enlace o está ausente;

U^5 es C o N;

U^6 es NH, O o S;

m+ es 0, 1, 2 o 3 .

4. Un compuesto de la reivindicación 2 donde R^2 es H, halo, ciano, alquinilo, $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=O)OR^4$, fenilo, naftilo, pirrolilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo, furanilo, tienilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, piridinilo, tetrahidropiridinilo, piridinonilo, pirazinilo, pirimidinilo, piridazinilo, indolilo, isoindolilo, indolinilo, indolinonilo, isoidolinilo, isoindolinonilo, dihidrobenzofuranilo, dihidroisobenzofuranilo, benzofuranilo, isobenzofuranilo, quinolinilo, isoquinolinilo, quinazolinilo, quinazolinonilo, tetrahidroquinolinilo, tetrahidroisoquinolinilo, dihidroquinolinonilo, dihidroisoquinolinonilo, quinoxalinilo, tetrahidroquinoxalinilo, benzomorfolinilo, dihidrobenzodioxinilo, imidazopiridinilo, naftiridinilo, benzotriazinilo, triazolopiridinilo, triazolopirimidinilo, triazolopiridazinilo, imidazopiridinilo, imidazopirimidinilo, imidazopiridazinilo, pirrolpiridinilo, pirrolpirimidinilo, pirrolpiridazinilo, pirazolpiridinilo, pirazolpirimidinilo, pirazolpiridazinilo, cinnolinilo, tienopirrolilo, tetrahidrotienopirrolilo, dihidrotienopirrolnilo, tienopiridinilo, tienopirimidinilo, tienopiridazinilo, furopiridinilo,

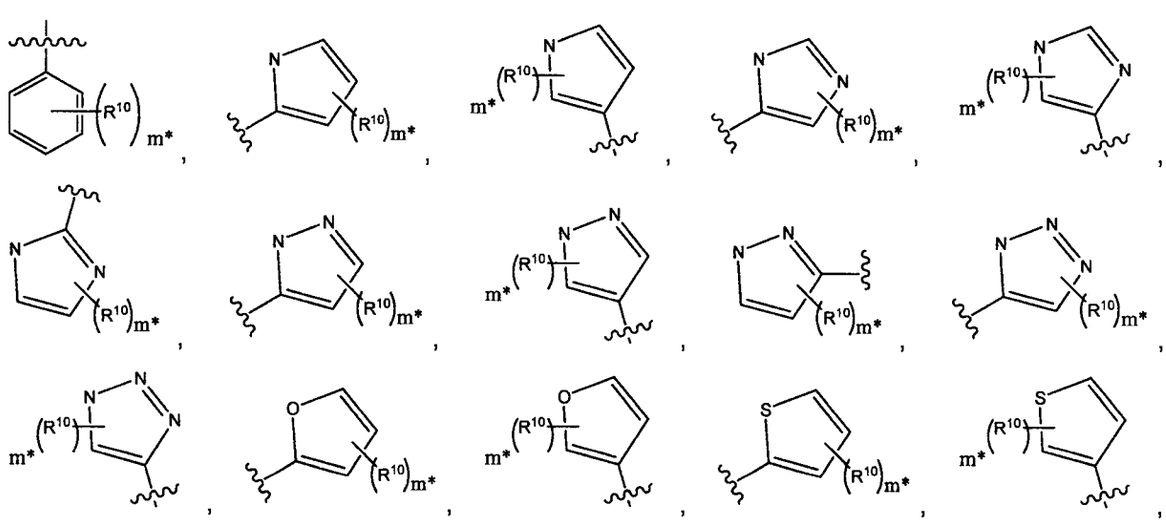
furopirimidinilo, furopirazidinilo, benzofuranilo, benzoimidazolilo, benzoisoxazolilo, benzotiazolilo, o benzoisotiazolilo cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia.

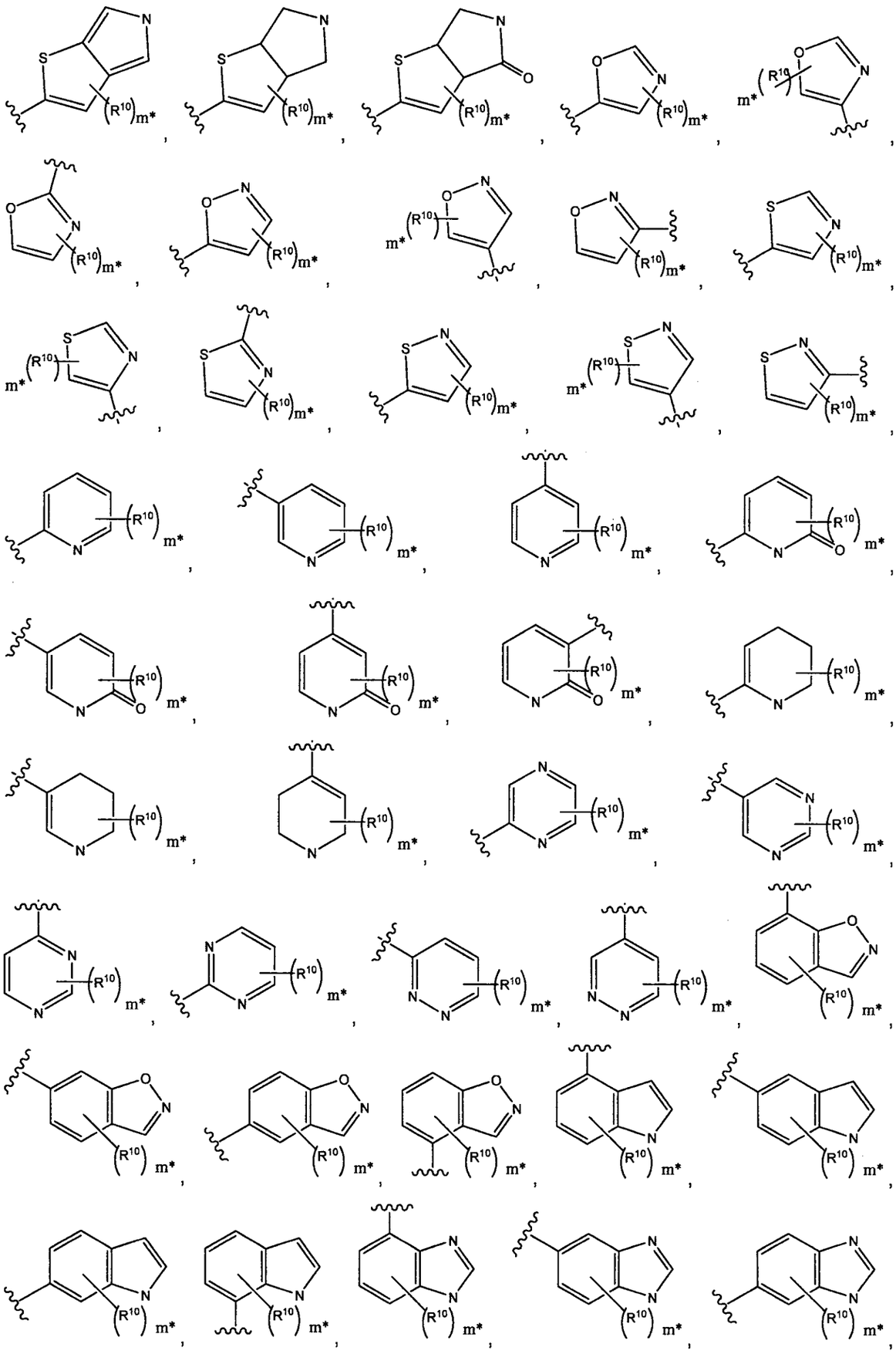
5. Un compuesto de la reivindicación 3 donde R^2 es H, halo, ciano, alquinilo, $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=O)OR^4$, fenilo, naftilo, pirrolilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo, furanilo, tienilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, piridinilo, tetrahidropiridinilo, piridinonilo, pirazinilo, pirimidinilo, piridazinilo, indolilo, isoindolilo, indolinilo, indolinonilo, isoidolinilo, isoindolinonilo, dihidrobenzofuranilo, dihidroisobenzofuranilo, benzofuranilo, isobenzofuranilo, quinolinilo, isoquinolinilo, quinazolinilo, quinazolinonilo, tetrahidroquinolinilo, tetrahidroisoquinolinilo, dihidroquinolinonilo, dihidroisoquinolinonilo, quinoxalinilo, tetrahidroquinoxalinilo, benzomorfolinilo, dihidrobenzodioxinilo, imidazopiridinilo, naftiridinilo, benzotriazinilo, triazolopiridinilo, triazolopirimidinilo, triazolopiridazinilo, imidazopiridinilo, imidazopirimidinilo, imidazopiridazinilo, pirrolpiridinilo, pirrolpirimidinilo, pirrolpiridazinilo, pirazolpiridinilo, pirazolpirimidinilo, pirazolpiridazinilo, cinolinilo, tienopirrolilo, tetrahidrotienopirrolilo, dihidrotienopirrolnilo, tienopiridinilo, tienopirimidinilo, tienopiridazinilo, furopiridinilo, furopirimidinilo, furopirazidinilo, benzofuranilo, benzoimidazolilo, benzoisoxazolilo, benzotiazolilo, o benzoisotiazolilo cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia.

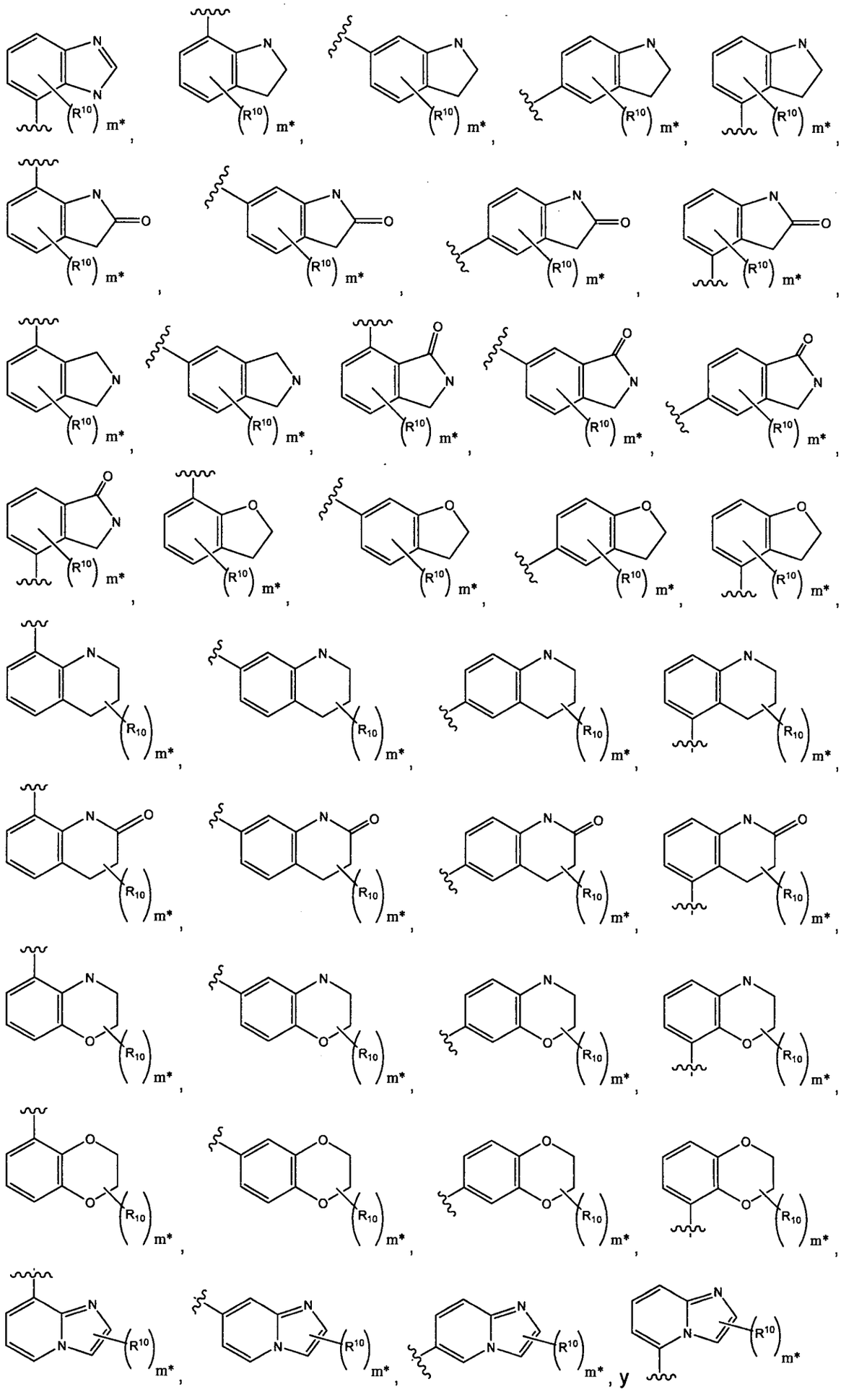
6. Un compuesto de la reivindicación 5 donde R^2 es

(a) halo, alquinilo, $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$ o $-N(R^5)C(=O)OR^4$ cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia; o

(b) un sistema de anillo arilo, heteroarilo o heterociclo seleccionado de



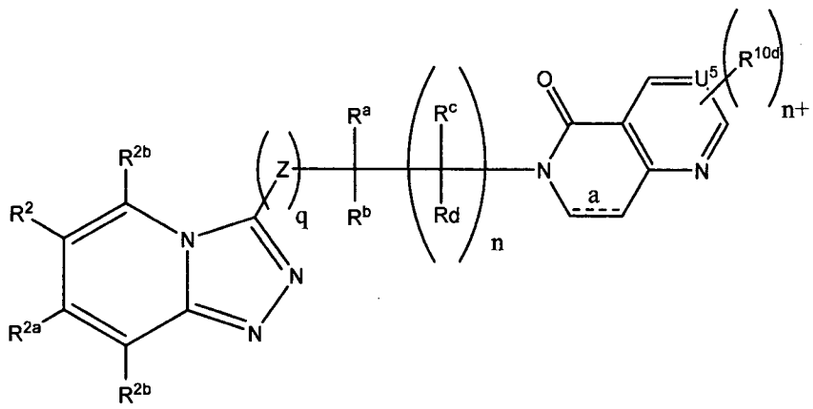




y

donde m* es 0, 1, 2, 3, 4, 5 o 6, según lo permita la valencia.

7. Un compuesto que tiene la siguiente fórmula IJ



IJ

a es un enlace o está ausente;

U^5 es C o N;

Z es –O–, $–S(O)_v–$, o $–NR^5–$;

R^a, R^b, R^c y R^d son cada uno independientemente H, halo, alquilo, alquenilo, alquinilo, haloalquilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, $–NO_2$, –CN, $–NR^5R^{5a}$, $–OR^4$, $–C(=O)R^4$, $–C(=O)OR^4$; $–C(=O)NR^5R^{5a}$, $–N(R^5)C(=O)NR^5R^{5a}$, $–OC(=O)NR^5R^{5a}$, $–S(O)_vR^4$, $–S(O)_2NR^5R^{5a}$, $–N(R^5)SO_2R^4$ cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia;

o R^a y R^b conjuntamente con el átomo de carbono al cual están unidos pueden combinarse para formar un cicloalquilo de 3–10 miembros, un anillo cicloalquenilo de 3–10 miembros o un anillo heterociclo, cualquiera de los cuales puede estar opcionalmente sustituido con uno o más grupos R^{10} según lo permita la valencia;

o R^c y R^d conjuntamente con el átomo de carbono al cual están unidos pueden combinarse para formar un cicloalquilo de 3–10 miembros, un anillo cicloalquenilo de 3–10 miembros o un anillo heterociclo, cualquiera de los cuales puede estar opcionalmente sustituido con uno o más grupos R^{10} según lo permita la valencia;

o R^a y/o R^b pueden combinarse con cualquiera de R^c o R^d para formar un anillo cicloalquilo parcial o totalmente saturado de 3–8 miembros o un anillo heterociclo, cualquiera de los cuales puede estar opcionalmente sustituido con uno o más grupos R^{10} según lo permita la valencia;

o R^a y R^b pueden combinarse para formar un grupo carbonilo;

o R^c y R^d unidos al mismo átomo de carbono pueden combinarse para formar un grupo carbonilo;

con la condición de que cuando q es 1, R^a y R^b son independientemente distintos de halo, $-NO_2$, $-CN$, $-NR^5R^{5a}$, $-OR^4$, $-N(R^5)C(=O)NR^5R^{5a}$, $-OC(=O)NR^5R^{5a}$, $-S(O)_vR^4$, $-S(O)_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$;

R^2 es

(i) H, halo, ciano, nitro, o

(ii) alquilo, haloalquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilo, $-OR^4$, $-NR^5R^{5a}$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más R^{10} según lo permita la valencia,

R^{2a} y R^{2b} están independientemente seleccionados en cada caso de H, halo, ciano, nitro, alquilo, haloalquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilo, $-OR^4$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia;

R^4 está independientemente seleccionado en cada caso de H, alquilo, haloalquilo, cicloalquilo, alquenilo, alquinilo, arilo, heteroarilo, heterociclo, arilalquilo, heteroarilalquilo, heterocicloalquilo, y cicloalquilalquilo, cada uno de los cuales puede estar opcionalmente independientemente sustituido según lo permita la valencia con uno o más grupos R^{10};

R^5 y R^{5a} están independientemente seleccionados en cada caso de H, alquilo, haloalquilo, cicloalquilo, alquenilo, alquinilo, arilo, heteroarilo, heterociclo, arilalquilo, heteroarilalquilo, heterocicloalquilo, y cicloalquilalquilo, cualquiera de los cuales puede estar opcionalmente sustituuido según lo permita la valencia con uno o más R^{10};

o R^5 y R^{5a} pueden combinarse para formar un anillo heterociclo opcionalmente sustituido con uno o más R^{10};

R^{10} y R^{10d} son independientemente en cada caso, halo, ciano, nitro, oxo, alquilo, haloalquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo,

arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilo, $-(alquileno)_m-OR^4$, $-(alquileno)_m-S(O)_vR^4$, $-(alquileno)_m-NR^5R^{5a}$, $-(alquileno)_m-C(=O)R^4$, $-(alquileno)_m-C(=S)R^4$, $-(alquileno)_m-C(=O)OR^4$, $-(alquileno)_m-OC(=O)R^4$, $-(alquileno)_m-C(=S)OR^4$, $-(alquileno)_m-C(=O)NR^5R^{5a}$, $-(alquileno)_m-C(=S)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=S)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)R^4$, $-(alquileno)_m-N(R^5)C(=S)R^4$, $-(alquileno)_m-OC(=O)NR^5R^{5a}$, $-(alquileno)_m-OC(=S)NR^5R^{5a}$, $-(alquileno)_m-SO_2NR^5R^{5a}$, $-(alquileno)_m-N(R^5)SO_2R^4$, $-(alquileno)_m-N(R^5)C(=O)OR^4$, $-(alquileno)_m-N(R^5)C(=S)OR^4$, o $-(alquileno)_m-N(R^5)SO_2R^4$;

donde dichos grupos alquilo, haloalquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilo pueden estar además independientemente sustituidos con uno o más $-(alquileno)_m-OR^4$, $-(alquileno)_m-S(O)_vR^4$, $-(alquileno)_m-NR^5R^{5a}$, $-(alquileno)_m-C(=O)R^4$, $-(alquileno)_m-C(=S)R^4$, $-(alquileno)_m-C(=O)OR^4$, $-(alquileno)_m-OC(=O)R^4$, $-(alquileno)_m-C(=S)OR^4$, $-(alquileno)_m-C(=O)NR^5R^{5a}$, $-(alquileno)_m-C(=S)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=S)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)R^4$, $-(alquileno)_m-N(R^5)C(=S)R^4$, $-(alquileno)_m-OC(=O)NR^5R^{5a}$, $-(alquileno)_m-OC(=S)NR^5R^{5a}$, $-(alquileno)_m-SO_2NR^5R^{5a}$, $-(alquileno)_m-N(R^5)SO_2R^4$, $-(alquileno)_m-N(R^5)SO_2NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)OR^4$, $-(alquileno)_m-N(R^5)C(=S)OR^4$, o $-(alquileno)_m-N(R^5)SO_2R^4$;

y además donde cualquiera de los dos grupos R^{10} unidos al mismo átomo de carbono o unidos a átomos adyacentes pueden combinarse para formar un sistema de anillo opcionalmente sustituido de 3– a 8 miembros;

m es 0 o 1;

n es 0, 1 o 2;

n+ es 0, 1, 2 o 3;

q es 0 o 1;

v es 0, 1 o 2.

8. Un compuesto de la reivindicación 7 donde q y n son cada uno cero, y a es un enlace.

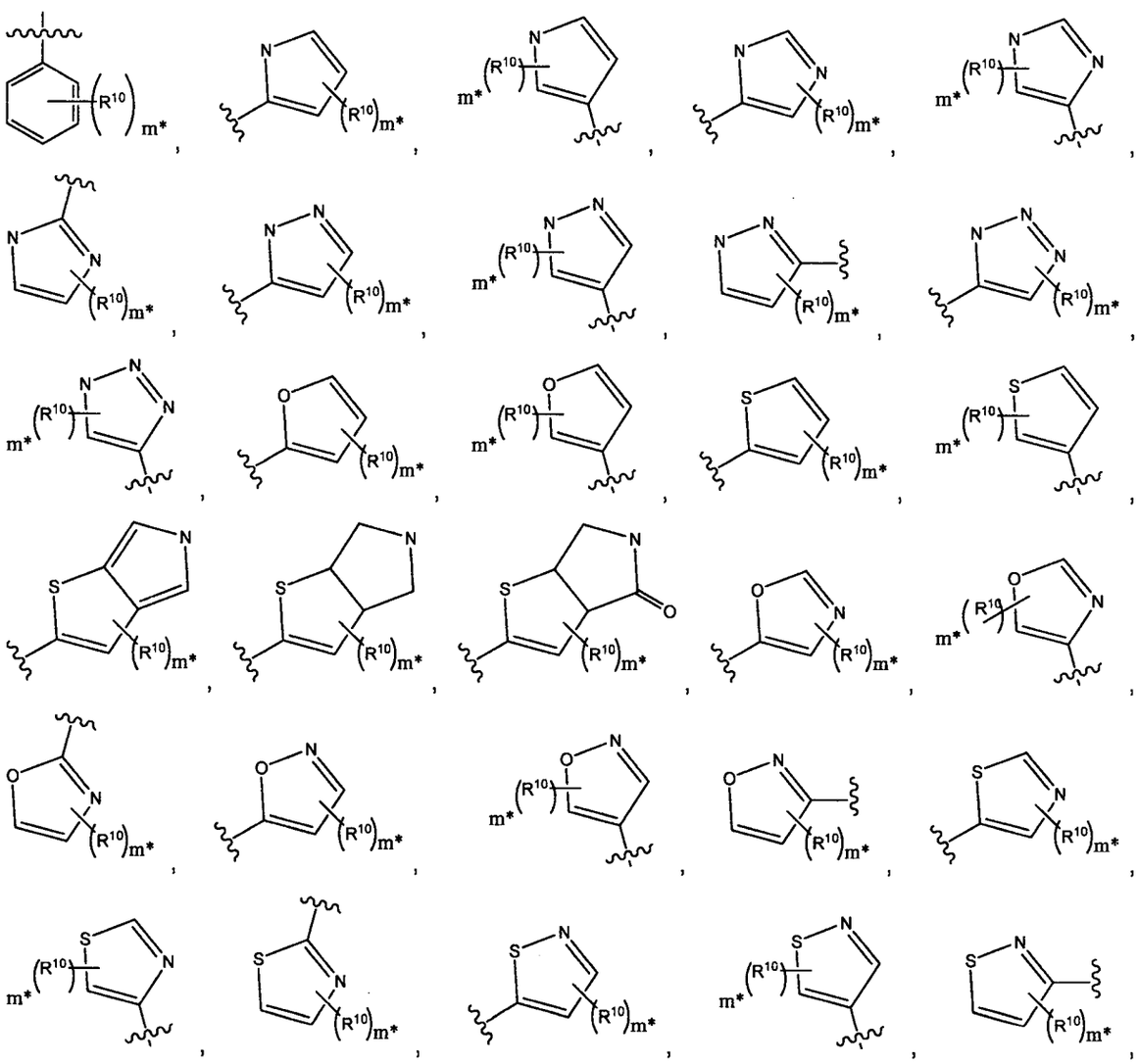
9. Un compuesto de la reivindicación 7 donde R^2 es H, halo, ciano, alquinilo, $-NR^5R^{5a}$, $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=O)OR^4$, fenilo, naftilo, pirrolilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo, furanilo, tienilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, piridinilo, tetrahidropiridinilo, piridinonilo, pirazinilo, pirimidinilo, piridazinilo, indolilo, isoindolilo, indolinilo, indolinonilo, isoidolinilo, isoindolinonilo, dihidrobenzofuranilo, dihidroisobenzofuranilo, benzofuranilo, isobenzofuranilo, quinolinilo, isoquinolinilo, quinazolinilo, quinazolinonilo, tetrahidroquinolinilo, tetrahidroisoquinolinilo,

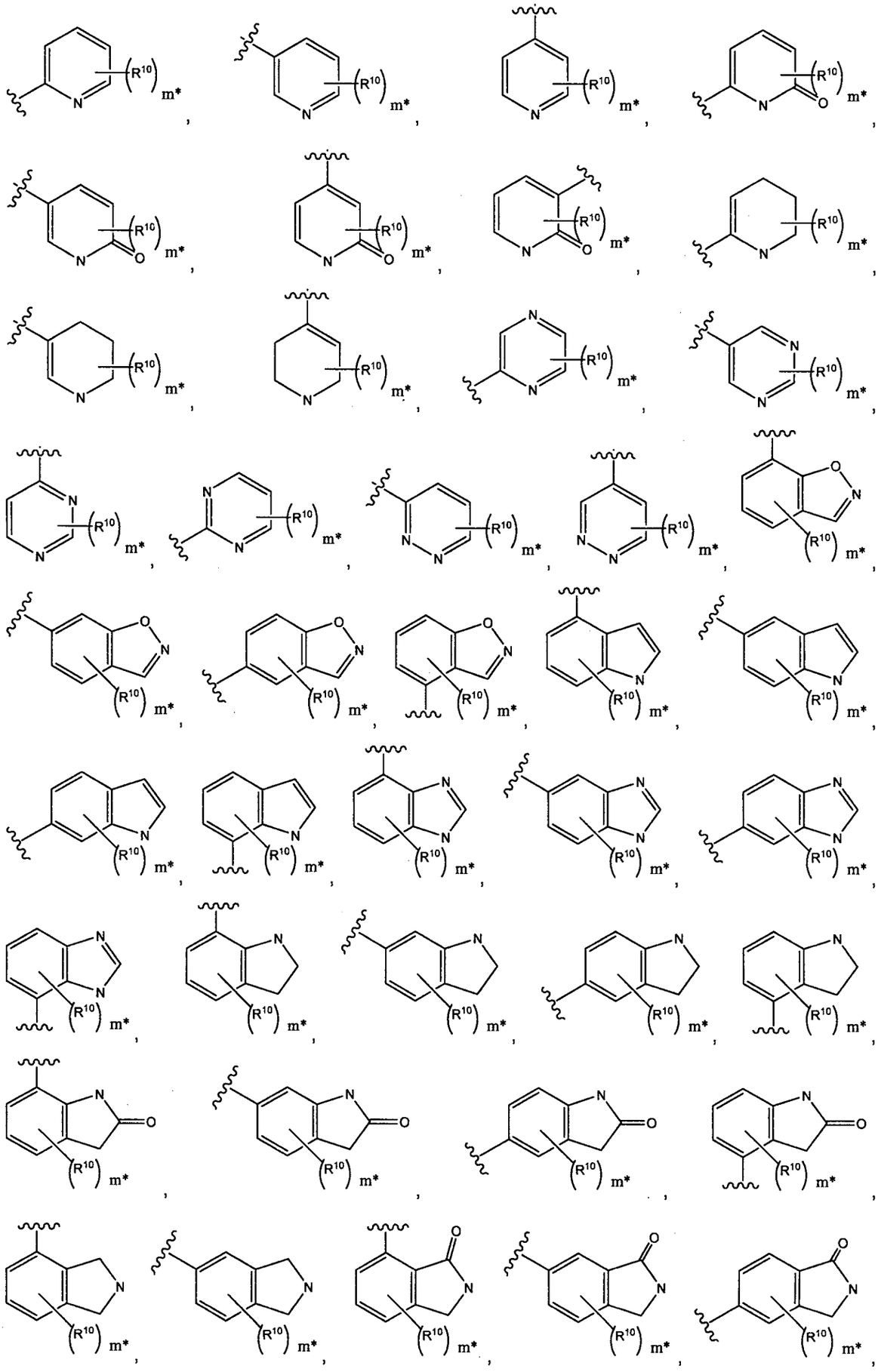
dihidroquinolinonilo, dihidroisoquinolinonilo, quinoxalinilo, tetrahidroquinoxalinilo, benzomorfolinilo, dihidrobenzodioxinilo, imidazopiridinilo, naftiridinilo, benzotriazinilo, triazolopiridinilo, triazolopirimidinilo, triazolopiridazinilo, imidazopiridinilo, imidazopirimidinilo, imidazopiridazinilo, pirrolpiridinilo, pirrolpirimidinilo, pirrolpiridazinilo, pirazolpiridinilo, pirazolpirimidinilo, pirazolpiridazinilo, cinnolinilo, tienopirrolilo, tetrahidrotienopirrolilo, dihidrotienopirrolnilo, tienopiridinilo, tienopirimidinilo, tienopiridazinilo, furopiridinilo, furopirimidinilo, furopirazidinilo, benzofuranilo, benzoimidazolilo, benzoisoxazolilo, benzotiazolilo, o benzoisotiazolilo cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia.

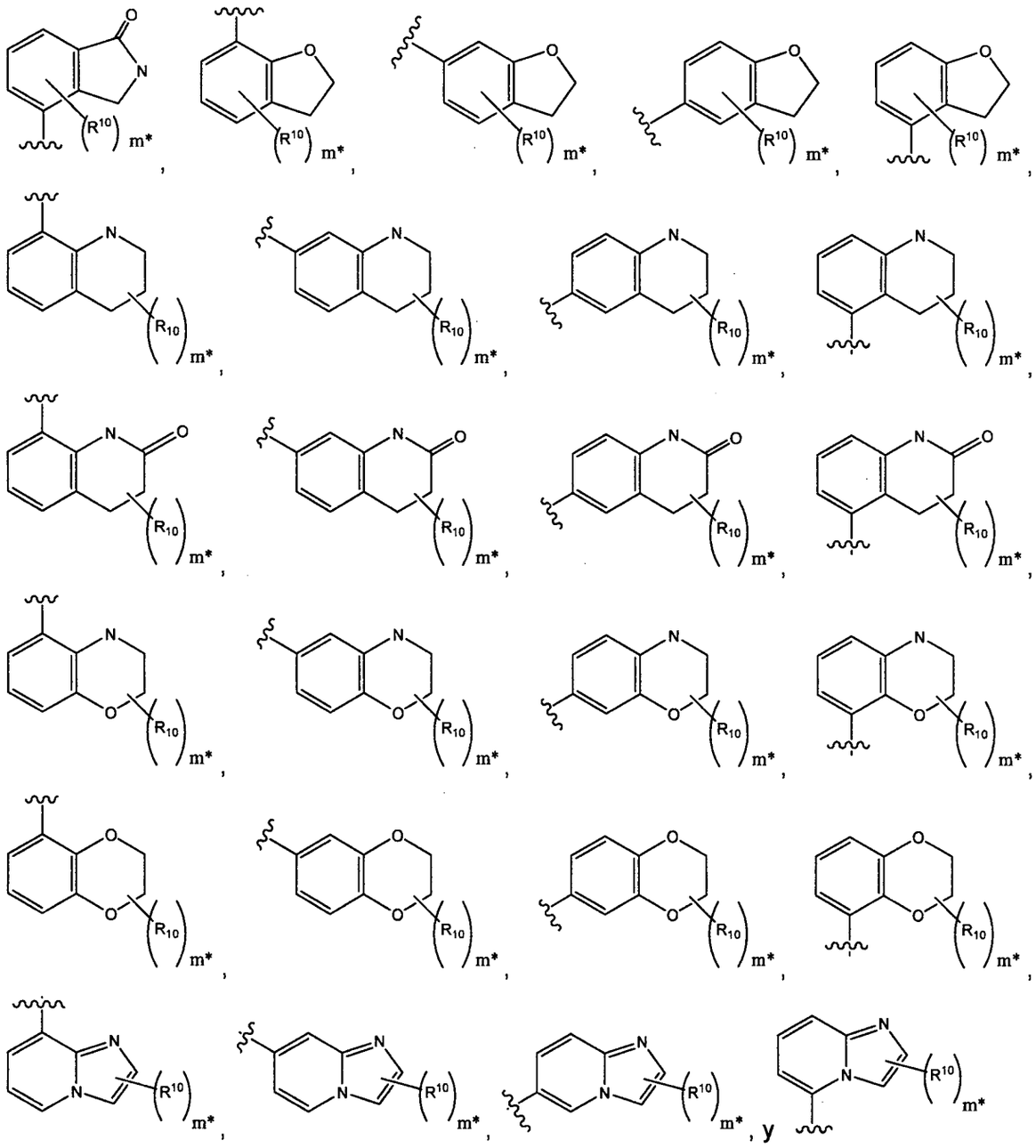
10. Un compuesto de la reivindicación 9 donde R^2 es

(a) halo, alquinilo, $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$ o $-N(R^5)C(=O)OR^4$ cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia; o

(b) un sistema de anillo arilo, heteroarilo o heterociclo seleccionado de

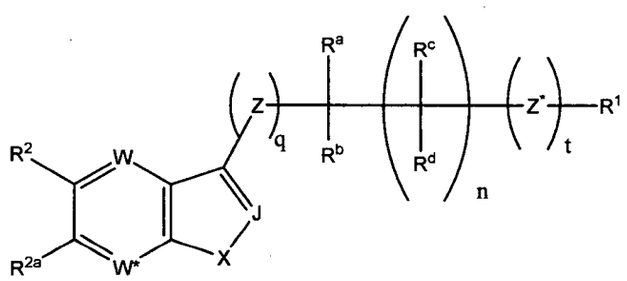






donde m* es 0, 1, 2, 3, 4, 5 o 6, según lo permita la valencia.

11. Un compuesto de Fórmula VII



VII

enantiómeros, diaestereómeros, sales y solvatos de los mismos donde

J es N o CR^3;

W es CR^{2b};

W* es N o CR^{2b};

X es O o S;

Z y Z* son independientemente –O–, $-S(O)_v-$, o $-NR^5-$;

R^a, R^b, R^c y R^d son cada uno independientemente H, halo, alquilo, alquenilo, alquinilo, haloalquilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, $-NO_2$, –CN, $-NR^5R^{5a}$, $-OR^4$, $-C(=O)R^4$, $-C(=O)OR^4$; $-C(=O)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-OC(=O)NR^5R^{5a}$, $-S(O)_vR^4$, $-S(O)_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$ cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia;

o R^a y R^b conjuntamente con el átomo de carbono al cual están unidos pueden combinarse para formar un cicloalquilo de 3–10 miembros, un anillo cicloalquenilo de 3–10 miembros, o un anillo heterociclo, cualquiera de los cuales puede estar opcionalmente sustituido con uno o más grupos R^{10} según lo permita la valencia.;

o R^c y R^d conjuntamente con el átomo de carbono al cual están unidos pueden combinarse para formar un cicloalquilo de 3–10 miembros, un anillo cicloalquenilo de 3–10 miembros, o un anillo heterociclo, cualquiera de los cuales puede estar opcionalmente sustituido con uno o más grupos R^{10} según lo permita la valencia;

o R^a y/o R^b pueden combinarse con cualquiera de R^c o R^d para formar un anillo cicloalquilo parcial o totalmente saturado de 3–8 miembros, o un anillo heterociclo, cualquiera de los cuales puede estar opcionalmente sustituido con uno o más grupos R^{10} según lo permita la valencia;

o R^a y R^b pueden combinarse para formar un grupo carbonilo;

o R^c y R^d unidos al mismo átomo de carbono pueden combinarse para formar un grupo carbonilo;

R^1 es arilo, heteroarilo o heterociclo cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia;

R^2 es

(i) H, halo, ciano, nitro, o

(ii) alquilo, haloalquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilo, $-OR^4$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más R^{10} según lo permita la valencia,

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R^{2a}, R^{2b} y R^3 están independientemente seleccionados en cada caso de H, halo, ciano, nitro, alquilo, haloalquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilo, $-OR^4$, $-S(O)_vR^4$, $-NR^5R^{5a}$, $-C(=O)R^4$, $-C(=S)R^4$, $-C(=O)OR^4$, $-C(=S)OR^4$, $-C(=O)NR^5R^{5a}$, $-C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)NR^5R^{5a}$, $-N(R^5)C(=S)NR^5R^{5a}$, $-N(R^5)C(=O)R^4$, $-N(R^5)C(=S)R^4$, $-OC(=O)NR^5R^{5a}$, $-OC(=S)NR^5R^{5a}$, $-SO_2NR^5R^{5a}$, $-N(R^5)SO_2R^4$, $-N(R^5)SO_2NR^5R^{5a}$, $-N(R^5)C(=O)OR^4$, $-N(R^5)C(=S)OR^4$, $-N(R^5)SO_2R^4$, cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia;

R^4 está independientemente seleccionado en cada caso de H, alquilo, haloalquilo, cicloalquilo, alquenilo, alquinilo, arilo, heteroarilo, heterociclo, arilalquilo, heteroarilalquilo, heterocicloalquilo, y cicloalquilalquilo, cada uno de los cuales puede estar opcionalmente independientemente sustituido según lo permita la valencia con uno o más grupos R^{10};

R^5 y R^{5a} están independientemente seleccionados en cada caso de H, alquilo, haloalquilo, cicloalquilo, alquenilo, alquinilo, arilo, heteroarilo, heterociclo, arilalquilo, heteroarilalquilo, heterocicloalquilo, y cicloalquilalquilo, cada uno de los cuales puede estar opcionalmente sustituido según lo permita la valencia con uno o más R^{10};

o R^5 y R^{5a} pueden combinarse para formar un anillo heterociclo opcionalmente sustituido con uno o más R^{10};

R^{10} es independientemente en cada caso, halo, ciano, nitro, oxo, alquilo, haloalquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilo, $-(alquileno)_m-OR^4$, $-(alquileno)_m-S(O)_vR^4$, $-(alquileno)_m-NR^5R^{5a}$, $-(alquileno)_m-C(=O)R^4$, $-(alquileno)_m-C(=S)R^4$, $-(alquileno)_m-C(=O)OR^4$, $-(alquileno)_m-OC(=O)R^4$, $-(alquileno)_m-C(=S)OR^4$, $-(alquileno)_m-C(=O)NR^5R^{5a}$, $-(alquileno)_m-C(=S)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=S)NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)R^4$, $-(alquileno)_m-N(R^5)C(=S)R^4$, $-(alquileno)_m-OC(=O)NR^5R^{5a}$, $-(alquileno)_m-OC(=S)NR^5R^{5a}$, $-(alquileno)_m-SO_2NR^5R^{5a}$, $-(alquileno)_m-N(R^5)SO_2R^4$, $-(alquileno)_m-N(R^5)SO_2NR^5R^{5a}$, $-(alquileno)_m-N(R^5)C(=O)OR^4$, $-(alquileno)_m-N(R^5)C(=S)OR^4$, o $-(alquileno)_m-N(R^5)SO_2R^4$;

donde dichos grupos alquilo, haloalquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, y heterocicloalquilo pueden estar además independientemente sustituidos con uno o más $-(alquileno)_m-OR^4$, $-(alquileno)_m-S(O)_vR^4$, $-(alquileno)_m-NR^5R^{5a}$, $-(alquileno)_m-C(=O)R^4$, $-(alquileno)_m-C(=S)R^4$, $-(alquileno)_m-C(=O)OR^4$, $-(alquileno)_m-OC(=O)R^4$, $-$

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$(alquileno)_m–C(=S)OR^4$, $–(alquileno)_m–C(=O)NR^5R^{5a}$, $–(alquileno)_m–C(=S)NR^5R^{5a}$, $–(alquileno)_m–N(R^5)C(=O)NR^5R^{5a}$, $–(alquileno)_m–N(R^5)C(=S)NR^5R^{5a}$, $–(alquileno)_m–N(R^5)C(=O)R^4$, $–(alquileno)_m–N(R^5)C(=S)R^4$, $–(alquileno)_m–OC(=O)NR^5R^{5a}$, $–(alquileno)_m–OC(=S)NR^5R^{5a}$, $–(alquileno)_m–SO_2NR^5R^{5a}$, $–(alquileno)_m–N(R^5)SO_2R^4$, $–(alquileno)_m–N(R^5)SO_2NR^5R^{5a}$, $–(alquileno)_m–N(R^5)C(=O)OR^4$, $–(alquileno)_m–N(R^5)C(=S)OR^4$, o $–(alquileno)_m–N(R^5)SO_2R^4$;

y además donde cualquiera de los dos grupos R^{10} unidos al mismo átomo de carbono o unidos a átomos adyacentes pueden combinarse para formar un sistema de anillo opcionalmente sustituuido de 3–8 miembros;

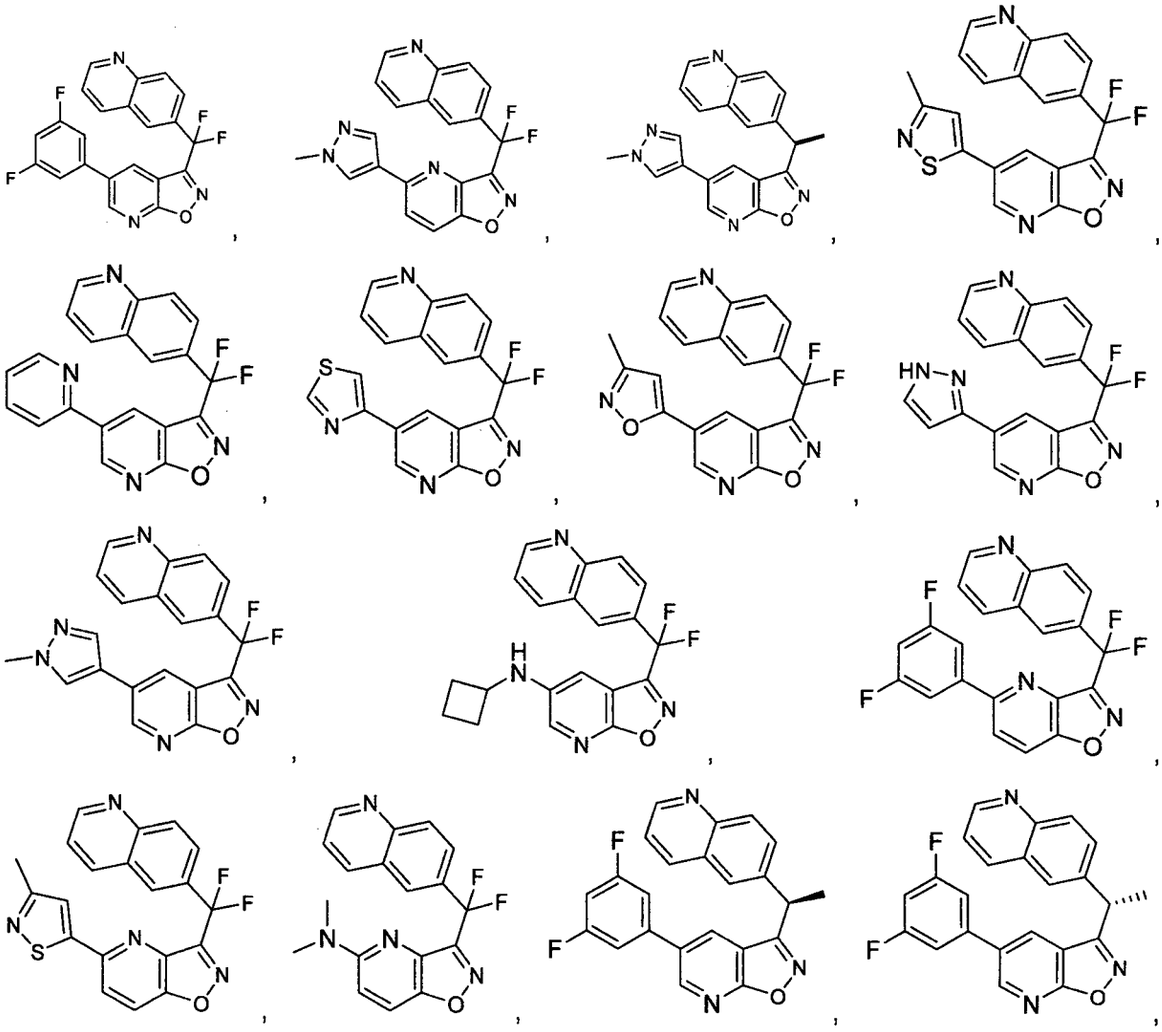
m es 0 o 1;

n es 0, 1 o 2;

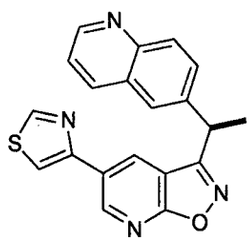
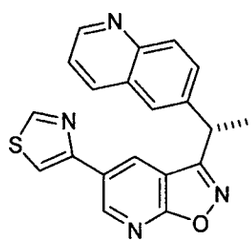
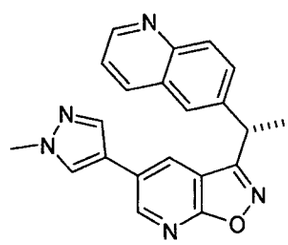
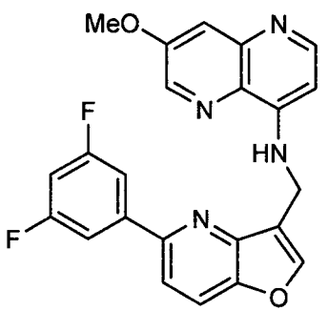
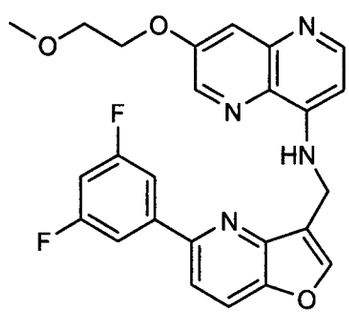
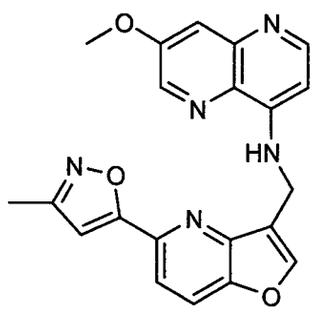
q y t son cada uno independientemente 0 o 1;

v es 0, 1 o 2;

donde dicho compuesto está seleccioando de



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, y

sales de los mismos.

11. Una composición farmacéutica que comprende un compuesto de la reivindicación 1 o la reivindicación 7 conjuntamente con un vehículo o portador farmacéuticamente aceptable.

12. Un método de tratamiento de cáncer en un sujeto, donde dicho método comprende administrar una cantidad eficaz de un compuesto tal como en la reivindicación 1 o en la reivindicación 7.

13. El método de la reivindicación 12 donde dicho compuesto es administrado en combinación con por lo menos un compuesto seleccionado entre agentes del tipo de los antibióticos, agentes alquilantes, agentes antimetabolitos, agentes hormonales, agentes inmunológicos, agentes del tipo de interferon y agentes misceláneos.

14. Un método de reducción del tamaño de un tumor en un sujeto, donde dicho método comprende administrar una cantidad eficaz de un compuesto de la reivindicación 1.

15. Un método de tratamiento de trastornos mediados por HGF en un sujeto, donde dicho método comprende administrar una cantidad eficaz de un compuesto de la reivindicación 1.

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16. Un método de reducción de metástasis de un tumor en un sujeto, donde dicho método comprende administrar una cantidad eficaz de un compuesto de la reivindicación 1.

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RESUMEN

Los compuestos seleccionados son eficaces para la profiláxis y tratamiento de enfermedades, tales como trastornos mediados por HGF. La invención comprende nuevos compuestos, análogos, profármacos y sales farmacéuticamente aceptables de los mismos, composiciones farmacéuticas y métodos para profilaxis y tratamiento de enfermedades y otras afecciones o trastornos que comprenden cáncer y similares. La presente invención se refiere también a procedimientos para la preparación de dichos compuestos así como también intermediarios útiles en dichos procedimientos

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PATENT COOPERATION TREATY PCT/US2008/011724

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From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

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

To:

MEKHOVICH Olga
AMGEN INC.
1120 Veterans Boulevard
South San Francisco, California 94080
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
17 June 2010 (17.06.2010)

Applicant's or agent's file reference
A1151WOPCT2

IMPORTANT NOTIFICATION

International application No.
PCT/US2008/011724

International filing date *(day/month/year)*
14 October 2008 (14.10.2008)

1. The following indications appeared on record concerning:

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

Name and Address
LOHMAN, Julia
420 First Avenue
Half Moon Bay, CA 94019
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

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

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

Name and Address
LOHMAN, Julia
94A Sussex Street
San Francisco, CA 94131
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

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

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

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

Facsimile No. +41 22 338 87 20

Authorized officer
Porohovski Youri
e-mail pt03.pct@wipo.int
Telephone No. +41 22 338 74 03

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To:

HERMENAU, Ronald S.
1120 Veterans Boulevard
South San Francisco, California 94080
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
26 May 2010 (26.05.2010)

Applicant's or agent's file reference
A1151WOPCT2

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Name and Address
LOHMAN, Julia
9 Dana Street
Cambridge, Massachusetts 02138
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

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420 First Avenue
Half Moon Bay, CA 94019
United States of America

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

Facsimile No. +41 22 338 87 20

Authorized officer
Valente Gabriela
e-mail pt03.pct@wipo.int
Telephone No. +41 22 338 74 03

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Name and Address
D'AMICO, Erin
4571 Calle Norte
Newbury Park, California 91320
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

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

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Name and Address
D'AMICO, Derin
4571 Calle Norte
Newbury Park, California 91320
United States of America

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Telephone No.:
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☐ other:

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

Facsimile No. +41 22 338 87 20

Authorized officer
Deblue Natalia
e-mail pt03.pct@wipo.int
Telephone No. +41 22 338 74 03

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Name and Address
HUNGATE, Randall W.
650 W. Highland Drive
Camarillo, California 93010
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

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

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

Name and Address
HUNGATE, Randall, W.
640 W. Highland Drive
Camarillo, CA 93010
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
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1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 87 20

Authorized officer
Valente Gabriela
e-mail pt03.pct@wipo.int
Telephone No. +41 22 338 74 03

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Name and Address
ALBRECHT, Brian K.
179 Chestnut Street, #2
Cambridge, Massachusetts 02139
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:

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

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

Name and Address
ALBRECHT, Brian K.
163 Allston Street, #3
Cambridge, MA 02139
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

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1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 87 20

Authorized officer
Valente Gabriela
e-mail pt03.pct@wipo.int
Telephone No. +41 22 338 74 03

Industria y Comercio
SUPERINTENDENCIA

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

000488

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad (31) N° Prioridad 32) Fecha (33) País
12/009.123 **15/01/2008** **US**

(51) Int. Cl.:

(71)Solicitante(s) **AMGEN INC.**

(72) Inventor(es) **TAE-SEONG KIM**
DAVID BAUER
STEVEN BELLON
Y OTROS

(74) Apoderado: **MARGARITA CASTELLANOS ABONDANO**

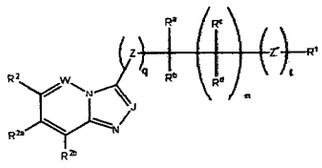
(85) Fecha limite inicio fase nacional:
(86) Datos relativos a la presentación de la solicitud PCT
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(87) Publicación internacional
Fecha: **23/07/2009**
N° publicación: **WO 2009/091374 A2**

(54) Titulo: **DERIVADOS HETEROCÍCLICOS FUSIONADOS Y MÉTODOS DE USO COMO INHIBIDORES C-MET**

Reivindicación(es):

1. Un compuesto de fórmula I



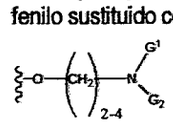
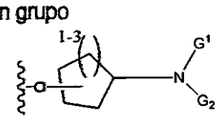
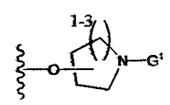
I

donde
J es N o CR^3;
W es CR^{2b} o N;
Z y Z* son independientemente –O–, $–S(O)_v–$, o $–NR^5–$;
R^a, R^b, R^c y R^d son cada uno independientemente H, halo, alquilo, alquenilo, alquinilo, haloalquilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, $–NO_2$, –CN, $–NR^5R^{5a}$, $–OR^4$, $–C(=O)R^4$, $–C(=O)OR^4$; $–C(=O)NR^5R^{5a}$, $–N(R^5)C(=O)NR^5R^{5a}$, $–OC(=O)NR^5R^{5a}$, $–S(O)_vR^4$, $–S(O)_2NR^5R^{5a}$, $–N(R^5)SO_2R^4$ cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia;
o R^a y R^b conjuntamente con el átomo de carbono al cual están unidos pueden combinarse para formar un cicloalquilo de 3–10 miembros, un anillo cicloalquenilo de 3–10 miembros, o un anillo heterociclo, cualquiera de los cuales puede estar opcionalmente sustituido con uno o más grupos R^{10} según lo permita la valencia.;
o R^c y R^d conjuntamente con el átomo de carbono al cual están unidos pueden combinarse para formar un cicloalquilo de 3–10 miembros, un anillo cicloalquenilo de 3–10 miembros, o un anillo heterociclo, cualquiera de los cuales puede estar opcionalmente sustituido con uno o más grupos R^{10} según lo permita la valencia.;
o R^a y/o R^b pueden combinarse con cualquiera de R^c o R^d para formar un anillo cicloalquilo de 3–8 miembros parcial o totalmente saturado o un anillo heterociclo, cualquiera de los cuales puede estar opcionalmente sustituido con uno o más grupos R^{10} según lo permita la valencia;
o R^a y R^b pueden combinarse para formar un grupo carbonilo;
o R^c y R^d unidos al mismo átomo de carbono pueden combinarse para formar un grupo carbonilo;

R^1 es arilo, heteroarilo o heterociclo cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más grupos R^{10} según lo permita la valencia;

R^2 es
(i) H, halo, ciano, nitro, o
(ii) alquilo, haloalquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, heterociclo, arilo, heteroarilo, arilalquilo, heteroarilalquilo, cicloalquilalquilo, heterocicloalquilo, $–OR^4$, $–S(O)_vR^4$, $–NR^5R^{5a}$, $–C(=O)R^4$, $–C(=S)R^4$, $–C(=O)OR^4$, $–C(=S)OR^4$, $–C(=O)NR^5R^{5a}$, $–C(=S)NR^5R^{5a}$, $–N(R^5)C(=O)NR^5R^{5a}$, $–N(R^5)C(=S)NR^5R^{5a}$, $–N(R^5)C(=O)R^4$, $–N(R^5)C(=S)R^4$, $–OC(=O)NR^5R^{5a}$, $–OC(=S)NR^5R^{5a}$, $–SO_2NR^5R^{5a}$, $–N(R^5)SO_2R^4$, $–N(R^5)SO_2NR^5R^{5a}$, $–N(R^5)C(=O)OR^4$, $–N(R^5)C(=S)OR^4$, $–N(R^5)SO_2R^4$, cada uno de los cuales puede estar opcionalmente independientemente sustituido con uno o más R^{10} según lo permita la valencia,

con la condición de que en los compuestos de fórmula I cuando W y J son ambos N, R^2 es distinto
(a) $–NR^5R^{5a}$ donde R^5 y R^{5a} son independientemente H, alquilo, haloalquilo, cicloalquilo, alquenilo, alquinilo, arilo, heteroarilo, heterociclo, arilalquilo, heteroarilalquilo, heterocicloalquilo, y cicloalquilalquilo; y
(b) fenilo sustituido con un grupo



o


donde G^1 y G^2 are independently alquilo, cicloalquilo, o G^1 y G^2 together with the nitrogen atom to which they are attached combine to form a 5– to 8–membered heterociclo ring;

R^{2a}, R^{2b} y R^3 están independientemente seleccionados en cada caso de H, halo, ciano, nitro, alquilo, ...

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-098383- -00000-0000
Fecha: 2010-08-11 13:38:17 Dep: 2020 DIR NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 488

ONES

PATENTE DE INVENCION [ ] **MODELO DE UTILIDAD** [ ] **Art. 33 Decisión 486/00**

- [ ] Indicación que se solicita una patente
- [ ] Datos de identificación del solicitante o de la persona que presenta la solicitud
- [ ] Descripción de la invención
- [ ] Dibujos de ser estos pertinentes
- [ ] Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa [ ] Incompleta [ ]

PATENTE DE INVENCION PCT [X] **MODELO DE UTILIDAD PCT** [ ] **Art. 33 Decisión 486/00 Circular Única**

- [X] Indicación que se solicita una PCT
- [X] Datos de identificación del solicitante o de la persona que presenta la solicitud
- [X] Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- [ ] Dibujos de ser estos pertinentes
- [X] Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa [X] Incompleta [ ]

DISEÑO INDUSTRIAL [ ] **(Art. 119 Decisión 486/00)**

- [ ] Indicación que se solicita diseño industrial
- [ ] Datos de identificación del solicitante o de la persona que presenta la solicitud
- [ ] Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño
- [ ] Comprobante de pago de las tasas establecidas

Completa [ ] Incompleta [ ]

ESQUEMA DE TRAZADO [ ] **(Art. 92 Decisión 486/00)**

- [ ] Indicación que se solicita un esquema de trazado
- [ ] Datos de identificación del solicitante o de la persona que presenta la solicitud
- [ ] Representación gráfica de un esquema de trazado
- [ ] Comprobante de pago de las tasas establecidas

Completa [ ] Incompleta [ ]

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
MARGARITA CASTELLANOS ABONDANO
Apoderado(a) y/o Representante de
AMGEN INC.

REFERENCIA		
	Radicación No.	10 098383
	Solicitud internacional	PCT/US2008/011724
	Fecha inicio fase nacional	15/08/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	13102

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. El solicitante debe presentar un nuevo titulo que permita identificar la materia de la cual trata la solicitud, ya que el titulo relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular única 5.2.9)

3. 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.

Continua en la página siguiente...

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5 , 7 y 10 PBX: 5870000
Sede CAN: Av. Cra 50 No. 26-55 int. 2 Tel: 5880070
Call Center 6513240. Linea 01800-910165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 08 OCT. 2010
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